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Optional Pre-Course Reading

2025 Edition

Optional pre-course reading: papers and resources

Headache	Carville 2012 Diagnosis and management of headaches in young people and adults: summary of NICE guidance Conicella 2008 The Child With Headache in a Pediatric Emergency Department Amin 2024 Consensus recommendations for the assessment and management of idiopathic intracranial hypertension in children and young people
Assessment of GCS	Tatman 1997 Development of a modified paediatric coma scale in intensive care clinical practice
When to LP	LP tips sheet O'Herlihy 2024 Comparison of international guidelines for CT prior to lumbar puncture in patients with suspected meningitis
Confused child / Decreased consciousness	Prasad 2017 Fifteen-minute consultation: Approach to the child with an acute confusional state RCPCH poster - The management of children and young people with an acute decrease in conscious level (DECON) Cellucci 2020 Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient
Unusual movements	Garone 2019 Acute ataxia in paediatric emergency departments: a multicentre Italian study Raucci 2018 Acute hyperkinetic movement disorders in Italian paediatric emergency departments Bacon 2022 Review of the new APLS guideline (2022): Management of the convulsing child Lumsden 2025 Fifteen-minute consultation: Management of acute dystonia exacerbation and status dystonicus
Abnormal gait	Localising the lesion tips sheet Leonhard 2019 Diagnosis and management of Guillain–Barré syndrome in ten steps Smith 2018 Neurological gait disorders in childhood Stone 2020 Recognising and explaining functional neurological disorder
Acute neuroimaging	Mirsky 2017 Pathways for Neuroimaging of Childhood Stroke Ramgopal 2020 Rapid brain MRI protocols reduce head computerized tomography use in the pediatric emergency department Marin 2024 Optimizing Advanced Imaging of the Pediatric Patient in the Emergency Department: Policy Statement
Acute brain attack	RCPCH poster – Stroke in childhood Ped-NIHSS scoring: https://www.youtube.com/watch?v=exaFmw1422g Bhate 2015 A practical approach to acute hemiparesis in children Mackay 2016 Differentiating Childhood Stroke From Mimics in the Emergency Department Mackay 2014 Stroke and nonstroke brain attacks in children
Complex cases – real world challenges	Hauer 2017 Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System Vogt 2024 Recommendations for the Management of Initial and Refractory Pediatric Status Dystonicus

BMJ

BMJ 2012;345:e5765 doi: 10.1136/bmj.e5765 (Published 19 September 2012)

PRACTICE

GUIDELINES

Diagnosis and management of headaches in young people and adults: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Headaches are a common problem that many clinicians in primary and secondary care find difficult to treat.[1 2] Once the serious causes of headache have been excluded (such as infection, tumour, bleeding, and arteritis), the major health and social burden of headaches can be attributed to primary headache disorders (cluster headache, migraine, and tension-type headache) and headache caused by the overuse of medications. Straightforward advice is needed for anyone working in the NHS on the diagnosis and treatment of these common disorders and the prevention of medication overuse headache.

This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the diagnosis and management of headaches in young people and adults.[3]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Assessment: indications for considering additional investigation

- Evaluate people who present with headache and any of the following features, and consider the need for further investigations or referral (or both):
  - -Worsening headache with fever
  - -Sudden onset headache that reaches maximum intensity within five minutes
  - -New onset neurological deficit
  - -New onset cognitive dysfunction
  - -Change in personality
  - -Impaired level of consciousness
  - -Recent (typically within the past three months) head trauma
  - -Headache triggered by cough, valsalva (trying to breathe out with nose and mouth blocked), or sneeze
  - -Headache triggered by exercise
  - -Orthostatic headache (headache that changes with posture)
  - -Symptoms suggestive of giant cell arteritis
  - -Symptoms and signs of acute narrow angle glaucoma
  - -A substantial change in the characteristics of their headache.

[*All based on the experience and opinion of the Guideline Development Group (GDG)*]

- Consider further investigations or referral (or both) for people who present with new onset headache and any of the following:
  - -Compromised immunity, caused, for example, by HIV or immunosuppressive drugs
  - -Age under 20 years and a history of malignancy
  - -A history of malignancy known to metastasise to the brain
  - -Vomiting without other obvious cause.

[*Based on very low quality evidence from two cohort studies, one of which was in an indirect population, and the experience and opinion of the GDG*]

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Diagnosis

- Diagnose primary headaches such as tension-type headache, migraine, or cluster headache according to the features in the table⇓.

[*Based on the experience and opinion of the GDG, informed by the International Headache Society ICHD-II (International Classification of Headache Disorders II) criteria*][4]

- Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for three months or more:

  -Triptans, opioids, ergots, or combination analgesic drugs on 10 days a month or more, or

  -Paracetamol, aspirin, or a non-steroidal anti-inflammatory drug (NSAID), either alone or in any combination, on 15 days a month or more.

[*Based on the experience and opinion of the GDG, informed by the International Headache Society ICHD-II criteria*][4]

Management

All headaches

- Do not refer people diagnosed as having tension-type headache, migraine, cluster headache, or medication overuse headache for neuroimaging solely for reassurance.

[*Based very low quality to moderate quality evidence from one randomised controlled trial*]

- Include the following in discussions with the person with a headache disorder:

  -A positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded, and

  -The options for management, and

  -Recognition that headache is a valid medical disorder that can have a serious impact on the person and his or her family or carers.

[*Based on observational studies ranging from poorly reported to well reported*]

- Explain the risk of medication overuse headache to people who are using acute treatments for their headache disorder.

[*Based on the experience and opinion of the GDG*]

Tension-type headache

- Consider aspirin, paracetamol, or an NSAID for acute treatment, taking into account the person's preferences, comorbidities, and risks of adverse events.

[*Based on low quality evidence from randomised controlled trials*]

Because of an association with Reye's syndrome, do not offer preparations containing aspirin to people aged under 16 years.

- Do not offer opioids for acute treatment.

[*Based on the absence of evidence for effectiveness and the experience and opinion of the GDG*]

- Consider a course of up to 10 sessions of acupuncture over five to eight weeks for the prophylactic treatment of chronic tension-type headache.

[*Based on low and very low quality evidence from single blind randomised controlled trials*]

Migraine with or without aura

- Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for acute treatment, taking into account the person's preferences, comorbidities, and risk of adverse events. For people aged 12-17 years consider a nasal triptan in preference to an oral triptan.

[*Based on very low to low quality evidence from direct comparisons in randomised controlled trials, which fed into mixed treatment comparisons in a network meta-analysis, and corresponding cost effectiveness analysis*]

- For people in whom oral preparations (or nasal preparations in people aged 12-17 years) for acute treatment are ineffective or not tolerated:

  -Offer a non-oral preparation of metoclopramide or prochlorperazine, and

  -Consider adding a non-oral NSAID or triptan if these have not been tried.

[*The first point is based on very low to low quality evidence from randomised controlled trials. The second point is based on the experience and opinion of the GDG and indirect evidence of very low to low quality evidence from randomised controlled trials*]

- Offer topiramate or propranolol for prophylactic treatment according to the person's preference, comorbidities, and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception.

[*Based on low to high quality evidence from direct comparisons in randomised controlled trials, which fed into mixed treatment comparisons in a network meta-analysis, and corresponding cost effectiveness analysis*]

- If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over five to eight weeks or gabapentin (up to 1200 mg/day) according to the person's preference, comorbidities, and risk of adverse events.

[*Based on low to high quality evidence from direct comparisons in randomised controlled trials, which fed into mixed treatment comparisons in a network meta-analysis, and corresponding cost effectiveness analysis*]

- Advise people with migraine that riboflavin (400 mg once a day) can reduce the frequency and intensity of migraine in some people.

[*Based on moderate quality evidence from randomised controlled trials*]

Combined hormonal contraceptive use by women and girls with migraine

- For those who have migraine with aura, do not routinely offer combined hormonal contraceptives for contraception.

[*Based on the experience and opinion of the GDG*]

Menstrual migraine

- For women and girls with predictable menstrual related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days that migraine is expected.

[*Based on low quality evidence from two randomised controlled trials and the experience and opinion of the GDG*]

Cluster headache

- Offer oxygen and a subcutaneous or nasal triptan for acute treatment.

[*Based on moderate quality evidence from randomised controlled trials*]

- When using oxygen for acute treatment:
  -Use 100% oxygen at a flow rate of at least 12 L per minute with a non-rebreathing mask and a reservoir bag, and
  -Arrange provision of home and ambulatory oxygen.

[*The first point is based on moderate quality evidence from randomised controlled trials and the experience and opinion of the GDG. The second point is based on the experience and opinion of the GDG*]

- When using a subcutaneous or nasal triptan, ensure the person is offered an adequate supply of triptans. This should be calculated according to the person's history of cluster bouts, taking into account the manufacturer's maximum daily dose.

[*Based on the experience and opinion of the GDG*]

- Consider verapamil for prophylactic treatment during a bout of cluster headache. If unfamiliar with its use for cluster headache, seek specialist advice before starting verapamil, including advice on electrocardiographic monitoring.

[*Based on very low and low quality evidence from one randomised controlled trial*]

Primary headaches during pregnancy

- Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each drug during pregnancy.

[*Based on very low quality evidence from three prospective cohort studies and the experience and opinion of the GDG*]

- Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.

[*Based on the experience and opinion of the GDG*]

- Seek specialist advice if treatment for cluster headache is needed during pregnancy.

[*Based on low and very low quality evidence from one cohort study with an indirect population and the experience and opinion of the GDG*]

Medication overuse headache

- Explain to people with medication overuse headache that it is treated by withdrawing the drugs that are overused.

[*Based on very low quality evidence from one open label randomised controlled trial and the experience and opinion of the GDG*]

- Advise people to stop taking all overused acute headache drugs for at least one month and to stop abruptly rather than gradually.

[*Based on the experience and opinion of the GDG*]

- Advise people that headache symptoms will probably get worse in the short term before they improve and that there may be associated withdrawal symptoms. Provide them with close follow-up and support according to their needs.

[*Based on the experience and opinion of the GDG*]

- Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused drugs.

[*Based on the experience and opinion of the GDG*]

Overcoming barriers

The use of combination therapy as the first choice treatment for migraine is innovative and should improve acute treatment. Compliance may, however, be better when people take one drug only, and the guideline provides this alternative. Alongside other considerations, patient preference should inform choice of acute migraine treatments. At the time of publication (September 2012), not all the recommended drugs had marketing authorisation in the United Kingdom for the indication specified or for young people. Prescribers should follow relevant professional guidance and take full responsibility for the decision when prescribing drugs that do not have marketing authorisation. Because topiramate is recommended as first line agent for migraine prophylaxis, prescribers and patients will need to be aware of its safe use in women and girls of childbearing potential. Its enzyme inducing potential means that many hormonal contraceptives may be unreliable. Prescribers should consult authoritative guidance, such as the *British National Formulary* (*BNF*) or guidance from the Royal College of Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare,[5] when advising on contraceptive use. In treating those with cluster headaches, general practitioners and oxygen supply companies should ensure that an urgent supply of oxygen is readily available. Challenges around medication overuse headaches include the need to recognise the risk factors, plus early preventive advice. Advice to stop taking drugs abruptly may not be welcome, especially as a definite diagnosis can be made only after the headaches resolve, which occurs in only half of those who succeed in stopping. No recommendation has been made for other therapist delivered interventions, such as manual therapy, exercise, cognitive behavioural therapy, or self management programmes because of the absence of evidence. The guideline makes research recommendations in some of these areas.

The members of the Guideline Development Group were Ria Bhola, Sam Chong, Brendan Davies, Mark Dunne-Willows, Carole Gavin, Kay Kennis, David Kernick, Manjit Matharu, Peter May, Wendy Thomas, Martin Underwood (chair), and William Whitehouse. The technical team at the National Clinical Guideline Centre comprised Sara Buckner, Serena Carville, Elisabetta Fenu, Zahra Naqvi, Norma O'Flynn, Smita Padhi, Tim Reason, and Carlos Sharpin.

Contributors: SC wrote first draft. All authors reviewed the draft, were involved in writing further drafts, and reviewed and approved the final version for publication. MU is guarantor.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors were funded by NICE for the submitted work; after completion of the guideline and before its publication a member of MU's division obtained substantial funding from Bayer for an investigator led study in an unrelated clinical area; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Further information on the guidance

Methods

The guideline was developed using current NICE guideline methodology (www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/developing_nice_clinical_guidelines.jsp). The Guideline Development Group (GDG) comprised three general practitioners (including the chair, and two with a special interest in headache), two neurologists, one paediatric neurologist, one pain specialist, three lay members, an emergency medicine physician, a pharmacist, and a specialist headache nurse.

The group developed clinical questions, collected and appraised clinical evidence, and evaluated the cost effectiveness of proposed interventions through literature review and original economic modelling. The draft guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the group took all comments into consideration when producing the final version of the guideline. Quality ratings of the evidence were based on GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes rather than the quality of the clinical study. Quality assessment of diagnostic studies was based on QUADAS-II methodology (www.bris.ac.uk/quadas/quadas-2) and presented in customised GRADE tables. When standard methodology could not be applied, a customised quality assessment was undertaken. These assessments were presented as a narrative summary of the evidence or in customised GRADE tables (for example, for qualitative and prognostic reviews).

Network meta-analysis for the acute and prophylactic treatment of migraine

Two network meta-analyses were conducted as part of the clinical review. The advantage of network meta-analysis over conventional meta-analysis is that it enables treatment effects to be calculated for all interventions simultaneously, so that they can be ranked on the basis of efficacy using all available direct and indirect evidence from randomised controlled trials, while preserving randomisation. Results of the network meta-analysis were used to facilitate recommendations through treatment rankings and parameterisation of effect sizes for the economic models. In the network meta-analysis for acute treatment of migraine, triptan plus NSAID combination therapy was found to be the most effective. In the network meta-analysis for prophylactic treatment of migraine topiramate was found to be the most effective.[7]

Cost effectiveness analysis for acute treatment of migraine

An economic model was developed from an NHS and Personal Social Services perspective to compare the cost effectiveness of six interventions for acute treatment of migraine. Triptan plus NSAID combination therapy was the most cost effective treatment at a willingness to pay threshold of £20 000 (€25 290; $31 790) per quality adjusted life year in the base case and all sensitivity analyses.

Cost effectiveness analysis for prophylactic treatment of migraine

An economic model was developed from an NHS and Personal Social Services perspective to compare the cost effectiveness of five interventions for prophylactic treatment of migraine. Topiramate was the most cost effective treatment, at a willingness to pay threshold of £20 000 per quality adjusted life year.

Points to consider

At the time of publication (September 2012), the following drugs did not have UK marketing authorisation for the indications they have been recommended for:

- Prochlorperazine (except for the relief of nausea and vomiting) and gabapentin for migraine
- Frovatriptan and zolmitriptan for menstrual migraine
- Nasal triptan for cluster headache.

The following drugs did not have a UK marketing authorisation for people aged under 18 years at the time of publication for the indication recommended:

- Triptan (except for nasal triptan) and topiramate for migraine
- Subcutaneous triptan or verapamil for cluster headache.

Riboflavin (400 mg) does not have marketing authorisation for migraine but is available as a food supplement.

The prescriber should follow relevant professional guidance and take full responsibility for the decision. The patient (or his or her parent or carer) should provide informed consent, which should be documented.

Future research

The GDG identified some important questions that need to be answered:

- Is amitriptyline a clinically and cost effective prophylactic treatment for recurrent migraine?
- Is pizotifen a clinically and cost effective prophylactic treatment for recurrent migraine?
- Is topiramate a clinically and cost effective prophylactic treatment for recurrent cluster headache?
- Can a psychological intervention such as cognitive behavioural therapy improve headache outcomes and quality of life for people with chronic headache disorders?
- Can a course of steroid treatment or drugs used for headache prophylaxis help people with medication overuse headaches withdraw from medication?

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Cite this as: *BMJ* 2012;345:e5765

Table

Table 1| Diagnosis of tension-type headache, migraine, and cluster headache

Headache feature	Tension-type headache		Migraine (with or without aura)		Cluster headache	
Pain location*	Bilateral		Unilateral or bilateral		Unilateral (around the eye, above the eye, and along the side of the head or face)	
Pain quality	Pressing or tightening (non-pulsating)		Pulsating (throbbing or banging in young people aged 12–17 years)		Variable (can be sharp, boring, burning, throbbing, or tightening)	
Pain intensity	Mild or moderate		Moderate or severe		Severe or very severe	
Effect on activities	Not aggravated by routine activities of daily living		Aggravated by, or causes avoidance of, routine activities of daily living		Restlessness or agitation	
Other symptoms	None		Unusual sensitivity to light or sound (or both), or nausea or vomiting (or both). †Aura symptoms can occur with or without headache; they are fully reversible, develop over at least 5 minutes, and last for 5-60 minutes. Typical aura symptoms include visual symptoms such as flickering lights, spots or lines, or partial loss of vision (or a combination thereof); sensory symptoms such as numbness or pins and needles (or both); and speech disturbance		On the same side as the headache: red or watery eye (or both); nasal congestion or runny nose (or both); swollen eyelid; forehead and facial sweating; constricted pupil or drooping eyelid (or both)	
Duration of headache	30 minutes to continuous		4-72 hours in adults; 1-72 hours in people aged 12-17 years		15-180 minutes	
Frequency	<15 days a month	≥15 days a month for more than 3 months	<15 days a month	≥15 days a month for more than 3 months	1 every other day to 8 per day,‡ with continuous remission§ >1 month	1 every other day to 8 per day,‡ with continuous remission§ <1 month in a 12 month period
Diagnosis	Episodic tension-type headache	Chronic tension type headache¶	Episodic migraine (with or without aura)	Chronic migraine with or without aura)**	Episodic cluster headache	Chronic cluster headache

*Headache pain can be felt in the head, face, or neck.

†See full guideline for further information on the diagnosis of migraine with aura.

‡The frequency of recurrent headaches during a cluster headache bout.

§The pain-free period between cluster headache bouts.

¶Chronic migraine and chronic tension-type headache commonly overlap; if the patient has any features of migraine, diagnose chronic migraine.

**The National Institute for Health and Clinical Excellence has developed technology appraisal guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine.[6]

Headache
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Journal compilation © 2008 American Headache Society

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2007.01052.x
Published by Wiley Periodicals, Inc.

Research Submission

The Child With Headache in a Pediatric Emergency Department

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Objectives.—To investigate clinical features of a pediatric population presenting with headache to a pediatric emergency department (ED) and to identify headache characteristics which are more likely associated with serious, life-threatening conditions in distinction from headaches due to more benign processes.

Background.—Although headache is a common problem in children visiting a pediatric ED, a few studies thus far have attempted to identify the clinical characteristics most likely associated with suspected life-threatening disease.

Methods.—A retrospective chart review of all consecutive patients who presented with a chief complaint of headache at ED over a 1-year period was conducted. Etiologies were classified according to the International Headache Society diagnostic criteria 2nd edition.

Results.—Four hundred and thirty-two children (0.8% of the total number of visits) aged from 2 to 18 years (mean age 8.9 years) were enrolled in our study. There were 228 boys (53%) and 204 girls (47%). School-age group was the most represented (66%). The most common cause of headache was upper respiratory tract infections (19.2%). The remaining majority of non-life-threatening headache included migraine (18.5%), posttraumatic headache (5.5%), tension-type headache (4.6%). Serious life-threatening intracranial disorders (4.1%) included meningitis (1.6%), acute hydrocephalus (0.9%), tumors (0.7%). We found several clinical clues which demonstrated a statistically significant correlation with dangerous conditions: pre-school age, recent onset of pain, occipital location, and child's inability to describe the quality of pain and objective neurological signs.

Conclusions.—Differential diagnosis between primary and secondary headaches can be very difficult, especially in an ED setting. The majority of headaches are secondary to respiratory infectious diseases and minor head trauma. Our data allowed us to identify clinical features useful to recognize intracranial life-threatening conditions.

Key words: headache, child, emergency department

(*Headache* 2008;48:1005-1011)

INTRODUCTION

Headache is a common complaint in children and adolescents. Headache prevalence rates among children range from 5.9% to 37.7% and increase in school-age (40-50%) and adolescent children (80%).[1] An attack of severe headache can produce anxiety in both parent and child; it represents one of the most common reasons for a visit to a pediatric emergency department (ED). In a pediatric ED, the primary objective is to recognize the serious life-threatening

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Accepted for publication December 10, 2007.

Conflict of Interest: None

conditions requiring immediate medical care among the wide spectrum of headache diagnoses. Moreover, in less severe headache types, appropriate evaluation and investigation may prevent unnecessary hospitalization.

In the previous literature, there are few data regarding the evaluation of headache in the pediatric ED.[2-7] Therefore, the aims of our retrospective study were: (1) to investigate the clinical characteristics of the pediatric patients presenting with headache to our ED during one year; and (2) to identify the clinical headache characteristics which may lead to suspect serious life-threatening diseases.

SUBJECTS AND METHODS

Patients.—A total of 432 consecutive patients who presented with a chief complaint of headache to our ED between January 1, 2004 and December 31, 2004 were reviewed retrospectively. Patients with headache associated with a moderate-severe cranial trauma were not included. Children with mild head trauma, according to the Canadian Pediatric Society (1990), were included in our sample. According to these guidelines, the criteria to define a head trauma as mild are: (1) asymptomatic; (2) mild headache; (3) 3 or fewer episodes of vomiting; (4) Glasgow Coma Scale score of 15; (5) loss of consciousness for less than 5 minutes.[8] During the period of the study, 55,273 children attended the pediatric ED. Headache-related cases represented around 0.8% of all visits.

The study was approved by the local ethical committee.

The following data were recorded from each ED chart: patient age, sex, family history and detailed history of headache, subjective characteristics of headache, associated symptoms, physical examination, radiological and laboratory tests, previous treatment sought, and diagnosis and treatment. Our patients were divided in groups according to 2 different criteria: (1) the patient's age; (2) the time interval from the onset of the headache attacks. These divisions are, of course, arbitrary, but they show the advantage to allow the possible identification of groups, related to age or headache onset, in which potentially life-threatening headaches may be more frequent.

1. According to a previous study on pediatric headaches in ED,[4] patients were divided into 3 groups based on their age: (1) pre-school children (2-5 years); (2) school-age group (6-12 years); (3) adolescent group (13-18 years).
2. Headaches were arbitrarily separated into 3 types on the basis of the time interval from the onset of the headache attacks: (1) recent-onset headaches, in which the attacks first occurred within 2 months before the ED visit; (2) medium-onset headaches, in which the attacks began from 2 to 8 months before; (3) late-onset headaches, in which patients had complained of attacks for a longer time than 8 months before ED consultation.

Headache features, determined from patient descriptions of pain, included: the location of pain (bilateral or unilateral, and frontal, temporal, or occipital) and the quality of pain (pulsating or constrictive). Pain intensity (slight, medium, and severe) was estimated based upon impact on daily activities. We considered that slight pain (grade 1) allowed all daily activities to be accomplished, while medium pain (grade 2) limited the daily activities and severe pain (grade 3) obliged the child to abandon any activity.[9] In order to assess a complete spectrum of diagnosis, charts of inpatient and outpatients, referred to the Department of Neurology for hospitalization, were examined. Headaches were classified according to the International Headache Society (IHS) diagnostic criteria 2nd edition.[10]

Statistical Analysis.—Statistical analysis was performed in order to investigate the clinical factors that enabled the prediction of the occurrence of benign or life-threatening headache. Based on etiological criteria, headaches were divided in 4 groups (see later). The possible correlation between the headache group and some clinical characteristics, such as patient age, time interval from onset, pain location, and neurological signs, was tested by means of the chi-square test. Significance levels were set at .05. All statistical analyses were performed using SPSS (version 13.0) software.

RESULTS

Clinical Characteristics.—In total, 432 headache patients were studied ranging from 2 to 18 years of

age with a mean of 8.9 years. The study group included 228 boys (53%) and 204 girls (47%). Patients were classed by age-related groups: 83 pre-school children (19%), 285 school-age children (66%), and 64 adolescents (15%).

Dividing patients according to the onset of the headache attacks, 404 patients (93%) reported a recent onset of headache, while only 3% and 4% of all patients presented with a medium and late onset headache.

As far as the pain location is concerned, only 119 patients (27.5% of all patients) could identify a precise location. Among this subgroup, 101 children (85%) indicated a bilateral, frontal or temporal, pain location, while one-sided headache or bilateral occipital pain was present in 15 (12.5%) children. Only 3 patients (2.5%) reported pain at the vertex. A description of the quality of pain could be obtained only from 35 patients (8% of all our patients). Pain was described as pulsating or constrictive in 23 (66%) and 12 (34%) patients, respectively. As for the pain intensity, it could be described only by 36 patients (8.3% of all our patients). Ten children (28%) referred slight pain, a medium pain was reported in 3 cases (8%), whereas most patients (23-64%) presented with a severe headache.

Associated symptoms were reported in 189 patients (44% of all our patients) and included vomiting, fever, motor/sensitive/visual troubles, abdominal pain, vertigo, and behavioral/consciousness impairment.

At the physical examination, 95 children (22% of all our patients) showed focal and/or general findings and, in particular 21 children (4.8% of all our patients) had focal neurological signs. Four children showed hypertension (0.9% of all our patients). Five children (1% of all our patients) showed papilloedema.

Diagnostic Examinations.—Laboratory and radiological tests (sinus series, blood studies, chest X-ray, electrocardiogram [EKG], head computed tomography [CT], abdominal ultrasound [US], lumbar puncture) were performed in 46 patients (11%). Although no brain magnetic resonance imaging (MRI) was performed in the ED, some children subsequently had this examination when moved to hospitalization units. Sinus series were the most common test (42%) in patients with suspected sinusitis. It confirmed the clinical hypothesis only in 7 patients.

Five patients (10.6%) had CT scan of the head. Two patients had abnormal findings: one child showed ventriculo-peritoneal (V-P) shunt malfunction and the other an ethmoid sinusitis.

Outcome After ED Consultation.—A total of 299 patients (69%) were discharged, while 126 children (29%) were hospitalized. Seven patients (2%) refused the hospitalization. A specific diagnosis was reached in 277 patients (64% of all our patients). The final diagnosis could be reached during either the ED consultation or the hospitalization.

1. Headache attributed to non-life-threatening diseases included in IHS criteria:[10] 134 patients (49%) (Table 1). The most common cause of headache was upper respiratory tract infections (URI) (30.8%) including pharyngitis, tonsillitis, pneumonia, sinusitis, otitis, and adenoiditis. One patient (0.3%) had a serious anemia possibly provoking headache. Posttraumatic headache was included in the non-life-threatening headache group according to IHS criteria of acute and chronic headache

Table 1.—Headache Attributed to Non-Life-Threatening Diseases

Headache attributed to non-life-threatening diseases (ICHD-II codes[10])	N	%
1. Respiratory tract infections (9.2)	37	14
2. Sinusitis (11.5), otitis (11.4), adenoiditis (11.8)	46	16.8
3. Viral infections (9.2.2)	4	1.4
4. Chronic medication (8.3)	5	1.8
5. Dehydratation (10.5)	3	1.3
6. Anemia (10.5)	1	0.3
7. Posttraumatic headache (5.1)	24	8.6
8. Chronic postcraniotomy headache (5.7.2)	2	0.7
9. Arterial hypertension (10.3)	4	1.4
10. Refractive errors (11.3.2.)/ heterophoria (11.3.3)	6	2
11. Teeth disorders (11.6)	2	0.7
Total	134	49

ICHD-II = International Classification of Headache Disorders, 2nd edition.

Table 2.—Primary Headache

Primary headache (ICHD-II codes[10])	N	%
1. Cluster headache (3.1)	2	0.7
2. Tension-type headache (2.1)	20	7
3. Migraine without aura (1.1)	67	24.1
4. Migraine with aura (1.2)	13	4.6
6. Chronic headache (1.5.1)	3	1.3
7. Migraine-triggered seizure (1.5.5)	1	0.3
Total	106	38

ICHD-II = International Classification of Headache Disorders, 2nd edition.

attributed to mild head injury.[10] In fact, all these patients had a normal neurological examination and only 25% were admitted and performed CT.

2. Primary headache: 106 patients (38%) (Table 2). Migraine represented the most common type (73.5%) and in particular, migraine without aura was found in 61% of children. Tension headache, chronic migraine, and cluster headache were diagnosed in 20%, 3%, and 2% of our patients, respectively.
3. Headache comorbidity: headache coexisting with diseases without a demonstrated causality relationship (unclassified in IHS criteria): 19 patients (7%). The most frequent comorbid conditions were epilepsy, vertigo, syncope, and urticaria.
4. Headache attributed to serious life-threatening intracranial disorders: 18 patients (6%) (Table 3). These children showed brain tumors, viral meningitis, V-P shunt malfunctions, pseudotumor cerebri, and brain malformations. The most common cause of secondary neurological headache was meningitis (39%).

In summary, among the 277 patients who had a final diagnosis, 259 children (94%) showed a benign headache, while 18 patients (6%) had a life-threatening headache.

Headaches in the Different Patient Groups.—*Age-Related Groups.*—The cause of the headache varied with age group. Secondary non-life-threatening headaches represented 49.4% of pre-school children headaches, whereas only 12.5% adolescent patients showed this headache type ($P < .001$). Secondary neurological headaches were diagnosed in 7.2% of pre-school children, in 9.4% of adolescents and in 2.1% of the school-age patients. Primary headaches were observed in 29.8% of school-age children and in 37.5% of adolescents ($P < .001$).

Time Interval From the Onset of the Headache Attacks.—The time interval from the onset of the headache attacks was not significantly correlated with the occurrence of benign or life-threatening headache ($P = .483$). However, 17 of 18 children with a serious neurological disease (94.5%) had headache attacks for less than 2 months. On the contrary, primary headaches represented 43.8% and 38.5% of the medium and late onset headaches, respectively.

Headaches Features and Associated Symptoms and Signs: Their Relationship With the Occurrence of Benign or Life-Threatening Headache.—Among headache features, location and quality of pain proved to be useful in secondary neurological headache diagnosis. Indeed, patients with intracranial diseases were either unable to indicate the location of pain (15/18 patients) or they had an occipital headache (3/18 patients). Primary headaches represented 73.3% of one-sided headaches ($P < .001$). All patients with primary headaches could describe the quality of pain (66% pulsating, and 34% constrictive). Only 8.3% of children with serious underlying illness described the pain as constrictive ($P < .001$). Also the

Table 3.—Headache Attributed to Dangerous Intracranial Diseases

Dangerous intracranial diseases (ICHD-II codes[10])	N	%
1. Brain malformation (Chiari type I, Dandy-Walker) (7.7, 7.9)	2	0.7
2. Brain tumors (7.4)	3	1.3
3. Viral meningitis (9.1.2)	7	1.9
4. Pseudotumor cerebri (7.1.1)	2	0.7
5. Ventriculo-peritoneal shunt malfunction (7.1.3)	4	1.4
Total	18	6

ICHD-II = International Classification of Headache Disorders, 2nd edition.

assessment of pain intensity could help in discriminating the occurrence of benign or life-threatening headache. The intensity of pain was reported as slight in 32.3% of children with a secondary nonneurological headache, while among patients who described a severe pain, 82.6% had a primary headache and 17.4% had a secondary nonneurological or neurological headache. All patients with a life-threatening secondary headache referred a very intense pain ($P < .001$).

Associated symptoms were not statistically associated with the occurrence of benign or life-threatening headache ($P = .071$). Vomiting was the most common and it was reported in primary and secondary headaches with the same rate (30%). In 67% of cases, secondary neurological headaches had other associated symptoms, including fever, focal neurological deficits, and behavioral disturbances. All children with a serious underlying neurological condition had objective neurological signs, including papilloedema (5/18 patients), ataxia (5/18 patients), hemiparesis (4/18 patients), abnormal eye movements (6/18 patients). Primary headaches were associated in 70.6% of cases to phonophobia and photophobia.

COMMENTS

There are only a few studies dealing with pediatric headaches in an ED.[2-7] In our study, the frequency of children with headache was 0.8%, similar to previously reported data (0.6-1.3%).[4,6] There was no significant difference between sexes, but school-age children recorded greater frequency (66%). Headaches of recent onset (2 months or less, prior to ED visit) represented the largest proportion (93%), as compared with those begun from 2 to 8 months or longer than 8 months before the ED visit. We chose to also consider the longer lasting headaches since they are observed, although much more rarely, in ED.

Among the secondary headaches, the ones due to non-life-threatening diseases were the most frequent. In particular, respiratory tract infections could be considered the etiologic factor of 30.8% of all the examined headaches, thus confirming previous results.[2,4,6] When the primary headaches are considered, migraine was far the more common type. According to literature,[4,6,7] meningitis was the most common cause of a headache due to a serious neurological condition. These patients did not constitute a diagnostic problem, however, as they had clear systemic and neurological signs of intracranial hypertension.

In our patients, some clinical elements were shown to correlate with the occurrence of benign or life-threatening headache. Looking at the patient's age, primary headaches were most common in school-age children and in the adolescent group while headaches associated with serious intracranial diseases occurred more frequently in pre-school children and adolescents. In pre-school children, special attention should be paid to performing a thorough neurological examination. Considering the onset of the headache attacks, 94.5% of patients with dangerous neurological disease experienced headache with an onset not earlier than 2 months before the ED visit, whereas most of the medium- and late-onset headaches were diagnosed as primary headaches (82%).

Some headache clinical characteristics can suggest secondary headache. In particular, children with serious neurological conditions either were unable to localize pain or referred an occipital headache; moreover, they could not readily describe the quality of pain. This result confirms previous findings (Table 4). In secondary non-life-threatening headaches, pain was located especially in the bilateral frontal or temporal region, whereas about 74% of unilateral headaches were classified as primary headaches.

In our study, vomiting did not prove to be useful for the differential diagnosis of headache, it being associated to all different etiologies. However, other associated symptoms, such as decreased consciousness, focal findings, vomiting, and fever, were very common in patients with headache attributed to a neurological disorder.

Primary headaches were more often associated with visual disturbances, sensitive troubles (migraine with aura, 26%), and phono-photophobia (22%). All patients with an intracranial disorder had neurological objective signs of the underlying condition, such as papilloedema, ataxia, hemiparesis, and abnormal eye movements.

Table 4.—Comparison of the Present Study With the Previous Ones

	Kan et al[4]	Lewis and Qureshi[2]†	Leon-Diaz et al[6]	Present study
Number of patients	130	150	185	432
Age (years)	<18	<18	2-15	2-18
Secondary benign headaches (%)	63.2	59.6	60.6	35.4
Secondary life-threatening headaches (%)	15.3	14.9	4.3	4.1
Primary headaches (%)	10	18	24.3	24.5
Unclassified (%)	11.5	7	10.8	36

†In this article (see Table 1, page 202), the total amount of headache type percentages is 99.5%.

Among the diagnostic tests performed in the ED, the most frequently used examination was the sinus series for suspected sinusitis. The sinus series, whose diagnostic value in this disease is still controversial,[11,12] showed sinusitis only in 7/20 patients, thus suggesting the low usefulness of this examination.

In our study, only 5 patients (1.5%) had a CT scan in the ED, as their clinical state was unclear. In 2 patients (40%), a neurological underlying disease was found. Patients with a life-threatening intracranial condition were immediately hospitalized and underwent more sophisticated diagnostic examinations later. Kan et al reported that 10% of their children had CT scans and that brain abnormalities were found in 10% of patients. The authors suggested that emergency CT scans should be limited to patients with secondary neurological headaches including head trauma and V-P shunt complications or should be considered in patients with a high risk of developing intracranial complication and in patients with a abrupt onset of headache without a clear specific etiology.[4] We cannot make a direct comparison with these previous data, because some patients in this study received a brain CT or MRI during hospitalization. This may explain a difference in the rate of performed neuroimaging studies between Kan et al's patients and our headache children.

In conclusion, the majority of the headaches in the pediatric ED were secondary to concurrent acute respiratory illness and minor head trauma. In a small minority of patients, headaches were secondary to serious life-threatening intracranial disorders. As shown in Table 5, several clinical features such as preschool age, recent onset of headache attacks, occipital location, patient's inability to describe headache characteristics, and neurological signs are useful to identify headaches secondary to underlying brain processes.

Table 5.—Factors Associated With the Occurrence of Benign or Life-Threatening Headache

	Benign	Life-threatening
Age*	School	Pre-school
Onset of headache attacks	>2 months	<2 months
Pain location*	Unilateral/bilateral, frontal or temporal region	Unable to describe or occipital region
Pain quality*	Able to describe or pulsating	Unable to describe or constrictive
Pain intensity*	From slight to intense	Very intense
Associated neurological signs*	None	Focal neurological deficits, papilloedema, ataxia, consciousness disturbances

*Statistically significant associations ($P < .05$).

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Consensus recommendations for the assessment and management of idiopathic intracranial hypertension in children and young people

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2023-326545).

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Received 28 November 2023
Accepted 22 April 2024
Published Online First
9 May 2024

To cite: Amin S, Monaghan M, Forrest K, *et al*. *Arch Dis Child* 2024;**109**:654–658.

ABSTRACT

Background Idiopathic intracranial hypertension (IIH) is a potentially disabling condition. There is a lack of evidence and national guidance on how to diagnose and treat paediatric IIH, leading to variation in clinical practice. We conducted a national Delphi consensus via the Children's Headache Network to propose a best-practice diagnostic and therapeutic pathway.

Methods The Delphi process was selected as the most appropriate methodology for examining current opinion among experts in the UK. 104 questions were considered by 66 healthcare professionals, addressing important aspects of IIH care: assessment, diagnosis, treatment, follow-up and surveillance. General paediatricians, paediatric neurologists, ophthalmologists, opticians, neuroradiologists and neurosurgeons with a clinical interest or experience in IIH, were invited to take part.

Results The Delphi process consisted of three rounds comprising 104 questions (round 1, 67; round 2, 24; round 3 (ophthalmological), 13) and was completed between March 2019 and August 2021. There were 54 and 65 responders in the first and second rounds, respectively. The Delphi was endorsed by the Royal College of Ophthalmologists, which engaged 59 ophthalmologists for round 3.

Conclusions This UK-based Delphi consensus process reached agreement for the management of paediatric IIH and has been endorsed by the Children's Headache Network and more broadly, the British Paediatric Neurology Association. It provides a basis for a pragmatic clinical approach. The recommendations will help to improve clinical care while minimising under and over diagnosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Incidence of paediatric idiopathic intracranial hypertension (IIH) is increasing.
⇒ Absence of randomised controlled trials on the management of paediatric IIH.
⇒ Management of IIH depends on treating physician, local/national policies and funding.

WHAT THIS STUDY ADDS

⇒ Recommendations to guide the management of paediatric IIH based on consensus.
⇒ The recommendations are pragmatic and can be implemented in most healthcare systems around the world.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These new UK guidelines for the management and surveillance of IIH provide consensus guidance for the delivery of the best clinical care.
⇒ The results will help policymakers and planners to plan and allocate budgets for the management of patients with IIH.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is characterised by elevated cerebrospinal fluid (CSF) pressure, without a known cause, typically presenting with headaches and visual disturbance and papilloedema, but otherwise normal neurological examination.[1] The most reported symptom, in 75–99% of cases, is headache.[2]

Pseudotumour cerebri syndrome (PTCS) is an alternative term, encompassing secondary causes.[3] The condition was first reported in the late 19th century by Heinrich Quincke who believed the condition was due to overproduction of CSF.[4] The condition saw several name changes; 'pseudotumor cerebri' in 1904,[5] and later, 'benign intracranial hypertension'(1955), prior to reports of visual loss, invalidating 'benign'. Subsequently referred to as PTCS or IIH.[4]

The classical modified Dandy criteria,[6] suggest that for a diagnosis of IIH, an individual must have: (1) symptoms of increased intracranial pressure (ICP); (2) a lack of localising neurological signs, except for unilateral or bilateral sixth nerve palsies; (3) increased CSF opening pressure with normal CSF; (4) normal brain imaging with no hydrocephalus; and (5) no other cause of raised ICP. Some have suggested that these criteria are sufficient.[7]

Alternative criteria are Friedman's criteria.[3] Per Friedman's criteria (online supplemental table 1),[3] required features for a definite diagnosis of IIH are;

A. Papilloedema.
B. Normal neurological examination except for cranial nerve abnormalities.
C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass or structural lesion and no abnormal meningeal enhancement on MRI, with and without gad-

olinium, for typical patients (women and obese) and MRI, with and without gadolinium, and magnetic resonance venogram (MRV) for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used.

D. Normal CSF composition.

E. Elevated lumbar puncture opening pressure (≥280 mm CSF in children (250 mm CSF if the child is not sedated and not obese)) in a properly performed lumbar puncture.

A diagnosis of IIH can still be made based on the Friedman's criteria if there is an absence of papilloedema, as long as there is an abducens nerve palsy and all of the criteria B–E. IIH can also be diagnosed if criteria B–E are met, in combination with at least three of four of the following neuroimaging criteria:

1. Empty sella.
2. Flattening of the posterior aspect of the globe.
3. Distension of the perioptic subarachnoid space with or without a tortuous optic nerve.
4. Transverse venous sinus stenosis.

A 'probable' diagnosis is possible if criteria A–D are met, with bilateral papilloedema, even if the CSF pressure (criterion E) is not diagnostically elevated.

IIH requires the absence of underlying structural causes, such as malignancies or autoimmune conditions. Neuroimaging findings, if any, include secondary empty sella syndrome,[8] flattened globes, abnormal optic nerve sheaths, optic nerve protrusion, posterior globe flattening, and transverse sinus stenosis.[9 10]

A cohort-based UK study found an incidence of IIH of 0.71 per 100 000 in ages 1–16 years, increasing with age and weight to 4.18 and 10.7 per 100 000 in obese 12–15 years old boys and girls, respectively.[11] The estimated incidence in the paediatric population ranges from 0.17 to 1.32 per 100 000 children.[12 13]

The goals of treatment are the preservation of vision and the amelioration of headaches. In adults, weight control is effective.[14 15] Medication typically consists of acetazolamide or topiramate. Research on topiramate's effect on weight loss may be beneficial, though yet to be demonstrated in larger studies.[16]

Surgical options consist of CSF diversion (eg, by ventriculoperitoneal shunt (VPS), lumboperitonral shunt, optic nerve sheath fenestration (ONSF), or venous sinus stenting (VSS). Interventions are decided on symptomatic presentation, degree of visual loss[17] and local availability. The role of lumbar puncture (LP) has been explored both diagnostically and therapeutically.[18] Doubts about the efficacy of LPs[19] have led to an interest in surgical options. There remains uncertainty as to the practical method of pressure measurement and the clinical response to elevated pressures.

In the absence of randomised control trials on the management of paediatric IIH, this triple-round Delphi study reviewed paediatric IIH diagnosis, investigation and management, aiming to provide clinicians with recommendations from experienced professionals. This study follows international consensus recommendations in the adult population.[20]

METHODS

Study design Delphi

An Ovid literature search was performed to inform the Delphi survey. The output included paediatric IIH-related mortality, morbidities, diagnosis, treatment and surveillance. A core group was established through the British Paediatric Neurology Association Childhood Headache Network specialist interest group. This group consisted of 11 experts including paediatric neurologists, paediatricians and ophthalmologists, who reviewed the literature, selected questions and consulted patient groups during the process.

Delphi consensus method

A Delphi process provides consensus recommendations. At least 15–20 expert participants are recommended.[21] Thresholds may be as low as 51%,[22] though higher may be preferred.[23] Predefined thresholds reduce the potential for bias.[24] For this Delphi, a priori consensus was defined as 70% agreement. The analysis excluded responses of 'do not know' or 'do not feel qualified to answer'.

The core group included paediatric: neurologists, ophthalmologists, neurodisability specialists, community paediatricians, general paediatricians, neurosurgeons, neuroradiologists and other representatives of IIH management. All were sent a weekly reminder for 3 months. No questions were repeated in subsequent rounds. Questions in the second and third rounds were derived from answers obtained from the previous round.

Three rounds were performed. In the first round, there were 67 questions, following which the core group decided areas needing further clarification, and set new questions for the second round. In the second round, 24 questions were posed. The questions in round 2 were refinements based on answers from round 1. After round 2, there was no repeat of earlier rounds. Round 3 specifically targeted ophthalmologists as the questions were relevant to their specialty and expertise. The Delphi was endorsed by the Royal College of Ophthalmologists, with round 3 sent to UK paediatric ophthalmologists, via their network. 13 ophthalmological questions were asked. No invited responder was excluded from any rounds.

RESULTS

Survey respondents

In round 1, 114 email invitations were sent and 54 responders completed the survey. These comprised paediatric neurologists 33 (61%), general paediatricians 5 (9%), neurosurgeons 5 (9%), ophthalmologists 4 (7%), neuroradiologists 2 (4%), a general paediatrician with a special interest in neurology (2%), an optometrist (2%), a community paediatrician (2%) and a patient group representative (2%). In Round 2, 127 email invitations were sent and 65 responders completed the survey. In Round 3, 59 paediatric ophthalmologists completed the survey.

The following includes recommendations derived from areas of consensus (recommendations summarised in online supplemental table 2), all survey questions and findings in online supplemental table 3).

Nomenclature

The condition should be referred to as 'Idiopathic Intracranial Hypertension'.

Timing of initial assessment—for patients with possible IIH, without red flags

Patients should be seen in the hospital for diagnosis and further management within two weeks.

Recording of auxology

A patient's weight and height should be checked at baseline and their body mass index (BMI) and BMI centile chart recorded, with Royal College of Paediatrics and Child Health (RCPCH) Growth Charts (UK-WHO).[25] Patients with suspected/confirmed IIH should be assessed for obstructive sleep apnoea if clinically indicated.

Diagnostic criteria

Friedman's diagnostic criteria should be used for the diagnosis of IIH (online supplemental table 1).

LP and CSF pressure related to diagnosis of IIH

If suspected IIH, LP should be performed for diagnosis, unless contraindicated.

In cases of acute visual loss associated with suspected IIH, perform the first LP (if no contraindications) 'within 48 hours'.

LP opening pressure <20 cm CSF (15 mm Hg) indicates normal CSF pressure.

A transducer should be used to record CSF pressure, if available.

Neuroimaging

Children with suspected raised ICP (early morning headache vomiting/visual disturbance/focal neurology) should have neuroimaging, ideally MRI (or CT, if unavailable) within 24 hours.

Children with suspected IIH with normal vision should have a brain MRI scan unless contraindicated.

Children with suspected IIH should have an MRI and MRV within 7 days.

MDT meetings for diagnosis of IIH

Those who did not meet the diagnostic criteria but had features of IIH should be discussed at a multidisciplinary team (MDT) meeting involving paediatric neurologists, ophthalmologists and neuroradiologists.

The minimum age for a diagnosis of IIH without prompting discussion at an MDT meeting was selected as 10 years.

Laboratory

Baseline laboratory investigations: thyroid function tests, sodium, potassium, creatinine, urea, liver function, calcium, phosphate, magnesium, glucose, vitamin D, and full blood count.

Children with BMI >25 kg/m^2 should have a lipid profile test at baseline.

Ophthalmological assessment

B-scan should be done at baseline where available. Opticians should refer children with suspected papilloedema urgently to an ophthalmologist.

Children should:

- be seen by an ophthalmologist with training and expertise in paediatric ophthalmology.
- have a detailed ophthalmological assessment, including visual fields, colour vision and visual acuity.
- have a baseline optical coherence tomography scan for diagnosis and monitoring
- be reviewed by an ophthalmologist, once they have started medical treatment for IIH, 3–6 monthly.

In IIH with severe grade 4 papilloedema where vision is threatened, neurosurgical options such as VPS should be considered as emergency treatment.

A regional MDT discussion for children with suspected IIH should be held which comprises paediatricians, and/or paediatric neurologists and ophthalmologists.

LP assessment of CSF pressure: method for LP

A 10–20 min online training resource on LP for IIH would be useful.

Families should be informed about the potential complications of LP.

During LP, a conscious patient should have their knees and hips flexed.

Patients should be positioned in the left lateral decubitus position.

Patients with suspected/confirmed IIH do not need to have their clotting checked before their LP unless clinically indicated.

CSF pressure should not be measured until the CSF stops rising in the manometer tube.

CSF should be sent for microscopy, glucose and protein at the time of the first LP in suspected IIH.

CSF should be sent for autoimmune screen (aquaporin and myelin oligodendrocyte glycoprotein (MOG) antibodies) and/or cytology at the time of first LP in suspected IIH only if clinically indicated.

LP assessment of CSF pressure with local or general anaesthetic

Local anaesthetic can be used for LP.

Patients having an LP under General Anaesthetic (GA), should have their GA medications documented.

Patients with suspected IIH should have their end-tidal carbon dioxide level checked during LP under GA (*reason given in online supplemental table 4). Patients with suspected IIH should have their end-tidal carbon dioxide level maintained within the normal reference range, at the discretion of attending anaesthetists.

Management: therapeutic LP

CSF pressure, if over 28 cm CSF (21 mm Hg) should be reduced down to 20–25 cm CSF (15–18 mm Hg).

The maximum number of (therapeutic) LPs a patient should have over the course of their illness is five, as other therapeutic options should be instigated before this point.

Management: weight management

A dietetic service should be available for weight management for patients with IIH.

Overweight or obese patients with IIH should be referred to a dietician for weight management or to a weight management team.

Management: first-line therapy in patients with IIH who do not have visual impairment

There was no consensus on medical management but the most selected answer by 46% of responders was that acetazolamide should be considered for all patients as first-line medical treatment, regardless of their BMI. This did not reach the threshold for consensus. The leading answer after 'acetazolamide' (46%) or 'other' (26%) was 'information, general advice, safety netting but no drug treatment for now' (18%). A minority of respondents supported topiramate (4%), no intervention (4%) or surgical approaches (2%).

Management: first-line therapy in patients with new visual impairment/loss of vision

If a patient is taking acetazolamide, blood urea, electrolytes and bicarbonate levels should be checked. Bicarbonate should be corrected when the value is equal to or lower than 18 mmol/L.

Management: second line

Repeated therapeutic LP should be offered when visual changes progress and there is a threat to vision on medical

management and/or when symptoms are not responsive to medical management.

Management: neurosurgical

ICP bolt monitoring for 48 hours should be considered for patients with persistently raised LP opening pressure measurements (on two LPs) and papilloedema.

VSS should be considered if there is evidence of stenosis of the dominant venous sinus.

DISCUSSION

The three rounds of questions revealed areas of consensus, namely in the timing of the first assessment, auxological measurements, neuroimaging, ophthalmological assessments, aspects of management and the role of a regional MDT. The use of Friedman's criteria (online supplemental table 1)[3] was recommended, which facilitates making a diagnosis based on clinical signs and neuroimaging criteria.

Areas lacking consensus

Areas of non-consensus (online supplemental table 4) included interpretation of values of CSF pressure, laboratory investigations, grading of papilloedema, aspects of LP methodology and neurosurgical management. ONSF was not supported. Historically, ONSF was considered an emergency procedure for sight preservation in IIH.[26] We question the relative indications in children, versus CSF diversion strategies, for example, VPS.[27 28] VSS has been a treatment option in adults[29] but there are no randomised control trials comparing ONSF, CSF diversion, and VSS and evidence in paediatrics is lacking.

There was no consensus on medical management though acetazolamide was the most selected response (46%) for first-line medical treatment, regardless of patient BMI. Following discussion by the Delphi working group, and exploration of the comments offered for respondents who had selected 'other' (eg, confirming a diagnostic/therapeutic LP had been performed, and weight management was happening in parallel), a recommendation was made for acetazolamide to be considered as first-line therapy. The recommendation is based on interpretation of the offered comments rather than consensus and is therefore an exception to the goals of the Delphi method.

Thematic agreement

Occasionally thematic agreement was identified. 'When should the CSF pressure be read on the manometer?' was answered by most as, 'When the CSF stops rising in the manometer tube' (38 responses, 81%). In round 2, 'When should the CSF pressure be read on the manometer after the CSF stops rising?', the leading response was 'As soon as it stops rising' (25 responses, 50%), followed by 'other' (12 responses, 24%) and 'after 5 min' (10 responses, 20%).

Similarly, 'If the CSF pressure is high, should it be reduced until normal CSF pressure is achieved?". Most responded in favour (25 responses, 57%) with some selecting 'other' (13 responses, 29%). Only six disagreed, suggesting 86% felt high CSF pressure should be reduced by some amount.

To manage uncertainty, we propose discussion within a regional and if required, national IIH MDT. An MDT meeting may assist in confirming diagnosis, as has been described in the UK.[30]

Limitations of survey

For future studies, we propose care over question construction and methods of assessing consensus. We would recommend strategies aimed at increasing enrolment and response rate. Targeted invitations to neurosurgeons would be beneficial. The Delphi survey invited responses from UK-based professionals experienced in paediatric IIH. Due to this limited professional pool, response rates were variable, particularly in more specialist areas. Response trends based on the location of respondents and the reproducibility of responses were not assessed.

Ambiguous or uncontextualised question wording may also have affected interpretation, for example, 'Is an LP opening pressure of greater than 28 cm CSF to be considered as diagnostic for IIH?'. Most agreed (27 responses, 56.3%) however 'no' may have been selected as raised ICP alone is insufficient for diagnosis and the threshold of 28 cm CSF was not contextualised. While thematic agreement was noted, such evaluation was not a primary aim, rendering interpretation subjective.

CONCLUSION

This Delphi process supplies practical guidance for clinicians aiming to improve the quality of care and service provision for children under investigation for IIH. The summary of recommendations (online supplemental table 2) provides a structured approach to guide the management of paediatric IIH, referencing Friedman's criteria (online supplemental table 1). The survey findings (online supplemental table 3) provides a breakdown of the areas discussed, and whether consensus was identified. This survey and its recommendations form the basis for (1) a nationally endorsed guideline, (2) a clinical audit and (3) further research to improve outcomes in paediatric IIH. The recommendations are pragmatic and can be implemented in most healthcare systems around the world.

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Collaborators N/A.

Contributors All individuals listed as authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted from the list. The authors and contributors have approved the acknowledgement of their contributions. All the authors had complete access to the study data that supports the publication. SA, KF, PH, VM, BMukhtyar, BMuthusamy, AP, PP, WPW and DK designed the questionnaire, analysed the data and drafted the manuscript. MMonaghan and MMoran analysed the data and drafted the manuscript. SAmin is guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Development of a modified paediatric coma scale in intensive care clinical practice

A Tatman, A Warren, A Williams, J E Powell, W Whitehouse

Abstract

James' adaptation of the Glasgow coma scale (JGCS) was designed for young children. Intubated patients are not allocated a verbal score, however, so important changes in a patient's conscious level may be missed. A grimace score was therefore developed and assessed for use in intubated children.

Two observers made a JGCS observation within 15 minutes of each other. One observer was the patient's nurse and the other a trained investigator. Interobserver reliability was determined between the first and second observation for each component of the scale. Reliability was measured using κ and weighted κ statistics.

Seventy three children had 104 sets of observations. Interobserver reliability was moderate to good for all components, with the grimace score better than the verbal score.

It is concluded that the grimace score is more reliable than the verbal score and may be useful in intubated patients in whom the verbal score cannot be used.

(*Arch Dis Child* 1997;**77**:519–521)

Keywords: coma scale; intensive care; conscious level

The Glasgow coma scale has been widely adopted in the management of adult and paediatric coma.[1 2] It should not be used in small children as the verbal component is not appropriate.[3] Several coma scores have been developed specifically for children in an attempt to compensate for their differences in verbal and motor capabilities.[4–11] Three years ago, we introduced into our intensive care unit (ICU) a modified Glasgow coma scale, which is Sharples' adaptation (personal communication) of the James' adaptation of the Glasgow coma scale (JGCS) (table1).[12]

During this time, our nursing staff reported that many children who were intubated showed varying degrees of orofacial grimacing when stimulated. Therefore we developed a grimace score to replace the verbal component in intubated children. We report the results of a study to assess the reliability of our modified coma scale in this clinical setting.

Subjects and methods

STUDY DESIGN

After receiving local ethical committee approval, children on the ICU with coma from any cause were selected in a quasirandom manner: whenever one of the three trained investigators was available, the patient accessible, and the patient had not been studied within 24 hours nor with the same JGCS (on the routine nursing JGCS chart).

Verbal consent was obtained from parents when available. A set of observations consisted of two JGCS (table 1) scores, the second score being completed within 15 minutes of the first. These were performed sequentially by two observers, one being the child's bedside nurse

Table 1 Modified Glasgow coma scale. Pain as nail bed pressure with pencil; score best response

Adult and child > 5 years	*Child < 5 years*
Eye opening	
E4 spontaneous	As older child
E3 to verbal stimulus	As older child
E2 to pain	As older child
E1 no response to pain	As older child
Verbal	
V5 orientated	Alert, babbles, coos, words or sentences to usual ability
V4 confused	Less than usual ability or spontaneous irritable cry
V3 inappropriate words	Cries to pain
V2 incomprehensible sounds	Moans to pain
V1 no response to pain	No reponse to pain
VT intubated	Intubated
Grimace	
G5 spontaneous normal facial/oromotor activity, for example sucks tube, coughs	
G4 less than usual spontaneous ability or only responds to touch	
G3 vigorous grimace to pain	
G2 mild grimace or some change in facial expression to pain	
G1 no response to pain	
Motor	
M6 obeys commands	Normal spontaneous movements or withdraws to touch
M5 localises to pain stimulus	As older child
M4 withdraws from pain	As older child
M3 abnormal flexion to pain	As older child
M2 abnormal extension to pain	As older child
M1 no response to pain	As older child

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Accepted 22 August 1997

and the other being one of three trained observers. The observers were blinded to the preceding score. Children who were not intubated were given a verbal score. Children who were intubated were given a grimace score. We excluded children with cervical spinal cord injury, peripheral nerve disease, or neuromuscular disorders, including residual paralysis from neuromuscular blockade. The painful stimulus was nail bed pressure on both upper limbs, using a pencil. The best response was taken for the observation.

Table 2 Diagnostic category on admission to ICU

Diagnosis	*Number*
Cardiac surgery	30
General surgery	12
Neurosurgery	5
Metabolic	7
General medical	3
Neurology	10
Head injury	6

Table 3 Each pair of observations for each component of the adapted JGCS

Eye opening E1–E2

	E2 score 1	2	3	4
E1 score				
1	35	6	1	1
2	5	8	0	5
3	0	2	0	3
4	2	5	3	24

Verbal V1–V2

	V2 score 1	2	3	4	5
V1 score					
1	5	1	0	0	0
2	0	1	1	1	0
3	0	0	1	1	0
4	2	1	1	3	1
5	1	0	3	0	5

Grimace G1–G2

	G2 score 1	2	3	4	5
G1 score					
1	14	2	0	1	0
2	6	9	4	1	1
3	0	2	5	3	1
4	0	2	3	1	0
5	0	2	0	0	11

Motor M1–M2

	M2 score 1	2	3	4	5	6
M1 score						
1	5	0	0	3	0	0
2	0	0	1	2	1	0
3	0	1	2	4	0	0
4	3	1	2	24	10	2
5	1	0	0	6	12	4
6	0	0	0	2	8	10

Table 4 Each pair of observations for the summated adapted JGCS, with grimace in place of verbal

Summated EGM1–EGM2

	EGM1 score 3	4	5	6	7	8	9	10	11	12	13	14	15
EGM2 score													
3	3	0	0	1	0	0	0	0	0	0	0	0	0
4	0	0	0	2	0	0	0	0	0	0	0	0	0
5	0	0	1	1	0	0	0	0	0	0	0	0	0
6	0	0	1	2	2	1	0	1	0	0	0	0	0
7	0	1	0	3	2	0	0	0	0	0	0	0	0
8	1	0	0	0	3	2	2	0	1	0	0	0	0
9	0	0	0	1	0	2	3	2	0	0	0	0	0
10	0	0	0	0	1	2	2	1	1	0	1	0	0
11	0	0	0	0	0	0	1	0	1	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	2	0	0
13	0	0	0	0	0	0	0	0	0	2	0	0	2
14	0	0	0	0	0	0	0	1	0	0	1	2	2
15	0	0	0	0	0	0	0	0	1	0	0	2	3

Table 5 Interobserver agreement

	No	*κ (95% CI)*	*Weighted κ (95% CI)*
E1–E2	100	0.50 (0.38 to 0.63)	0.64 (0.53 to 0.76)
V1–V2	28	0.41 (0.20 to 0.63)	0.49 (0.25 to 0.73)
G1–G2	68	0.50 (0.32 to 0.61)	0.63 (0.50 to 0.77)
M1–M2	104	0.33 (0.20 to 0.46)	0.49 (0.36 to 0.62)
EVM1–EVM2	28	0.29 (0.10 to 0.48)	0.57 (0.39 to 0.75)
EGM1–EGM2	68	0.25 (0.13 to 0.38)	0.69 (0.60 to 0.78)

CI=confidence interval.

STATISTICAL ANALYSIS

Interobserver reliability (E1–E2, V1–V2, G1–G2, M1–M2, and summated scores EVM1–EVM2 and EGM1–EGM2), that is, the level of agreement between the two observations, was measured by the κ and weighted κ statistics.[13] While the κ statistic measures the *level* of agreement above that expected by chance, it does not take into account the *degree* of disagreement between observations. The weighted κ statistic measures agreement and takes into account the magnitude of the disagreement.

For both κ and weighted κ, strength of agreement is interpreted as < 0.2 = poor; 0.21–0.40 = fair; 0.41–0.6 = moderate; 0.61–0.80 = good; > 0.8 = very good or near perfect.

Results

One hundred and four sets of observations were completed in 73 children of whom 42 were boys. Four children had severe orbital swelling and were not given an eye score. Forty one observers were involved (38 nurses and three trained observers). The children ranged in age from 1 day to 16 years (median age 73 days). Table 2 shows the diagnostic categories. Tables 3 and 4 show the raw data for each component and for summated scores using the grimace and verbal scores separately. Table 5 shows the interobserver reliability.

Discussion

We adopted the JGCS because it takes account of developmental immaturity in small children, uses the same number of points irrespective of the child's age, and is simple for the patient's nurse to use without additional staff or equipment.

Several studies have examined the reliability of paediatric coma scales using two or three trained observers.[5 10 14] This is useful for determining a scale's experimental reliability, but may not necessarily translate into clinical practice.[15] For example, in our ICU there are over 100 nurses with varying levels of experience. Therefore, any scale must be robust enough to produce reliable results given the observers who will be using it. Complicated scales, which are used relatively infrequently, are unlikely to be reliable.

Our results suggest that despite a large number of observers, there is moderate to good interobserver agreement for the components of this scale.

The grimace component appears to be more reliable than the verbal component. They may measure different aspects of brain function and cannot necessarily be equated clinically. Facial expression, however, is an important part of non-verbal communication, so facial grimace

and verbal language are not totally independent skills. Furthermore, we believe that in intubated patients the restoration of a third variable (eye opening, motor, *and grimace*) in assessing coma increases the likelihood of detecting an improvement or a deterioration in the patient's condition, particularly when the variables are measured independently.

We have included the summated values for interest. We do not summate the values clinically, as the variables have different weights and are not clinically comparable.[16 17]

Although the grimace score has not been validated for outcome, it is more reliable than the verbal score in this study and may be useful in intubated patients when the verbal score cannot be used.

This study has also shown the reliability of the other components of our adaptation of the JGCS when used by nurses and doctors in an ICU.

We are very grateful for the help of all the nurses at Birmingham Children's Hospital ICU for their contribution to the study and their continuing support.

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When to do an LP

Setting up for an LP – Consider a checklist

- Confirm patient details and indication for procedure
- Confirm parental/carer consent – they may wish to be present throughout
- Skin sterilising solution
- Appropriate length LP needle
- Sterile dressing pack or LP set incl bottles x 3
- Glucose bottle
- Opsite spray +/- dressing
- Sterile gloves
- Monitoring for patient (HR, sats minimum) & O2/BVM available
- Optimal positioning discussed with additional staff present
- Iv antibiotics drawn up
- Documentation of procedure in notes incl any interventions required/tolerability

Top tips for a successful LP:

- Consider use of local anaesthetic to the skin in all ages
- Use sucrose 20% in addition for neonates for analgesic properties Consider neonates in sitting position (hips flexed,legs forward) - associated with wider intervertebral spaces and less hypoxia than the left lateral position in this age group
- Replace stylet prior to needle removal to reduce post LP headache
- Orientate the needle with the bevel parallel to the spine so it will separate the longitudinally running fibres of the Dura (this feels natural in the left lateral position but requires more thought in the sitting position)
- Consider CSF lactate - quite a good discriminator between viral and bacterial meningitis with levels over 3.5 suggestive of bacterial CNS infection
- Request rapid CSF analysis to reduce misinterpretation due to cell lysis
- Consider CSF PCR if locally available
- Be careful interpreting WBC count in the context of bloodstained CSF

Late LP lowers the yield of culture:

- In paediatric patients with bacterial meningitis antibiotic pre-treatment is associated with:
  - Higher cerebrospinal fluid glucose levels
  - Lower cerebrospinal fluid protein levels
  - Pre-treatment does not modify cerebrospinal fluid white blood cell count or absolute neutrophil count results
- 245 patients aged 1 month to 18 years of age with bacterial meningitis presenting to 20 paediatric emergency departments
- Antibiotic pre-treatment was defined as any antibiotic administrated within 72 hours before the lumbar puncture
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Emergency Radiology (2024) 31:373–379
https://doi.org/10.1007/s10140-024-02234-0

ORIGINAL ARTICLE

Comparison of international guidelines for CT prior to lumbar puncture in patients with suspected meningitis

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Received: 13 March 2024 / Accepted: 23 April 2024 / Published online: 2 May 2024

Abstract

Purpose To compare the performance of multiple international guidelines in selecting patients for head CT prior to lumbar puncture (LP) in suspected meningitis, focusing on identification of potential contraindications to immediate LP.

Methods Retrospective study of 196 patients with suspected meningitis presenting to an emergency department between March 2013 and March 2023 and undergoing head CT prior to LP. UK Joint Specialist Society Guidelines (UK), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Diseases Society of America (IDSA) guidelines were evaluated by cross-referencing imaging criteria with clinical characteristics present at time of presentation. Sensitivity of each guideline for recommending neuroimaging in cases with brain shift on CT was evaluated, along with the number of normal studies and incidental or spurious findings.

Results 2/196 (1%) patients had abnormal CTs with evidence of brain shift, while 14/196 (7%) had other abnormalities on CT without brain shift. UK, ESCMID and IDSA guidelines recommended imaging in 10%, 14% and 33% of cases respectively. All three guidelines recommended imaging pre-LP in 2/2 (100%) cases with brain shift. IDSA guidelines recommended more CT studies with normal findings (59 vs 16 and 24 for UK and ESCMID guidelines respectively) and CT abnormalities without brain shift (4 vs 1 and 2 respectively) than the other guidelines.

Conclusion UK, ESCMID and IDSA guidelines are all effective at identifying the small cohort of patients who benefit from a head CT prior to LP. Following the more selective UK/ESCMID guidelines limits the number of normal studies and incidental or spurious CT findings.

Keywords Meningitis · CT head · Lumbar puncture · Guidelines · Herniation

Introduction

Most patients presenting acutely with suspected meningitis undergo CT imaging of the head prior to lumbar puncture (LP), up to 89–94% in recent studies [1–3]. The primary purpose is to identify those with brain shift due to space-occupying lesion or diffuse cerebral oedema [4], as these patients are traditionally assumed to be at higher risk of caudal brainstem herniation following LP [4, 5]. However, despite numerous society guidelines recommending immediate antibiotic administration prior to CT, performing CT prior to LP has been shown to delay the performance of the LP [6], the establishment of the diagnosis of meningitis [7] and the commencement of antibiotics [8, 9]. The risk of unfavourable clinical outcome has been shown to increase in cases of delayed diagnosis [7], and with each hour of delay in antibiotic treatment [10]. These concerns have led to various international guidelines being developed to

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select patients who may benefit from CT prior to LP. These include those by the Infectious Disease Society of America (IDSA) [11], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [12] and the UK Joint Specialist Society Guidelines [13].

Previous studies have shown that these guidelines differ significantly in the proportion of patients for whom they recommend CT prior to LP [14–16]. A 2019 study showed that while IDSA guidelines recommended imaging in more patients than the other studied guidelines (64 vs. 39–40%), all of the guidelines detected 100% of cases with mass effect [15]. In 2022 Park et al. [16] showed that IDSA guidelines were the most sensitive for detecting minor and major intracranial abnormalities. However neither of the above studies was designed to assess detection of contraindications to LP, which is the primary purpose of initial CT performed prior to LP in suspected meningitis. Specified contraindications to LP differ somewhat between sources in the literature, though many similarities exist between different guidelines [5, 11–13, 17, 18]. A representative guideline provided by the UK Joint Specialist Society Guidelines is listed in Table 1 [13]. To our knowledge no prior study has compared UK, ESCMID and IDSA guidelines in a population of suspected meningitis presenting acutely to the emergency department.

In this retrospective review, we aimed to examine a large group of patients presenting to a single centre tertiary hospital with suspected meningitis, determine which patients would be selected for CT prior to LP by UK, ESCMID and IDSA guidelines, and correlate these results with imaging findings. We aimed to determine which guideline performed best in detecting all cases in which deferral of CT would be reasonable due to brain shift, without excessive numbers of normal studies. We planned an exploratory analysis of subsequent investigations, treatment and outcomes following normal and abnormal CT studies.

Materials & methods

Study population

This study comprised adult patients (age > 16 years, the conventional cut-off for the paediatric population in the Irish healthcare system) presenting to the emergency department of the Mater Misericordiae University Hospital (MMUH) with suspected meningitis who underwent head CT as part of their initial management. MMUH is a large tertiary hospital with 744 inpatient beds and 99,417 ED attendances in 2022 [19]. We conducted a systematic search of the hospital Picture Archive and Communication System (PACS) over a defined period of ten years (March 2013 to March 2023), identifying patients that underwent a non-contrast CT scan of the head prior to LP for investigation of suspected meningitis. This was performed by filtering all CT head requests for the keywords "meningitis OR meningism" in the scan requisition supplied by the clinical team. Inclusion criteria were those presenting acutely with suspected meningitis, in whom meningitis was the primary working diagnosis, and for whom a CT scan was requested as part of the acute assessment. Patients were excluded if an alternate condition was listed as the suspected diagnosis, if acute intracranial haemorrhage was the working diagnosis or equally likely, or if an LP had been performed prior to CT being requested. Patients transferred from other hospitals or patients with an established diagnosis of meningitis were also excluded. Working and alternative diagnoses were determined by the first author (prior to evaluation of CT findings) based on clinical information supplied by the referrer on the imaging request, with equivocal cases resolved by consensus with the second author.

Data Collection

The patient's electronic health record was used to extract retrospectively the demographic data (including age and gender) and clinical details (which were documented contemporaneously) at time of presentation. These included

Table 1 Contraindications to immediate lumbar puncture in suspected meningitis, UK Joint Specialist Society Guidelines 2016

Clinical signs	Signs suggestive of severe sepsis or rapidly evolving rash
	Respiratory or cardiac compromise
	Anticoagulant therapy or known thrombocytopaenia
	Infection at the site of LP
	Rapidly deteriorating GCS
	GCS ≤ 12[a]
	Focal neurological signs [a]
	Papilloedema [a]
	Continuous or uncontrolled seizures [a]
Radiological signs	CT reveals significant brain shift

[a] Neuroimaging advised pre-LP for these indications

time of presentation, LP completion status and result, clinical course following performance of LP and the patient's diagnosis upon discharge (based on national Hospital In-Patient Enquiry (HIPE) data). The component clinical signs/symptoms of each guideline were recorded including Glasgow Coma Scale (GCS) at time of presentation, and the presence and nature of focal neurologic deficits, seizures, papilledema, immunocompromised state and history of central nervous system disease. PACS data was reviewed to record the time of CT, CT findings and any subsequently performed neuroimaging.

Definitions

The result of a CT scan was defined by the initial report at time of acute presentation. This included cases where further neuroimaging clarified or contradicted the initial report, in order to capture this potential negative consequence of widespread CT imaging. A scan was defined as normal if there were no acute intracranial abnormalities. This included cases of cerebral atrophy, white matter disease and other similar chronic findings. Studies were defined as *abnormal with brain shift* if there was evidence of gyral flattening, obliteration of cerebrospinal fluid (CSF) spaces or cerebral herniation. This could be secondary to diffuse edema from generalised infection or localised mass effect, for example from abscess, mass or infarct.

All other abnormalities were defined as *other abnormals*. This included suspected long-standing findings (such as intracranial aneurysms and low-lying cerebellar tonsils) as well as all abnormalities suspected to be acute or potentially relevant to the presentation (for example intracranial haemorrhage or possible temporal lobe oedema), other than those with significant brain shift.

The criteria of IDSA, ESCMID and UK guidelines are outlined in Table 2. If the provided clinical information included at least one of the guideline-specified criteria for performing an upfront CT, imaging was considered to be recommended by that guideline. When a criterion was not specified in the scan requisition or electronic health record, it was assumed not to have been present.

Statistical analysis

Simple descriptive statistics were used to define the frequency of clinical features and imaging findings. Clinical features as per the referral information was cross-referenced against the UK, IDSA and ESCMID guidelines to assess whether a criterion for neuroimaging prior to LP was present. Results of initial CT were then used to evaluate the ability of each guideline to identify those with significant intracranial abnormalities in whom deferral of LP may be reasonable.

Results

Between March 2013 and March 2023, 453 non-contrast CT head studies were performed in which the scan requisition included the terms *meningitis* or *meningism.* There were 257 cases excluded, including 126 in whom the working diagnosis was not meningitis, 86 in whom intracranial haemorrhage was the leading diagnosis or equally likely, 24 in whom an LP was performed prior to CT and 21 with known meningitis at time of CT request. This left 196 patients for analysis (Fig. 1**).** Of the 196 patients, 118 were female (60%), with an average age of 36 (SD +/- 16). 15% (29/196) patients had a final diagnosis of meningitis at time of discharge, including 11 with bacterial meningitis, 16 with viral meningitis, 1 with fungal meningitis and 1 with aseptic meningitis.

The majority, 180/196 (92%) of CT studies were normal. Of the remaining studies, 2 (1%) were *abnormal with brain shift*, while 14 (7%) were *other abnormals.* The *abnormal with brain shift* studies were both cases of diffuse cerebral edema. No cerebral abscess was identified. Findings of all abnormal CT studies (and relevant follow-up studies) are described in Table 3.

Table 2 Criteria for neuroimaging prior to LP as recommended by UK, ESCMID and IDSA guidelines respectively

Criteria for Neuroimaging before LP	UK	ESCMID	IDSA
GCS	≤ 12	≤ 10	< 15
Focal neurological deficit	Present	Present (excluding cranial nerve palsies)	Present
Seizures	Continuous or uncontrolled	New-onset	Within one week of presentation
Papilloedema	Present (inability to view the fundus is not a contraindication)	Not included	Present
Immunocompromised state	Not included	Severely immunocompromised (e.g. post-transplant, HIV)	Post-transplant, HIV, immunosuppressive medication
History of CNS disease	Not included	Not included	Mass lesion, stroke or focal infection

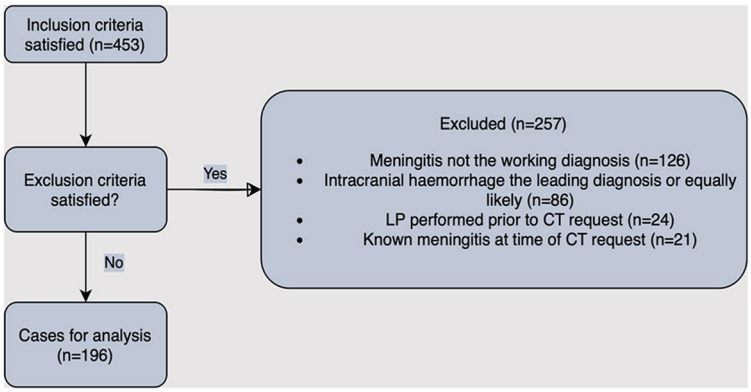

Fig. 1 Enrolment and exclusion process

Table 3 Abnormal CT findings and whether imaging was recommended by each guideline

Abnormal imaging finding	Imaging recommended by			Notes	Significance
	UK	ESCMID	IDSA		
Diffuse cerebral oedema	✓	✓	✓	GCS 3	Highly significant
Diffuse cerebral oedema	✓	✓	✓	GCS 9	Highly significant
Small volume acute perimesencephalic subarachnoid haemorrhage	✗	✗	✗	No hydrocephalus	Significant
Bilateral subdural effusions	✓	✓	✓	4 mm thickness, no mass effect	Significant
Distension of subarachnoid spaces, possible communicating hydrocephalus	✗	✗	✗		Potentially relevant [a]
Prominent CSF around the optic nerves	✗	✗	✗		Potentially relevant [a]
Arnold-Chiari Type 1 malformation	✗	✗	✗		Incidental [b]
Low-lying cerebellar tonsils	✗	✗	✗		Incidental [b]
Low-lying cerebellar tonsils	✗	✗	✓		Incidental [b]
Low-lying cerebellar tonsils	✗	✗	✗		Incidental [b]
6 mm middle cerebral artery aneurysm	✗	✗	✗		Incidental
Focus of hyperattenuation in midbrain	✗	✓	✓	Follow-up CT with contrast was normal	Spurious
Focus of hyperattenuation in right caudate nucleus	✗	✗	✗	Follow-up CT with contrast was normal	Spurious
Hypoattenuation in temporal lobe, possible encephalitis	✗	✗	✗	Follow-up MRI was normal	Spurious
Hypoattenuation in temporal lobe, possible encephalitis	✗	✗	✓	Follow-up CT and MRI were normal	Spurious
Asymmetric cavernous sinuses, possible internal carotid artery aneurysm	✗	✗	✗	Follow-up CT angiogram normal	Spurious

[a] Signs of raised CSF pressure, while clinically relevant in the setting of suspected meningitis, is not considered a contraindication to lumbar puncture

[b] While precautions have been advised in performing LP in the setting of a Chiari malformation [18, 28], it is not an absolute contraindication, particularly in an emergent setting such as suspected meningitis [28]

Only a minority, 19/196 (10%) of requests met the criteria for pre-LP CT imaging under UK Joint Specialist Society guidelines, compared with 28/196 (14%) and 65/196 (33%) under ESCMID and IDSA guidelines respectively. All three guidelines identified 2/2 (100%) of the *abnormal with brain shift* cases. Of the remaining cases identified for imaging by each guideline, 16/19, 24/28 and 59/65 cases were normal for UK, ESCMID and IDSA guidelines respectively. UK, ESCMID and IDSA identified 1, 2 and 4 *other abnormal* cases respectively, and did not detect any additional cases of brain shift. The performance of each algorithm is described in Table 4. The criterion within the IDSA guidelines that contributed most to the burden of imaging was GCS < 15, followed by history of central nervous system (CNS) disease and immunocompromise. Satisfied criteria for each algorithm are detailed in Table 5.

LP was performed following CT in 129 patients (66%). This followed a normal CT in 121 cases and *other abnormal* CT results in 6 cases. In the two cases of diffuse cerebral oedema LP was initially deferred. It was then safely

Table 4 Performance of the algorithm recommended by each guideline

Imaging findings	Number of cases in which imaging pre-LP was recommended (%)		
	UK	ESCMID	IDSA
Abnormal with brain shift [a]	2/2 (100%)	2/2 (100%)	2/2 (100%)
Other abnormal studies [b]	1/14 (7%)	2/14 (14%)	4/14 (29%)
Normal studies	16/180 (9%)	24/180 (13%)	59/180 (33%)
Total	19/196 (10%)	28/196 (14%)	65/196 (33%)

[a] Immediate LP likely contraindicated based on imaging findings

[b] Abnormal, but no imaging-related contraindication to immediate LP

Table 5 Number of cases satisfying each component criterion of each guideline. A number of patients satisifed more than one criterion

Criterion satisfied	UK	ESCMID	IDSA
GCS	8	4	26
Focal neurological deficit	9	4	9
Seizures	2	9	9
Papilloedema	0	N/A	0
Immunocompromised state	N/A	13	18
History of CNS disease	N/A	N/A	21

performed after follow-up neuroimaging was normal, with an average time to follow-up study of 32 h. Of patients with *other abnormal* CTs, 8/14 underwent subsequent LP. 3 of these patients had their LP delayed until after subsequent neuroimaging showed their initial CT finding to be artefactual, with an average time to follow-up study of 16 h. In total, subsequent imaging showed that 5/14 *other abnormal* findings were artefactual. 1/121 (1%) patients had a clinical deterioration within 24 h of LP requiring repeat imaging. This patient had an initially normal CT, a normal follow-up CT and a discharge diagnosis of a psychiatric disorder.

Discussion

Our data suggests that in patients presenting to hospital with suspected meningitis, in whom the true incidence of meningitis is low (15% in our cohort), the likelihood of CT revealing a potential contraindication to LP is very low. We identified two such patients, 1% of all those imaged. These patients are readily identified by following any of the studied guidelines, including the more restrictive UK and ESCMID guidelines. Adopting a more cautious guideline (IDSA) results in more normal studies and detection of mild abnormalities which did not preclude LP. The studies recommended by IDSA guidelines were more likely to reveal artefactual or spurious CT findings (resulting in delay of their LP until after further imaging) than they were to reveal a true potential contraindication to LP. In our cohort, IDSA guidelines recommended imaging more than twice as many patients as ESCMID guidelines, and more than three times as many as UK guidelines.

Understanding the purpose of the various international guidelines is key to interpreting the results of our study and those described above. The UK and ESCMID guidelines are designed to identify patients who are at higher risk of having a contraindication to LP and so require a CT prior to same. IDSA guidelines, meanwhile, are based on clinical criteria that have been shown to predict the presence of an abnormality on CT [20]. It is understandable, therefore, that studies comparing relative performance in detection of minor and major abnormalities (such as the recent study by Park et al.) will favour IDSA guidelines, while those comparing detection of contraindication to LP will not. Neuroimaging will often be required in the course of treatment of meningitis to assess for potential complications such as hydrocephalus, infarct and haemorrhage or for underlying mastoiditis/sinusitis. However, this can be performed based on the urgency of the entity being investigated, and should only precede LP if a contraindication to LP is suspected.

Brain shift (defined anatomically as gyral flattening and/or effacement of the CSF spaces, and herniation in late stages) should be differentiated from cases of isolated raised CSF pressure [4, 5]. Unhelpfully, these entities are often considered together as “raised intracranial pressure”. Isolated raised CSF pressure is present in the majority of patients with meningitis [21], but poorly evaluated at CT [22, 23] and is not thought to carry an increased risk of herniation following LP [4, 5, 24]. UK and ESCMID guidelines focus on detection of cases of brain shift and recommend against LP in such cases. We chose to classify only those with significant brain shift as being a positive case, with all other abnormal studies classified as negative. This included cases with clinically significant findings such as intracranial haemorrhage, small subdural effusion and isolated raised CSF pressure. In our view these findings could appropriately be identified on CT imaging in the course of the

patient's hospital treatment, and did not need to be detected prior to LP.

There are fundamental flaws in the concept of a "screening CT" for a contraindication to LP. As with any screening test, a recognisable latent/presymptomatic stage should exist that can be detected reliably by screening [25]. This has never been demonstrated for patients who deteriorate following LP. A causative relationship between lumbar puncture and brainstem herniation was first suggested on a case series with autopsy data in 1938 [26]. However, there is limited prospective evidence of LP precipitating cerebral herniation in patients with raised ICP. Furthermore, CT has limited sensitivity and specificity for predicting patients at risk of post-LP deterioration [27].

In one analysis of published case reports and series, 43% of patients who deteriorated after LP did so following a normal initial CT brain [5]. It has also been shown that when blinded to outcome and shown initial CT brain imaging neuroradiologists and neurologists display only moderate agreement on which patients had an imaging contraindication to LP, and were unable to differentiate those who would go on to deteriorate following LP from those who would not [24]. Notably, following a 2009 update to the Swedish guidelines removing "impaired mental status" as a criteria for CT prior to LP, a reduction was observed in door-to-antibiotic times, as was a concomitant reduction in mortality from 11.7–6.9% [14]. While there are many possible confounders, this highlights the potential for improved patient outcomes with more restrictive use of head CT in suspected bacterial meningitis. In this context, guidelines which recommend widespread use of CT with potential associated treatment delays are difficult to justify.

We did not identify any patients with an intracranial mass or abscess in our cohort. This is in keeping with the low rates of such conditions noted in similar studies, some of which have also identified no such cases [1, 24]. Reassuringly previous studies in similar populations suggest that all algorithms perform equally well in detection of such patients [15]. Our data also highlights the difficulty clinicians face in differentiating meningitis from subarachnoid haemorrhage, with 86/453 (19%) of our initial cohort excluded due to haemorrhage being suspected or equally likely to meningitis. In spite of these exclusions, one patient had a small volume subarachnoid haemorrhage on CT. Patients who do not meet criteria for urgent CT imaging prior to LP may still require a CT for another indication, and clinicians and radiologists alike should take this into consideration.

The primary limitation of our study is its retrospective nature and potential for selection bias. As with any such study, it is possible that clinical features were present but not specified. The exclusion of patients with possible haemorrhage, known meningitis or in whom LP had already been performed may have led to the exclusion of more cases of brain shift, which would have allowed further assessment of the relative performance of the various guidelines. We believe, however, that the question of CT prior to LP invariably arises in the emergency department in cases for whom meningitis is the leading differential, and so we felt that it was appropriate to limit our study population to such patients.

Other guidelines, including Swedish [17]] and Dutch [15], have been published for selecting patients for CT, and comparison with these guidelines was beyond the scope of this study. Some criteria in the Swedish guideline, in particular, are left to the discretion of the treating doctor (such as "cerebral symptoms" or "disturbed breathing patterns"), and undoubtedly retrospective evaluation of these criteria would be challenging. Finally, our study was performed in a defined population in a single tertiary care adult hospital. While our results should be generalisable for many centres, in which pre-test probability of meningitis is low and of brain shift is very low, this may not hold true for all institutions.

Our findings indicate that in patients with suspected meningitis who undergo CT head, there is a low incidence of potential contraindications to LP on imaging. Following the more cautious approach to imaging advocated by the IDSA would not help to identify any additional cases with a potential contraindication to LP, and would result in two and three times more patients requiring initial imaging than the ESC-MID and UK guidelines respectively. Our data support the adoption of the UK guidelines, which are equally sensitive for cases of brain shift, while limiting the amount of unnecessary imaging performed thereby improving the efficiency and safety of this patient care pathway.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Fergus O'Herlihy, Philip Dempsey and Dora Gorman. The first draft of the manuscript was written by Fergus O'Herlihy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate The authors did not receive support from any organization for the submitted work.

Consent for publication The authors have no relevant financial or non-financial interests to disclose.

Competing interests This quality improvement initiative was approved by the hospital's Clinical Audit and Effectiveness Committee. As this was a retrospective review informed consent was waived by the committee.

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Fifteen-minute consultation: Approach to the child with an acute confusional state

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Received 19 July 2016
Revised 6 September 2016
Accepted 4 October 2016
Published Online First 31 October 2016

ABSTRACT

Acute confusional state (ACS) refers to sudden impairment of cognitive function and represents a major medical emergency. The impairment may be global or confined specifically to a particular faculty of higher mental function, such as memory. This review highlights the importance of relevant medical history and clinical signs and symptoms in reaching the correct diagnosis. In this review, we have presented a diagnostic approach to a child presenting with ACS and described commonly encountered causes, their treatments and outcomes. We have also presented an algorithm for the diagnostic approach to the child with ACS.

INTRODUCTION

Acute confusional state (ACS) represents a major medical emergency due to its possible association with serious underlying pathological process, some of which can be reversible with timely diagnosis and management, such as non-convulsive status epilepticus (NCSE) or basilar migraine. ACS remains a diagnostic and therapeutic challenge at presentation due to a wide variety of possible aetiologies (table 1) and the urgent need to rule out serious conditions.

ACS can be defined as the sudden impairment of mental state in a previously healthy child.[1] This impairment can be global and severe or could be very specific and mild, such as short-term memory impairment in 'transient global amnesia', in which only the memory faculty is impaired.[1]

Clinically ACS can be divided into 'silent' or 'agitated' types.[1] Silent type can be more difficult to notice and sometimes only becomes apparent when specific mental status test is carried out (table 2). Assessment can be difficult when there is pre-existent neurodevelopmental disability. In such situations parent/carer concerns should be sought, taken seriously and actively investigated. Agitated form manifests as variable degree of psychomotor unrest. Even mild deficit in intellectual function can lead to behavioural change owing to the frustration and anxiety.

The overall incidence of ACS in paediatric age group is not known but it is not a rare presentation in emergency departments. It is commonly encountered in conditions frequently seen in paediatric practice such as high fever, drug ingestion/intoxication, head trauma, nervous system infections and inflammations (table 1).

In this review, we have presented three interesting cases that posed diagnostic dilemma at presentation and highlighted the learning points. This is followed by brief discussions about other common aetiologies.

We have also proposed a diagnostic algorithmic approach to the child with ACS.

CASE REPORTS

Case 1

A girl, aged 9 years, required admission to hospital following a generalised convulsion lasting 20 min. She had been given one dose of rescue medication with buccal midazolam at home before being brought to hospital by ambulance. She had been alert, oriented and her usual self prior to the onset of the seizure. Mary has a diagnosis of four-limb cerebral palsy, moderate learning disability and epilepsy with multiple seizure types, including generalised motor seizures, focal motor seizures and absences. She is on sodium valproate with reasonable

To cite: Prasad M, Seal A, Mordekar SR. *Arch Dis Child Educ Pract Ed* 2017;**102**:72–77.

Table 1 Conditions associated with acute confusional state in childhood

High fever	Fever-induced delirium
Sleep disturbances/parasomnias	Confusional arousal, night terrors, somnambulism
Head trauma	Bleeding Postconcussion syndrome even after mild injury
Central nervous system (CNS) infections and inflammations	Meningitis, encephalitis, brain abscess Parainfectious Autoimmune
Metabolic derangements	Hyponatremia Hypoglycaemia Hyperammonaemia Uraemia Severe acidosis Hyperglycinaemia (in non-ketotic hyperglycinaemia)—rare disorder
Intoxication	Drug abuse/accidents Alcohol Medication side effect
Epilepsy	Postictal state Focal seizures with impairment of consciousness Non-convulsive status epilepticus
Migraine	Basilar migraine, hemiplegic migraine, acute confusional migraine
Vascular, raised intracranial pressure	Arteriovenous malformation-bleed Hydrocephalus/blocked shunt CNS tumours
Medically unexplained (psychogenic)	More common in adolescent girls
Miscellaneous	Hypoxia Hypovolaemia Hypotension Hypertension (hypertensive encephalopathy) Septicaemia

seizure control. Parents report that she has only occasional convulsions but does have a few vacant episodes in a week. On admission she was noted to be febrile and, after initial investigations, was started on antibiotics for a chest infection. In the next two days parents remained concerned that Mary seemed 'out of it' and not herself. She did not respond consistently to her name, did not seem to recognise family members, and was less vocal, drooling and struggling to eat. Further investigations for the 'encephalopathic presentation' showed normal blood biochemistry and a normal lumbar puncture, though her inflammatory markers were still raised. An electroencephalogram (EEG) showed continuous electrical seizures confirming a diagnosis of NCSE. Treatment with intravenous lorazepam terminated the electrical status and Mary's responsiveness improved. She was discharged from hospital after 5 days with a recovered chest and her normal happy persona.

Learning points

NCSE can present as an ACS.[3] It may occur in the context of acute or chronic neurological insults, chronic neurodisability and in children with existent epilepsy, epileptic encephalopathies or epilepsy syndromes. It is often difficult to recognise due to pre-existent neurodevelopmental disability, particularly learning disability or pre-existent epileptic encephalopathy.[3] Parent/carer report of a clear and persistent change in behaviour, arousal level, cognition or memory in 'at risk' contexts should always raise suspicion and trigger a request for an EEG, which can confirm the diagnosis. Prognosis tends to be good unless initial presentation is with coma or the NCSE is refractory to treatment.[3]

Case 2

A 14-year-old boy presented with a 24-hour history of acute confusion and vomiting. There was no history of trauma, infection or substance abuse. He had family history of migraine. On examination, his Glasgow Coma Scale Score (GCS) was 11 and he was mildly feverish (37.7°C). Neurological examination showed weak right side with right extensor plantar. Systemic examination was unremarkable. He was treated for encephalitis with antibiotics and antiviral medications. Twenty hours later, on review by a neurologist, it was clear that he had an expressive dysphasia rather than confusion. He could communicate clearly in writing, but was unable to initiate meaningful verbal conversation. MR imaging of brain 50 hours from onset showed mild cortical swelling in the left parietal region with no enhancement with gadolinium. Over the next 48 hours he understood some verbal commands, but clearly had difficulty finding some words. Right hemiparesis completely resolved. MRI 4 months later was normal. Clinical review at 6 months showed complete recovery. Subsequently, he did have further similar attacks.

Sequencing of the genomic DNA showed evidence of p[Thr666Mrt] mutation in exon 16 of the CACNA1A gene in this child and his father confirming diagnosis of familial hemiplegic migraine. (This case was previously published as one of the patients in the case series of three cases of familial hemiplegic migraine presenting with encephalopathy.[4])

Learning points

Hemiplegic migraine is a rare disorder characterised by migraine attacks with hallmark unilateral motor weakness during the aura phase. Hemiplegic migraine may occur either in families (familial) or only in one individual (sporadic).[5] Mutations in three genes (CACNA1A, ATP1A2, SCN1A) have been identified as causative factor for familial type.

A typical attack is characterised by motor weakness during the aura phase. Weakness is never the only aura during the attack, and various associated

Table 2 Suggested mini-mental state examination (adapted from Jain[2])

Functions	Tests
1. Orientation	• Sex/name/last name/recognises relative (one point for each, total score 4) • Place/city/state/country (one point for each total score 4) • Day/date/month/year (one point for each, total score 4)
2. Attention and concentration	• Minimum of 2 and maximum of 5 digits forward (one point for each, total score 4) • Minimum of 2 and maximum of 4 digits backward (one point for each, total score 3)
3. Registration and sensory perception	• Identify three objects by name (one point for each, total score 3)
4. Recall	• Tell three objects presented previously (one point for each, total score 3)
5. Language	
Name body parts	Points to five body parts (one point for each, total score 5)
Command (three steps)	Unwrap the toffee, give the wrapper to the doctor and then eat it (one point for each, total score 3)
Repeat sentence	Cat drinks milk (total score 1)
Reading	Reads his/her name (total score 1)
Writing	Writes own name (total score 1)
Copy a design	For example, circle (total score 1)

• Scores 2 SD below normal for various ages may be used to pick up early encephalopathy. Scores at 2 SD for various age groups: 3–5 years, 24; 6–8 years, 28; 9–11 years, 30; 12–14 years, 35.[2]
• A score less than 10 on day 4 after therapy has a specificity of 100% and sensitivity of 68% in predicting poor outcome in children with encephalopathy.[2]

symptoms include visual field defect, scintillating scotoma, numbness, paraesthesia, aphasia and lethargy.[5] Typically motor weakness starts in the hand and spreads up the arm to the face. Auras are usually prolonged, with nearly 50% lasting more than 1 hour and in nearly 5% of patients last even more than 24 hours.[6]

Headache typically occurs during the aura phase but may even occur before the aura. It may be mild or severe, unilateral or bilateral. The symptoms can last for hours to days, or rarely weeks, but most resolve completely.

Severe attack with confusion—in addition to the typical attacks, some patients have more severe episodes manifesting with confusion, agitation, drowsiness and even seizures and coma.[7] In majority these aura symptoms including hemiplegia and confusion last for days or even months before resolving completely.[6]

The acute presentation with confusion can be a diagnostic challenge, especially if it is the first severe attack. Thorough history and clinical examination along with family history is required. Relevant investigations including neuroimaging would be required to rule out the differentials. The diagnosis of hemiplegic migraine remains clinical and should meet the diagnostic criteria.[8]

The differential diagnosis should include cerebrovascular disease (eg, transient ischaemic attack and ischaemic or haemorrhagic stroke), seizure with postictal paralysis, and brain tumour.

Case 3

A 15-year-old girl presented with a 24-hour history of acute confusion and hallucination to emergency department. There was no history of infection or trauma. Her GCS was 12. She was not feverish and neurological examination was normal. Her blood glucose and infection screen were normal. 'Blood toxicology' was normal. Her metabolic investigations and MRI brain were normal. On review by neurologist, she was confused, agitated but surprisingly drowsy and sleepy in between. She gradually made recovery without any treatment.

Urine toxicology revealed that she had raised levels of tetrahydrocannabinol. She then disclosed that she had taken cannabis with her friends at a party.

Learning points

Intoxication can be either exotoxins (overdose) or endotoxins (metabolic disorders). For exotoxins, the history will hopefully give some clues but urine and blood for toxicology should be obtained as soon as possible in any child with confusion. Blood should also be taken for paracetamol and salicylate levels, and a heavy metal screen where poisoning could be a possibility. Drug levels of anticonvulsants in known epileptic children should be done in situations of acute deterioration in conscious level as toxicity may be the cause.

Endotoxins are a broad category and children with suspected metabolic disease are at risk of being overinvestigated while missing the one crucial investigation necessary for diagnosis. Blood, urine and cerebrospinal fluid (CSF) are important in many cases and ammonia, lactate, venous blood gas, plasma amino acids, urine organic and amino acids and sometimes CSF lactate, glucose and amino acids should be done acutely. Early discussion with a metabolic specialist or neurologist is advised. Endocrine causes should also

be addressed in this category and blood glucose, blood gas and urine dipstick will identify diabetic ketoacidosis, and blood and urine electrolytes will point to adrenal insufficiency.

Case 4

An 11-year-old previously well boy presented with a 48-hour history of fever and confusion to emergency department. He had a viral prodrome 5 days prior to presentation. His general physician prescribed him oral antibiotics 24 hours before his presentation to hospital. His parents and teachers reported a 72-hour history of change of personality with episodic agitation and altered sleep pattern. On examination his GCS was 12, he was feverish (37.9°C) and had intermittent extreme agitation. His neurology examination was normal. His blood glucose, toxicology screen and metabolic investigations were normal. His urgent CT brain was normal. He was started on intravenous antibiotics and intravenous aciclovir on admission. Twenty-four hours later he had a left focal seizure. His EEG showed periodic lateralised epileptiform discharges suggestive of viral encephalitis. His blood and CSF investigations confirmed that he had herpes simplex virus positive on PCR and cultures. His MRI brain 3 days later showed changes in frontal lobe and temporal lobe on right side suggestive of viral encephalitis. He was treated with 2 weeks of high-dose intravenous aciclovir.

On discharge he made a full physical recovery but continues to have problems with behaviour with agitated depression needing treatment with fluoxetine and risperidone at 12 months follow-up.

Learning points

Infections are a common presentation of ACS. Early assessment and treatment with prophylactic antibiotics/antivirals are especially important until an alternative explanation is found for presentation of ACS to prevent morbidity and in rare cases mortality.[9]

OTHER COMMON AETIOLOGIES

Various aetiologies that can be associated with ACS in childhood are presented in table 1. Review of all the causes is beyond the scope of this article. We have elaborated on some of the causes that can pose a greater diagnostic challenge.

Other migraine subtypes associated with confusion

Acute confusional migraine (ACM):[10] ACM, a rare migraine variant, is a diagnosis of exclusion. The confusional state is hypothesised to be complex aura phenomenon secondary to cortical wave spreading leading to transient hypoperfusion and dysfunction in those brain areas. Manifestation can be as speech difficulties, agitation, hyperalertness and also amnesia. More sinister causes of acute confusion (see table 1) needs to be excluded first. Detailed history, clinical examination, neuroimaging and EEG are often required.

Migraine with brainstem aura (MBA): Previously called basilar-type migraine is a rare subtype of migraine with aura presenting with brainstem symptoms and signs without weakness.[11] Diagnosis should be suspected when presenting with episodic attacks of vertigo, dysarthria, visual symptoms, ataxia and confusion particularly when associated with more typical features of migraine. MBA remains a diagnostic challenge and requires fulfilment of diagnostic criteria.[8]

Detailed personal and family history and clinical examination is required and neuroimaging (MRI with MR angiogram) is strongly advised during the first presentation to rule out posterior fossa structural or vascular abnormalities.

Epilepsy

Postictal state: Confusion is well recognised following the convulsive epileptic seizure. It can pose diagnostic difficulties if the patient is not known to have epilepsy and especially if the seizure was not witnessed. Confusion is usually short lasting for 30–45 min with gradual complete recovery. In the case of diagnostic uncertainties, relevant investigations to rule out other causes are often required. EEG may show features of postictal slowing or interictal epileptiform discharges, which may be of supporting value.

Focal seizures with impairment of consciousness or awareness (previously referred to as complex partial seizures):[12] Confusion and memory impairment are features of ictal phenomenon and may well be the only manifestations of the epileptic seizure. Epileptogenic focus is most commonly in the temporal lobe but can be in frontal lobe, parietal or occipital lobes. Typical attack from temporal lobe origin lasts for 2–3 min and manifests as impairment of consciousness, psychomotor arrest, vacant staring and automatism. Postictal confusion is often prolonged (minutes), which distinguishes it from absence seizures. EEG is often helpful for diagnostic confirmation and neuroimaging is required to look for any structural causes.

Absence status:[13] This is defined as a prolonged generalised absence seizure usually lasting for at least 30 min but can go on for hours and even last for days. This is a type of NCSE. Main feature is the impairment of consciousness in a patient who is alert but only partially responsive. It is rare before 10 years of age and majority of the patients suffer from idiopathic generalised epilepsy, although it may be the only seizure type. Diagnosis is established by ictal EEG recording of 3 Hz/sec spike and wave discharges.

Infection/parainfection

Inflammatory markers would be expected to be raised in meningitis, encephalitis and cerebral abscesses, though not invariably.[9] One should not be reassured

by unremarkable values when there is good clinical suspicion of central nervous system infection. Blood cultures and viral serology (including mycoplasma and Borrelia) are useful as is blood PCR for suspected viruses. Viral throat swab, urine and stool samples can also help identify a precipitant. In demyelinating conditions, it would also be important to send blood oligoclonal bands (paired with CSF). Aquaporin-4 antibodies are becoming increasingly used but are not as sensitive for neuromyelitis optica as in adults. Lumbar puncture is the gold standard for diagnosis and should be performed as soon as is safe. Microscopy, culture and sensitivity, protein and glucose should be sent in addition to viral samples.

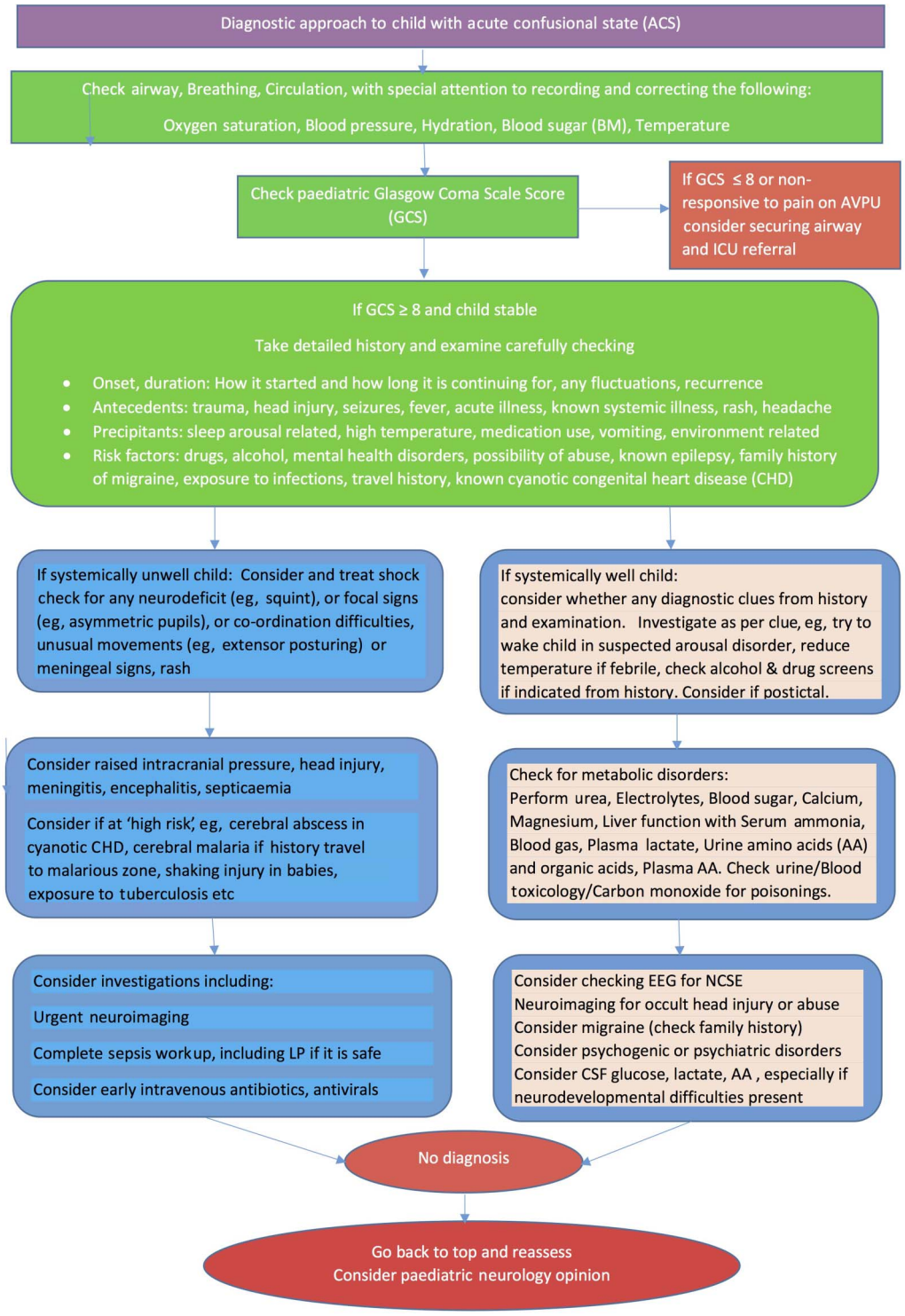

Figure 1 Algorithm for diagnostic approach in child with acute confusion state. AVPU, alert voice pain unresponsive; CSF, cerebrospinal fluid; ICU, intensive care unit; LP, lumbar puncture; NCSE, non-convulsive status epilepticus.

The list of viruses causing encephalitis/acute disseminated encephalomyelitis is long and pointers in the history, and results from throat/stool/urine will allow targeted testing of the CSF.

ACS in teenagers

This is a commonly encountered presentation in paediatric practice. Every attempt should be made to get detailed history from the patient and the family and friends. Drug/alcohol intoxication is particularly common in this age group and therefore should be sought even when the history is not forthcoming, as highlighted in case 3. ACM may also present for the first time in teenage years posing diagnostic dilemma. As mentioned before, this is a diagnosis of exclusion and other causes should first be ruled out. Autoimmune encephalitis, especially anti-*N*-methyl-d-aspartate (NMDA) receptor antibody encephalitis, can also pose diagnostic challenge. Investigation should include autoimmune screening (anti-NMDA receptor antibody, anti-voltage-gated potassium channel antibody, anti-glutamic-acid-decarboxylase antibody) along with all the investigations mentioned in the section Infection/parainfectious causes.

Once the organic disorders are ruled out with confidence, one should think about 'medically unexplained (psychogenic) confusion' as the likely diagnosis, as this is very common in this age group. History of abuse and bullying, mental health problems, adverse life events, difficulties with peer and social relationships, and insecure or sensitive personality are often reported and may provide the clue towards the diagnosis. Early diagnosis and prompt involvement of child and adolescent mental health services is paramount.

Diagnosis and management: Please refer to figure 1, which presents the algorithm for diagnostic approach to a child with ACS. Initial management is as directed in the algorithm. Subsequent management is dictated by the diagnosis made. Regular close monitoring including vital signs, Paediatric GCS and neuro-observations is essential till the diagnosis is reached, as some of the underlying causes can be life threatening. Refer to the Royal College of Paediatrics and Child Health-produced guideline 'The Management of children and young people with an acute decrease in conscious level' (2015 update)[14] and National Institute for Health and Care Excellence guidance on 'Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management'[15] for more detailed advice on assessment and management.

CONCLUSION

ACS is not an uncommon presentation in children and should be considered a medical emergency. A detailed history, systemic and neurological examination and routine laboratory tests may help in diagnosing majority of the cases in children. For those posing diagnostic dilemma, less frequent causes should be considered and further investigations should be undertaken urgently to avoid diagnostic delays.

Contributors MP, SM and AS contributed equally towards this article.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

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THE MANAGEMENT OF CHILDREN AND YOUNG PEOPLE WITH AN ACUTE DECREASE IN CONSCIOUS LEVEL (DECON)

RCPCH
Royal College of Paediatrics and Child Health
Leading the way in Children's Health

Population: Children aged from 4 weeks up to 18 years who have a decreased conscious level†

IDENTIFY DECON

1 Identify DeCon

GCS ≤ 14
AVPU = P or U

See 'Neurological assessment' box

2 Perform DeCon specific ABCD

A
- Intubate if GCS <9, AVPU = U or if there is suspected/proven raised intracranial pressure* **See 'Signs of raised ICP' box**

B
- 100% Oxygen if oxygen SaO_2 <95%

C
- If circulation compromised give 10 ml/kg isotonic fluid bolus if DeCon associated with either signs of raised Intracranial pressure (ICP) or ketoacidosis (as opposed to 20 ml/kg)*

D
- Perform a capillary glucose test ≤15 minutes of presentation*
- If capillary blood glucose ≤3 mmol/L give 2ml/kg of 10% dextrose and consider a hypoglycaemia screen
- In a child with a clinical diagnosis of raised ICP, before imaging consider sedation, intubation and ventilation to maintain the $PaCO_2$ between 4.5 and 5.0 kPa

***Based on consensus methodology or weaker evidence**

3 Take core investigations

Point of care tests	Capillary blood glucose, Blood gas (arterial, capillary or venous) for pH, PCO_2, BE, Lactate & Urine dipstick
Laboratory tests	Glucose, U&Es, LFTs, FBC, Blood culture, Ammonia (venous or arterial only)
Saved samples	10ml of urine for later analysis including toxicology

4 Start observations

Record hourly:
HR, RR, SaO_2, BP, Temp, physical state/appearance

Continuously monitor:
SaO_2, ECG

Consider differential diagnoses

DIFFERENTIAL DIAGNOSIS

Hypertensive encephalopathy

Investigation	• Look for signs of raised ICP + papilloedema • Do 4 limb BP • Urinalysis for blood/protein + U&Es
PICU and NEPHROLOGY	• Discuss when DeCon + Hypertension (BP >95th centile for age)

Metabolic

Hypoglycaemia	• Hypoglycaemia screen if lab Glucose <3mmol/L • 2ml/kg bolus 10% Dextrose • Then Infusion of 10% Dextrose (Target 4-7mmol/L)
Hyperammonaemia	• If plasma level >100micromol/L • Send a free flowing venous (or arterial) sample of ammonia to the laboratory, which should be informed it is coming. Samples should be transported on ice in case of a delay before analysis which might affect the interpretation • **SEEK EXPERT METABOLIC ADVICE**
DKA	www.bsped.org.uk/media/1629/bsped-dka-aug15_.pdf

Prolonged fits/Post convulsive

Investigation	Mg^{2+} **and** Ca^{2+} **and** Na^{+}
PICU	**Discuss treatment if:** • Na <125 mmol/L • Ionised Ca^{2+} <0.75 mmol/L • Mg^{2+} <0.65 mmol/L and the convulsion is ongoing despite anticonvulsant treatment

Cause unclear

Consider additional tests and involvement of specialists e.g. Neurologist or Metabolic expert

Investigation

Additional tests:
- CT/MRI
- LP
- Urine Toxicology
- Urine organic and plasma aminoacids
- Plasma lactate/EEG

See 'LP WARNING' box

Sepsis

Diagnosis	T^0 >38°C **or** <35.5°C **or** ↑HR **or** ↑RR WCC >12×10⁹/L **or** <4×10⁹/L **or** a purpuric rash
Investigation	• CXR • Urine culture • Blood PCR (meningococcus+pneumococcus) • Clotting • Skin swab (from areas of inflammation) • Joint aspiration (if septic arthritis) • Thick and thin film (for malarial parasites if foreign travel to endemic area)
Treatment	Broad spectrum antibiotics ≤1 Hour **+** Follow 'Sepsis 6 pathway': http://www.survivingsepsis.org/Bundles/Pages/default.aspx **+ EARLY SENIOR REVIEW**

Intracranial infection

Differential	• Bacterial meningitis • Herpes Simplex Encephalitis (HSE) • Intracranial abscess • TB meningitis
Investigation	• LP including CSF HSV PCR if no contraindications **See 'LP WARNING' box**
Treatment	• **Bacterial:** www.nice.org.uk/guidance/cg102 • **HSE:** Aciclovir (Duration decided by local ID experts) • **TB:** www.nice.org.uk/guidance/cg117

Raised ICP

Diagnosis	**See 'Signs of raised ICP'**
Treatment	• Refer to the NICE Bacterial meningitis and meningococcal septicaemia guideline for recognition and Rx www.nice.org.uk/guidance/cg102
PICU	• Discuss acute management with local PICU • Position head in midline • 20⁰ head up tilt • Avoid internal jugular CVCs • Isotonic fluids (restricted) • Mannitol or Hypertonic saline • Intubate and ventilate to a $PaCO_2$ of 4.5-5.0 kPa **BEFORE IMAGING**

Alcohol intoxication

Investigation	Consider blood alcohol test when suspected as a cause of DeCon
Treatment	• ABCD/APLS • Treat hypoglycaemia with IV glucose + maintenance Dex/Saline • Beware of and if present treat respiratory failure/aspiration pneumonia and hypotension • Other concurrent ingestions • And avoid emetics (in case of aspiration)
Considerations	• Consider all other likely contributory drugs • Consider contacting local poisons unit

Shock

Diagnosis	Mottled, cool extremities or diminished peripheral pulses **+** systolic BP <5th centile for age **or** urine output <1mL/kg/hr
Differential	Sepsis, trauma, anaphylaxis, heart failure
Treatment	20 ml/kg isotonic fluid bolus (10 ml/kg if raised ICP or ketoacidosis)
Reassessment	↓ HR **See 'Observation'** ↓ Capillary refill time ↑ Level of consciousness **See 'Neurological assessment'** ↑ Blood pressure (to normal level for age) ↓ Lactate concentration and/or improvement in base excess ↑ In urine output
PICU	Consider for intubation/ventilation/inotropes if >40ml/kg fluid given

Neurological assessment

GLASGOW COMA SCORE (GCS)

Eyes	Motor	Voice
4 Open	6 Obeys commands	5 Converses
3 To command	5 Localises pain	4 Confused
2 To pain	4 Flexion withdrawal	3 Inappropriate words
1 No response	3 Abnormal flexion	2 Incomprehensible
	2 Abnormal extension	1 No response
	1 No response	

GCS MODIFICATIONS IN CHILDREN UNDER 5 YEARS

Motor	Voice
6 Normal spontaneous movements	5 Alert, babbles, coos, words or sentences to usual ability
5 Localises to supraorbital pain (SOP) **or** withdraws from touch	4 Less than usual ability, irritable cry
4 Withdraws from nailbed pain	3 Cries to pain
	2 Moans to pain

AVPU SCALE

A = Alert **V** = Responds to voice **P** = Responds to pain **U** = Unresponsive

Observation – normal ranges

Age	Respiratory Rate	Heart Rate	Systolic BP
Neonate	60	160	70
<1 year	35-45	110-160	75
1-5 years	25-35	95-140	80-90
5-12 years	20-25	80-120	90-110
>12 years	adult	adult	100-120

Signs of raised ICP

BRADYCARDIA (heart rate ≤60 bpm) **or** HYPERTENSION MAP ≥95th centile for age)

Pupillary dilation (unilateral or bilateral) **or** loss/impairment of reaction to light

Abnormal breathing pattern **or** posture

LP WARNING

Do not attempt an LP if...
- There are signs of raised ICP (Even if GCS is 15)
  See 'Signs of raised ICP'
- GCS ≤8 **or** deteriorating **or** focal neurological signs **or** GCS ≤12 after a seizure lasting ≥10 minutes
- CT/MRI suggesting CSF pathway obstruction
- Clinical evidence of circulatory shock/meningococcal disease

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†**This does not include:** Children with a previously diagnosed condition which may decompensate causing a decreased conscious level (e.g. epilepsy, ventriculo-peritoneal shunt, previously diagnosed metabolic condition), who already have an agreed management plan for acute illness; **OR** Children who on a day to day basis score 14 or less on the Glasgow Coma Scale or Modified Glasgow Coma Scale (e.g. children with epileptic encephalopathy, minimally responsive state following acquired brain injury).

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ARTICLE OPEN ACCESS

Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient

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Neurol Neuroimmunol Neuroinflamm 2020;7:e663. doi:10.1212/NXI.0000000000000663

Abstract

Objective

Autoimmune encephalitis (AE) is an important and treatable cause of acute encephalitis. Diagnosis of AE in a developing child is challenging because of overlap in clinical presentations with other diseases and complexity of normal behavior changes. Existing diagnostic criteria for adult AE require modification to be applied to children, who differ from adults in their clinical presentations, paraclinical findings, autoantibody profiles, treatment response, and long-term outcomes.

Methods

A subcommittee of the Autoimmune Encephalitis International Working Group collaborated through conference calls and email correspondence to consider the pediatric-specific approach to AE. The subcommittee reviewed the literature of relevant AE studies and sought additional input from other expert clinicians and researchers.

Results

Existing consensus criteria for adult AE were refined for use in children. Provisional pediatric AE classification criteria and an algorithm to facilitate early diagnosis are proposed. There is also discussion about how to distinguish pediatric AE from conditions within the differential diagnosis.

Conclusions

Diagnosing AE is based on the combination of a clinical history consistent with pediatric AE and supportive diagnostic testing, which includes but is not dependent on antibody testing. The proposed criteria and algorithm require validation in prospective pediatric cohorts.

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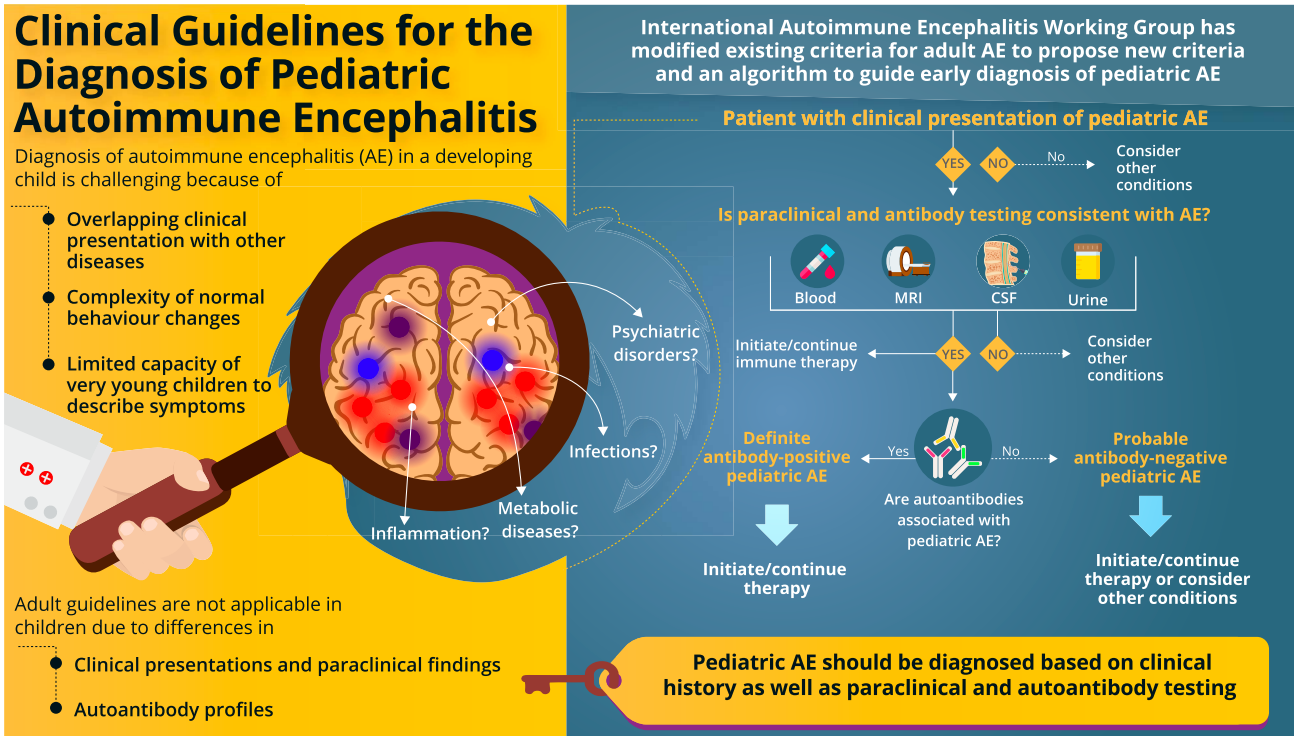
Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by *Neurology: Neuroimmunology & Neuroinflammation*.

Glossary

AE = autoimmune encephalitis; **Caspr2** = contactin-associated protein-like 2; **FIRES** = febrile infection-related epilepsy syndrome; **GABA$_A$R** = gamma-aminobutyric acid A receptor; **GAD65** = glutamic acid decarboxylase 65; **HE** = Hashimoto encephalopathy; **LGI1** = leucine-rich glioma-inactivated protein 1; **MOG** = myelin oligodendrocyte glycoprotein; **NMDAR** = N-methyl-D-aspartate receptor; **PANDAS** = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; **PANS** = pediatric acute-onset neuropsychiatric syndrome; **VGKCC** = voltage-gated potassium channel complex.



doi:10.1212/NXI.0000000000000663

Neurology® Neuroimmunology & Neuroinflammation

Autoimmune encephalitis (AE) refers to an increasingly recognized group of inflammatory brain diseases. Children with AE present with acute or subacute onset of neuropsychiatric symptoms due to an underlying abnormal immune response to the CNS.[1,2] Many AE associate with antibodies directed toward extracellular antigens, such as synaptic receptors and ion channels.[2,3] Autoantibodies that bind to extracellular antigens are generally pathogenic, whereas antibodies that bind intracellular antigens are not considered pathogenic, instead general markers of autoimmunity.

A number of different antibodies have been described in children with AE.[4–21] Currently, the most common autoantibodies in children target the N-methyl-D-aspartate receptor (NMDAR), myelin oligodendrocyte glycoprotein (MOG), and glutamic acid decarboxylase 65 (GAD65).[5–12] It is also recognized that not all children with a clinical phenotype of AE have a known autoantibody.[1,4]

Diagnosing AE is challenging because of overlap in clinical presentations between the types of AE, other inflammatory brain diseases, infections, metabolic diseases, and psychiatric disorders.[1] It is especially difficult in children because of the complexity of normal behavioral changes during childhood and the limited capacity of younger children to describe their symptoms.[1] Compared to adults with AE, children may manifest important differences in symptoms, paraclinical findings, comorbidities, treatment response, and prognosis.[4–7,22–24] There is an urgent need to recognize pediatric AE because treatment delays worsen prognosis and increase the risk of permanent neurocognitive deficits.[6,25,26]

In this article, we build on existing consensus criteria for adult AE by refining them for use in children.[27] We propose provisional pediatric AE classification criteria and an algorithm to facilitate early diagnosis. Diagnosing AE is based on the combination of a clinical history consistent with the disease and supportive diagnostic testing, which includes but is not dependent on antibody testing. We also discuss the differential diagnosis in children with suspected AE.

Methodology

At the 2014 Autoimmune Encephalitis Alliance (AEalliance.org) conference in North Carolina, the Autoimmune Encephalitis International Working Group was formed and initiated discussions around developing diagnostic criteria for AE. A subcommittee of pediatric neurologists and rheumatologists

identified that adult-focused criteria may not apply well to children. As a result, this subcommittee collaborated through conference calls and email correspondence to consider the pediatric-specific approach to AE. The subcommittee reviewed the literature on relevant AE studies and sought additional input from other experts. The first author (T.C.) developed a draft based on the preceding discussions that was subsequently reviewed and modified by all authors.

Existing diagnostic criteria for AE

The International Encephalitis Consortium 2013 diagnostic criteria for encephalitis of presumed infectious or autoimmune etiology require patients to have altered mental status lasting more than 24 hours with no alternative cause identified.[28] Confirmation of this diagnosis requires at least 3 minor criteria, including fever within 72 hours of presentation; new onset focal neurologic findings; CSF leukocytosis; acute new neuroimaging abnormality suggestive of encephalitis; or EEG abnormalities consistent with encephalitis.[28] These criteria do not differentiate autoimmune from infectious encephalitis.

More recently, an international group developed diagnostic criteria for early diagnosis of AE in adults, which require (1) subacute onset over less than 3 months of working memory deficits, altered mental status, or psychiatric symptoms; (2) at least one of the following: new focal CNS findings, seizures not explained by a preexisting disorder, CSF pleocytosis, and/or MRI features suggestive of encephalitis; and (3) reasonable exclusion of alternative causes.[27] Specific neurologic syndromes were given criteria, including limbic encephalitis, anti-NMDAR encephalitis, and autoantibody-negative AE.[27]

These AE criteria required modification to be applied to children. For example, deficits in working memory are challenging to identify in younger children. Also, children are less likely to present with a well-defined neurologic syndrome and, even in anti-NMDAR encephalitis, the sequence of symptom development may differ from adults.[5–7] Furthermore, the differential diagnosis for a child presenting with temporal lobe seizures and cognitive slowing is broad, whereas this presentation in adults suggests limbic encephalitis or acquired temporal pathology.

Clinical features distinguishing adults and children with AE

Typically, children with AE are previously healthy and present with rapid onset of neuropsychiatric symptoms. Prodromal symptoms including fever occur in over 50% of patients.[2,4–6] Between disease onset and initiation of therapy, symptoms typically persist over time. This distinguishes AE from pediatric acute-onset neuropsychiatric syndrome (PANS), where patients often experience a relapsing-remitting course with rapid progression to maximum symptom severity and rapid return to previous function over hours or days, sometimes without therapy.

Neurologic manifestations of AE include altered level of consciousness, confusion, disturbed sleep, movement disorders and seizures. Seizures are the most common feature in AE and may be the predominant manifestation.[4–7,10–21] Seizures may be focal or generalized and are often multifocal.[4–7,10–21] Over one third of patients with AE have abnormal movements, such as ataxia, chorea, dystonia, myoclonus, or tremor.[4–7,13,15] Both seizures and movement disorders can be highly refractory to standard treatments in children with AE.[10,14,16,24] Some degree of cognitive impairment is seen in the overwhelming majority of AE patients and is considered a cardinal symptom.[4,5,13,14,16,19,21] As such, a diagnosis of AE would be highly questionable in patients with documented normal cognition, again differentiating AE from PANS where cognition is often preserved. Assessing memory deficits in young children may be challenging; however, developmental regression, language loss or speech impairments may be presenting features of pediatric AE.[5–7,29]

Behavioral changes, such as repetitive or stereotypical behaviors, irritability, hyperactivity, hypersexuality, insomnia and anger outbursts, are common in pediatric AE.[4–7] Psychiatric symptoms may range from mood swings and mild personality changes to fulminant psychosis and occur in over 50% of AE patients.[4–7] New-onset psychosis in children younger than 13 years is uncommon and considered a red flag for an underlying medical, rather than primary psychiatric, condition. It is critical to assess for cognitive changes, seizures, movement abnormalities, or other neurologic symptoms in children with acute psychiatric symptoms, as these symptoms are suggestive of AE.

Children with AE likely differ from adults in their clinical presentations due to evolution of neuronal circuits, neuroreceptor densities and myelination during normal development. Children with AE are more likely to present with multifocal neuropsychiatric symptoms, rather than isolated clinical syndromes. For example, children with GAD65 antibodies may not present with the classic stiff-person syndrome or cerebellar degeneration seen in adults.[11,12,22] Children with anti–NMDAR-associated encephalitis are more likely to present with movement abnormalities, agitation, insomnia, seizures, speech deficits, ataxia, and/or hemiparesis, whereas memory deficits, psychiatric manifestations, and central hypoventilation are more common in adults with the same antibody.[5–7] Pediatric AE is less associated with tumors compared with adults.[4–7]

Diagnostic evaluation of children and teenagers with suspected AE

Although no single investigation is diagnostic of pediatric AE, the presence of a suggestive clinical phenotype and supportive paraclinical testing is essential to diagnose an underlying inflammatory process and to exclude alternative diagnoses. Initial investigations to be considered for any child with suspected AE are listed in table 1, although diagnostic workup should be tailored to the individual.

Table 1 Recommended investigations for children with suspected AE

A. Initial investigations for patients with possible AE	
Diagnostic imaging	Brain MRI with gadolinium (including T1, T2, FLAIR, and diffusion-weighted sequences)
	Consider adding spine MRI if neurologic abnormalities potentially mediated by spinal cord involvement
Blood tests	Complete blood cell count and differential
	Erythrocyte sedimentation rate, C-reactive protein, and ferritin
	Vitamin B12 level and vitamin D level
	Serum lactate
	Thyroid-stimulating hormone, free thyroxine, and thyroid autoantibodies (e.g., antithyroid peroxidase, antithyroglobulin, and anti–thyroid-stimulating hormone receptor)
	Serologic testing for infectious causes (dependent on regional epidemiology)
	Consider antinuclear antibodies and specific antinuclear antibodies (e.g., anti–double-stranded DNA and anti-Smith) if indicated by clinical presentation
	Consider serum complement and immunoglobulin levels if personal or family history of autoimmunity or immune deficiency
Urine tests	Testing for recreational drugs (e.g., marijuana, cocaine, and opioids)
Lumbar puncture	Opening pressure
	CSF cell counts, protein, lactate, oligoclonal bands, and neopterin (if available)
	Infectious testing dependent on regional epidemiology, but often includes PCR for enterovirus, herpes simplex virus, and varicella zoster viruses
	Save 5–10 mL of CSF for future testing
Respiratory tests	Nasopharyngeal swab for respiratory viruses and mycoplasma PCR
EEG	Assess for focal or generalized seizures, epileptiform discharges, and changes in background activity
B. More specific investigations for patients with possible AE	
Blood tests	Serum testing for antibodies associated with AE[a]
Lumbar puncture	CSF testing for antibodies associated with AE[a]
Neurocognitive tests	Assess for cognitive deficits affecting memory, attention, problem solving, language, and cognitive processing
	Consider using symbol digit modalities test to screen for cognitive dysfunction
Other tests	Consider if available and/or if required based on initial investigations: PET and SPECT

Abbreviations: AE = autoimmune encephalitis; FLAIR = fluid-attenuated inversion recovery.
[a] See tables 2 and 3 for details regarding neural antibodies identified in children.

Blood tests are helpful to assess for systemic inflammatory changes, autoantibodies associated with systemic autoimmune diseases, vitamin B12 deficiency, markers of infection, elevated lactate due to metabolic conditions, and recreational drug use. Erythrocyte sedimentation rate, C-reactive protein, leukocyte counts, and platelet counts may be normal in children with AE.[1,4–21]

CSF pleocytosis and/or elevated protein levels may be seen at diagnosis or during disease course, but are not uniformly present.[1,4–21] Recommended tests to assess for infectious encephalitis were based on population-based studies in California and England (table 1).[30,31] However, workup for infectious etiologies varies depending on the season and region where the patient lives or has traveled. A recent report suggests that anti-NMDAR encephalitis may be more common in children than any specific infectious encephalitis, further highlighting the importance of considering AE when evaluating for infectious encephalitis.[32] CSF neopterin is a useful but not rapidly accessible biomarker that is frequently elevated in anti-NMDAR encephalitis and other encephalitides, but normal in PANS.[33] There is evidence that AE (particularly anti-NMDAR encephalitis) may be triggered by herpes simplex virus encephalitis and Japanese encephalitis.[34]

All patients should have a brain MRI with and without gadolinium. Over half of patients with AE will have a normal

Table 2 Antibodies that are commonly identified in pediatric AE

Antibody target (localization)	Typical clinical features in children	
GAD65[10–12] **(intracellular)**	Frequency	Common in AE, but only pathologic if high titers in serum and present in CSF
	Clinical	Encephalitis with memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures
	MRI	May be normal initially often progresses to lesions in the limbic system, cerebellum, and cortices with possible atrophy
	EEG	Epileptiform discharges may be multifocal
	Other	CSF leukocytosis may be mild with oligoclonal bands Associated personal or family history of autoimmunity Often resistant to immunotherapy
MOG[8,9,42,45–47] **(extracellular)**	Frequency	Common in AE
	Clinical	Acute disseminated encephalomyelitis including encephalopathy, optic neuritis, or transverse myelitis (but not typical MS); cortical encephalitis with seizures; brainstem encephalitis; and meningoencephalitis without demyelination
	MRI	Focal or multifocal white matter lesions, longitudinally extensive myelitis and optic neuritis
	EEG	Nonspecific slowing
	Other	Serum antibody testing preferable to CSF Higher titers of antibodies in younger children Persistent antibodies in relapsing disease
NMDAR[5–7] **(extracellular)**	Frequency	Most common antibody target in pediatric AE
	Clinical	Encephalitis with movement disorder, seizures, psychiatric symptoms, reduced verbal output/mutism, developmental regression (in younger children), sleep dysfunction (mainly insomnia), and autonomic instability
	MRI	Normal in at least 65% of patients; T2/FLAIR lesions may be identified in the cortex, white matter, cerebellum, or basal ganglia; reversible cerebral atrophy is a late finding
	EEG	Abnormal in over 90% of patients—most have generalized slowing, but may see focal epileptic activity, focal slowing, or "prolonged spindles/delta brush pattern"
	Other	CSF antibody testing preferable to serum Increased association with tumors in females and in patients older than 12 y

Abbreviations: AE = autoimmune encephalitis; FLAIR = fluid-attenuated inversion recovery; GAD65 = glutamic acid decarboxylase 65; MOG = myelin oligodendrocyte glycoprotein; NMDAR = NMDA receptor.

brain and spine MRI at diagnosis.[4–7,16,21,22] Inflammatory lesions (high signal on T2 and fluid-attenuated inversion recovery sequences) may develop over time, and cerebral atrophy may occur months later.[4,6,7,15] MRI lesions are most likely to be present in those with antibodies to MOG or the gamma-aminobutyric acid-A receptor ($GABA_AR$).[9,14,15] Neuroimaging findings are not limited to the temporal lobe or cortex.[1,5–21] A normal MRI lessens suspicion for CNS vasculitis, demyelinating diseases, infections, and malignancies.[1] In contrast, restriction on diffusion-weighted imaging reduces the likelihood of pediatric AE and should prompt consideration of other etiologies, such as infection-associated encephalopathies and vasculitis.[1] Small retrospective adult AE studies have proposed that functional PET and SPECT studies may demonstrate brain dysfunction, but experience is limited in pediatric AE.[35,36]

A normal EEG is unusual in children with AE during active disease, although prolonged EEG may be needed for improved sensitivity. Therefore, focal or generalized seizures, epileptiform discharges, and encephalopathic changes, such as diffuse or focal slowing, may help to distinguish AE from primary psychiatric disorders or PANS. Adults with AE are more likely to have EEG changes predominantly involving the temporal lobes, whereas EEG findings in children may be more generalized.[4–7,14–21] Specific EEG features, such as the "delta brush" pattern and extreme spindles, have been linked to anti-NMDAR encephalitis, but sensitivity is low.[6,22,23]

Neurocognitive testing may identify deficits in memory, attention, problem solving, language, and processing speed, particularly in younger children. A change in neurocognitive function supports a diagnosis of pediatric AE and may differentiate these patients from those with primary psychiatric disorders. However, interpretation of neurocognitive testing at diagnosis should be undertaken with caution, as there is often no premorbid testing for comparison.

Table 3 Antibodies that are identified less frequently in pediatric autoimmune encephalitis

Antibody target (localization)	Typical clinical features in children	
Dopamine-2 receptor[13] (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with predominant movement disorders, psychiatric symptoms, sleep disturbance, mutism, and decreased consciousness
	MRI	Abnormal in 50% of patients, usually symmetric selective involvement of basal ganglia
	EEG	No consistent pattern reported
	Other	Variable CSF findings, sometimes lymphocytic pleocytosis or oligoclonal bands
$GABA_A$ receptor[14,15] (extracellular)	Frequency	Uncommon
	Clinical	Encephalitis with refractory seizures, status epilepticus, or epilepsia partialis continua
	MRI	Multifocal T2/FLAIR lesions in cortical/subcortical areas
	EEG	Epileptiform activity and generalized slowing
	Other	Most patients have CSF leukocytosis Often associated with GAD or thyroid autoantibodies
GABA-B receptor[16,17] (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with focal or generalized seizures and mixed movement disorder
	MRI	Abnormal in over 50% with increased T2/FLAIR signal in the medial temporal lobe (may be multifocal and may be associated with changes on diffusion-weighted imaging)
	EEG	Diffuse slowing and epileptiform discharges
	Other	CSF abnormal in up to 90% with lymphocytic pleocytosis Pediatric cases not linked to infection or tumor
Glycine receptor[18,19] (extracellular)	Frequency	Uncommon
	Clinical	Progressive encephalomyelitis with rigidity and myoclonus; encephalitis; and other brainstem syndromes
	MRI	Frequently normal (70% reported cases)
	EEG	Abnormal in approximately 70%, usually slowing
	Other	Variable CSF findings of lymphocytosis, elevated protein, and oligoclonal bands May be associated with antibodies to other targets (e.g., GAD)
m-GluR5[20,21] (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with psychiatric symptoms
	MRI	Variable MRI findings, often T2/FLAIR
	EEG	Variable EEG findings, typically absent epileptiform discharges
	Other	CSF lymphocytic pleocytosis

Abbreviations: FLAIR = fluid-attenuated inversion recovery; GABA = gamma-aminobutyric acid; GAD = glutamic acid decarboxylase; m-GluR5 = metabotropic glutamate receptor 5.

Other diagnostic tests may be considered. Most children with AE do not require brain biopsy. However, a targeted brain biopsy of MRI abnormalities may be needed when the diagnosis remains uncertain after initial workup. The diagnostic yield of brain biopsy is higher in pediatric patients than in adults.[37]

Antibody testing and interpretation in children and teenagers with suspected AE

Antibodies associated with pediatric AE are listed in tables 2 and 3. Each antibody is associated with characteristic

Table 4 Proposed classification criteria for possible, definite antibody-positive and probable antibody-negative pediatric AE

		Diagnostic categories		
Categorical features of AE	**Specific diagnostic features**	Possible AE	Probable antibody-negative AE	Definite antibody-positive AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥2 features present	≥2 features present	≥2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties[a]			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available	≥1 features present	≥1[b] features present
	CSF inflammatory changes (leukocytosis >5 cells/mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. AE serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

Abbreviation: AE = autoimmune encephalitis.
[a] Severe cognitive dysfunction that is not attributable to a primary psychiatric syndrome as documented by a qualified clinician (e.g., neurologist, psychiatrist, and neuropsychologist) or a significant drop in IQ (>20 points).
[b] When antibodies against NMDA receptor, gamma-aminobutyric acid A receptor, or glutamic acid decarboxylase 65 are present in CSF, further paraclinical markers of neuroinflammation are not required to diagnose definite AE. When only serum antibodies are present, one or more paraclinical marker(s) of neuroinflammation is required.

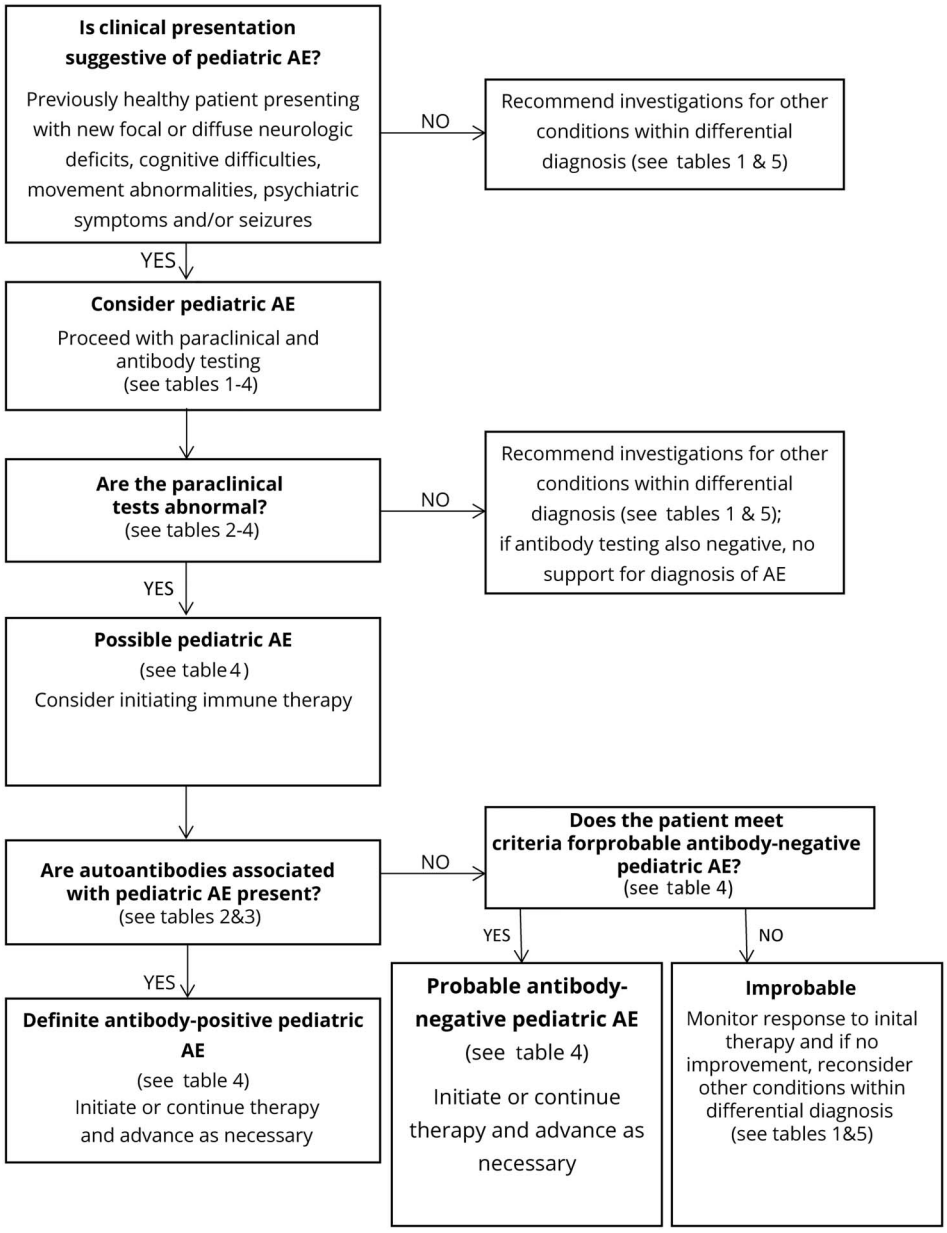
symptoms, seizure types, and other clinical findings. However, there is significant overlap between the different disorders and so testing a panel of neural autoantibodies is recommended for any child with suspected AE. The most common autoantibodies identified in children target NMDAR, MOG, GAD65, and $GABA_AR$. Given the rarity of other autoantibodies, further testing should be considered only if antibodies to these targets are negative and suspicion of AE persists (table 3).

Antibody testing should be performed in both CSF and serum to avoid false-negative and false-positive results. For example, testing for NMDAR antibodies typically has higher sensitivity in CSF compared with serum, with up to 15% of patients having negative serum results.[5–7] In contrast, MOG autoantibodies have higher sensitivity in serum.[9]

Interpretation of antibody test results should carefully consider the child's clinical presentation, especially when more than 1 antibody is identified. For example, GAD65 antibodies tend to be associated with personal or familial autoimmunity and low titers, such as those seen in type 1 diabetes mellitus, are not neurologically relevant.[22] The presence of more than 1 antibody in some patients with AE has been recognized and may be associated with overlapping syndromes. Antibody specificity is also important when interpreting antibody test results. For instance, only IgG isotype antibodies to the GluN1 subunit of the NMDAR on a cell-based assay are specifically associated with AE.[5,38]

In adults with AE, most antibodies to the voltage-gated potassium channel complex (VGKCC) do not bind to the channel, but to proteins in the complex, particularly leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-

Figure Algorithm for diagnostic workup of children with suspected AE using provisional criteria



AE = autoimmune encephalitis.

associated protein-like 2 (Caspr2).[39] In children, VGKCC antibodies rarely target LGI1 or Caspr2.[40,41] It has been argued that VGKCC antibodies without specific binding to LGl1 or Caspr2 have limited clinical significance.[40]

Proposed classification criteria and algorithm for diagnosis of pediatric AE

We modified the criteria for adult AE and propose provisional classification criteria for possible pediatric AE, probable antibody-negative pediatric AE, and definite antibody-positive pediatric AE in table 4.[27] A diagnostic algorithm is also provided in figure. The provisional criteria and algorithm should be assessed prospectively in future cohorts.

A diagnosis of pediatric AE should be considered in previously healthy children who present with acute or subacute (less than 3 months) onset of new focal or diffuse neurologic deficits, cognitive difficulties, developmental regression, movement abnormalities, psychiatric symptoms, and/or seizures. Although children with preexisting developmental delay or chronic behavior/psychiatric abnormalities may develop AE, alternative diagnoses, such as genetic, metabolic, or neurodegenerative etiologies, should be considered in these patients.

Children with a clinical presentation suggestive of AE should have serum and CSF examined for neuronal antibodies, undergo paraclinical testing for neuroinflammation, and have disease mimics excluded (tables 1 and 4). EEG is not included

Table 5 Differential diagnosis of AE in children and adolescents

Primary CNS inflammatory	**AE, including HE**
	Primary or secondary CNS vasculitis
	Demyelinating diseases: acute disseminated encephalomyelitis, MS, and neuromyelitis optica
	Rasmussen encephalitis
Systemic inflammatory	Autoimmune diseases: antiphospholipid syndrome, celiac disease, Behçet disease, sarcoidosis, systemic lupus erythematosus, and Sjögren syndrome
	Autoinflammatory diseases: interferonopathies and hemophagocytic lymphohistiocytosis
Infectious	Bacteria: *Borrelia burgdorferi, Listeria monocytogenes, Mycoplasma pneumoniae, Mycobacterium tuberculosis*, and *Treponema pallidum*
	Viruses: adenovirus, enterovirus, Epstein-Barr virus, HSV, HIV, influenza, JC virus, measles, rabies, varicella zoster virus, and West Nile virus
	Parasites: malaria
Postinfectious or infection-associated encephalopathy	Postmycoplasma basal ganglia encephalitis
	Post-HSV encephalitis movement disorder
	Poststreptococcal neuropsychiatric disorders (including Sydenham chorea)
	Encephalitis lethargica
Diseases with immune mechanisms under review	FIRES
	ANE
	AESD
	PANDAS
	PANS
Metabolic	Genetic/inherited diseases: leukodystrophies, mitochondrial diseases, mucopolysaccharidoses, organic acidurias, and Wilson disease
	Hepatic encephalopathy
Neoplastic	Primary CNS tumors (e.g., lymphoma, glioma, and astrocytoma)
	Metastatic disease (e.g., neuroblastoma and leukemia)
Nutritional	Vitamin B12 deficiency
Psychiatric	New onset schizophrenia, bipolar disorder, conversion disorder, childhood disintegrative disorder, and psychogenic seizures
Toxic	Recreational drugs (e.g., alcohol, marijuana, synthetic cannabinoids, cocaine, opioids, and methamphetamines)
	Ingestions (e.g., ethylene glycol, methanol, and inhalants)
	Medications, such as metronidazole and cyclosporine
Other	Child abuse and neglect

Abbreviations: AE = autoimmune encephalitis; AESD = acute encephalopathy with biphasic seizures and diffusion restriction; ANE = acute necrotizing encephalopathy; FIRES = febrile infection-related epilepsy syndrome; HE = Hashimoto encephalopathy; HSV = herpes simplex virus; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS = pediatric acute-onset neuropsychiatric syndrome.

as paraclinical evidence of neuroinflammation because EEG cannot differentiate AE from other encephalopathies. However, EEG encephalopathic features are allowable as an alternative for clinical features of encephalopathy. If a patient fulfills criteria for possible pediatric AE (table 4) and is functionally impaired, therapy may be started while awaiting the results of antibody and other testing, given the importance of early treatment to improve outcomes.[4,25,26] If a patient with possible AE subsequently does not have positive antibodies or paraclinical testing for neuroinflammation, a diagnosis of AE is not supported. For these children, careful further consideration of the differential diagnosis is warranted, and additional immune

therapy should only be undertaken with caution (table 5, figure).

Children may have AE caused by antibodies that have not yet been identified and may meet criteria for probable antibody-negative pediatric AE (table 4). These patients will have 1 or more positive paraclinical tests for neuroinflammation, but negative antibody testing. Children who meet the criteria for definite antibody-positive pediatric AE will have positive antibody testing. If CSF antibodies are present (e.g., NMDAR and GAD65), no other paraclinical evidence of neuroinflammation is required for a diagnosis of definite AE (table 4). If only serum antibodies are present, 1 or more paraclinical tests of neuroinflammation must be abnormal. There should be caution in diagnosing AE when only serum antibodies (particularly NMDAR, $GABA_AR$, and glycine receptor) are found in the absence of paraclinical evidence of neuroinflammation.

The proposed pediatric AE criteria differ from the adult criteria in several ways (table 4, table e-5, links.lww.com/nxi/A184).[27] First, the pediatric criteria include both acute and subacute time frames for symptom onset, reflecting the range in disease course observed in children. Adult AE criteria were developed for several well-defined syndromes (i.e., limbic encephalitis, acute disseminated encephalomyelitis [ADEM], and anti-NMDAR encephalitis) and the associated algorithm focuses on whether patients meet criteria for these syndromes.[27] In contrast, many pediatric patients with AE do not present with a well-defined syndrome and so the pediatric criteria were devised to capture the breadth of clinical and paraclinical findings reported in children. Similarly, the pediatric AE algorithm (figure) does not focus on syndrome identification, but is intended to guide a clinician in assessing clinical features and in paraclinical and antibody testing, so as to determine whether an AE diagnosis is appropriate. The adult AE criteria group clinical and paraclinical markers together, whereas the pediatric criteria distinguish clinical evidence of neurologic dysfunction from paraclinical evidence of neuroinflammation.

Patients with definite AE may benefit from continued or advanced immunosuppressive therapy, although specific protocols are not yet validated. Identification of an antibody associated with AE may facilitate counseling regarding expected course and outcomes. Timing of clinical responses to immunotherapy in children with AE may vary from immediate to months after starting.[5–7,24,42] Therefore, using response to therapy as confirmatory support for a diagnosis of AE may be misleading.

Approach to clinically recognizable syndromes

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is the most common pediatric AE. The current adult diagnostic criteria for anti–NMDAR-associated encephalitis have been tested and apply well in children.[43] However, children are more likely to present with neurologic symptoms, instead of psychiatric symptoms, and may not present with the classic sequence of symptoms described in adults—for example, movement disorders and autonomic dysfunction occur earlier in children.[5–7]

AE associated with antibodies to MOG, including acute disseminated encephalomyelitis

The most common autoantibody associated with autoimmune demyelination targets MOG.[8,9,42] Patients who have ADEM associated with MOG autoantibodies are more likely to exhibit large globular lesions and long segment myelitis compared with those without these antibodies.[44] Children with MOG antibodies are also less likely to have oligoclonal bands than those with MS.[42,44] However, the spectrum of brain disease associated with MOG antibodies in adults and children has broadened to include ADEM, meningoencephalitis, cortical encephalitis with seizures, brainstem encephalitis, and mimics of vasculitis.[45–47] Some of these patients will evolve into more typical demyelinating phenotypes, such as ADEM; therefore, MOG antibodies should be considered in pediatric AE presentations beyond ADEM.[45–47] MOG autoantibodies are typically transient in monophasic ADEM, but remain positive in relapsing phenotypes.[8,9,42]

Limbic encephalitis

The clinical, EEG, and radiologic features of limbic encephalitis are uncommon in children.[48] Autoantibodies associated with adult limbic encephalitis include those that target LGI1, GAD65, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, gamma-aminobutyric acid-B receptor, Caspr2, Hu, and Ma2.[3] With the exception of GAD65, these specific antibodies are rare in children.[48]

Hashimoto encephalopathy

Hashimoto encephalopathy (HE) presents with nonspecific neuropsychiatric symptoms accompanied by antithyroid antibodies, which are considered markers of autoimmunity, rather than pathogenic. Patients may develop seizures, altered mental status, cognitive decline, psychosis, paranoia, focal neurologic defects, and movement disorders.[49,50] Over 70% of children with HE have a normal brain MRI, CSF rarely shows pleocytosis, and EEG often shows generalized or focal slowing without seizures.[49,50] Most children have normal thyroid function despite having antithyroid antibodies.[49,50] Thoughtful interpretation is required because serum thyroid autoantibodies have been identified in healthy children.[49,50]

Approach to probable antibody-negative pediatric AE

Children with a clinical phenotype of AE and paraclinical findings of neuroinflammation, but negative testing for neural antibodies, may meet criteria for probable antibody-negative pediatric AE (table 4). It is well recognized that not all neural autoantibodies have been identified. Having CSF and serum

testing in a research laboratory may identify patients who have antibodies against neural cell surface antigens of yet unknown identity and who may respond to immunotherapy.

Probable antibody-negative AE is one of the most challenging clinical scenarios. It is appropriate that a child presenting with new onset encephalopathy, neuropsychiatric features, and changes in function be investigated for possible AE. However, the differential diagnosis in children is arguably broader than in adults, and so it is important to ensure that other diagnoses have been excluded before giving an AE diagnosis. Pathologic entities that often cause diagnostic difficulty are cortical dysplasias and genetic epilepsies presenting with fever-provoked symptomatic focal seizures, infection-provoked encephalopathy and PANS. In these syndromes, CSF pleocytosis or oligoclonal bands are usually absent, and MRI is either normal or demonstrates alternative pathology. Therefore, critical examination of paraclinical tests for evidence of CNS inflammation is mandatory to avoid unnecessary immune suppression. A diagnosis of probable antibody-negative pediatric AE should also be reassessed in children with atypical features.

Differential diagnosis of AE

The spectrum of inflammatory brain diseases in children has rapidly expanded as new diseases and new etiologies for existing conditions have been described. The underlying pathogenic mechanisms that lead to CNS inflammation may involve vessel wall inflammation, demyelination, or an immune response directed against neurons and supporting structures.[1,3] Inflammation may also occur secondary to infection, malignancy, or a systemic inflammatory disease. Diagnosing pediatric AE is especially challenging because of the clinical overlap between conditions in the differential diagnosis (table 5) and the clinical heterogeneity within patients having the same disease.

Specific conditions within the differential diagnosis of AE

Comprehensive evaluation is required to distinguish children with AE from those who have other inflammatory brain diseases. For example, children with large-vessel CNS vasculitis typically demonstrate a stroke phenotype, including paresis and speech deficits, and may be distinguished by the presence of ischemic changes on MRI and angiographic abnormalities, such as aneurysm and beading.[51] In contrast, children with small-vessel CNS vasculitis present with cognitive dysfunction, seizures, vision abnormalities, and bilateral nonischemic lesions on MRI and have inflammatory vessel wall changes identified on brain biopsy.[51]

Infection-associated encephalopathy disorders include febrile infection-related epilepsy syndrome (FIRES), acute necrotizing encephalopathy, mild encephalopathy with reversible splenium lesion, and acute encephalopathy with biphasic seizures and diffusion restriction.[52] These syndromes have typical clinical and radiologic features, often with diffusion restriction on imaging, which may infer cytotoxicity and distinguish these patients from those with AE. For example, children with FIRES develop a nonspecific febrile illness followed by sustained refractory status and then progress to chronic, drug-resistant epilepsy with neuropsychological impairment.[52] Neuroimaging and brain biopsy in FIRES are usually normal.[52] The pathogenesis of these diseases is unresolved, but may include genetic vulnerability leading to an infection-triggered "cytokine storm."[52]

Other diagnoses within the differential are PANS and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). These conditions describe an idiopathic or postinfectious onset of obsessive-compulsive disorder, eating restriction, other emotional syndromes, tics, loss of skills, or personality change.[53] Both clinical phenotypes lack robust biomarkers, and pathogenesis remains disputed; however, there is some evidence of immune mediation and immunotherapy responsiveness.[53,54] Although patients may appear to have an acquired brain syndrome, most children with PANDAS or PANS would not fulfill the proposed pediatric AE criteria.

Also, monogenic autoinflammatory syndromes may involve the brain, such as the genetic interferonopathies, vasculopathies, and hemophagocytic lymphohistiocytosis.[55] These disorders typically present in early childhood, result in chronic progressive disease, often involving increasing spasticity, intracranial calcifications and microcephaly, and are associated with persistent CSF immune activation.[55] These syndromes are distinguished from AE by the presence of non-neurologic features, such as skin lesions, cytopenias, hepatosplenomegaly, and lung disease.[55]

Finally, neuropsychiatric symptoms are common in pediatric AE and are also the hallmark of primary psychiatric disorders. Delusions, hallucinations, reduced speech, sleep disturbance, and cognitive difficulties may be seen in both disease groups. Features that distinguish patients with AE from those with psychiatric disease include autonomic instability, hyperkinesia, dyskinesia, rapid progression of psychosis despite therapy, seizures, slowing or epileptic activity on EEG, CSF pleocytosis, CSF oligoclonal bands, and MRI abnormalities.[56]

Discussion

Proposed pediatric AE criteria are intended to address differences in clinical presentations, paraclinical findings, and autoantibody profiles between children and adults. The accompanying algorithm aims to guide diagnostic workup and facilitate earlier initiation of therapy.

Study funding

There was no external funding for this manuscript.

Disclosure

The authors have no conflicts of interest relevant to this article to disclose, with the exception of Dr. Dalmau being the editor of *Neurology: Neuroimmunology & Neuroinflammation.* Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* July 31, 2019. Accepted in final form November 25, 2019.

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Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient

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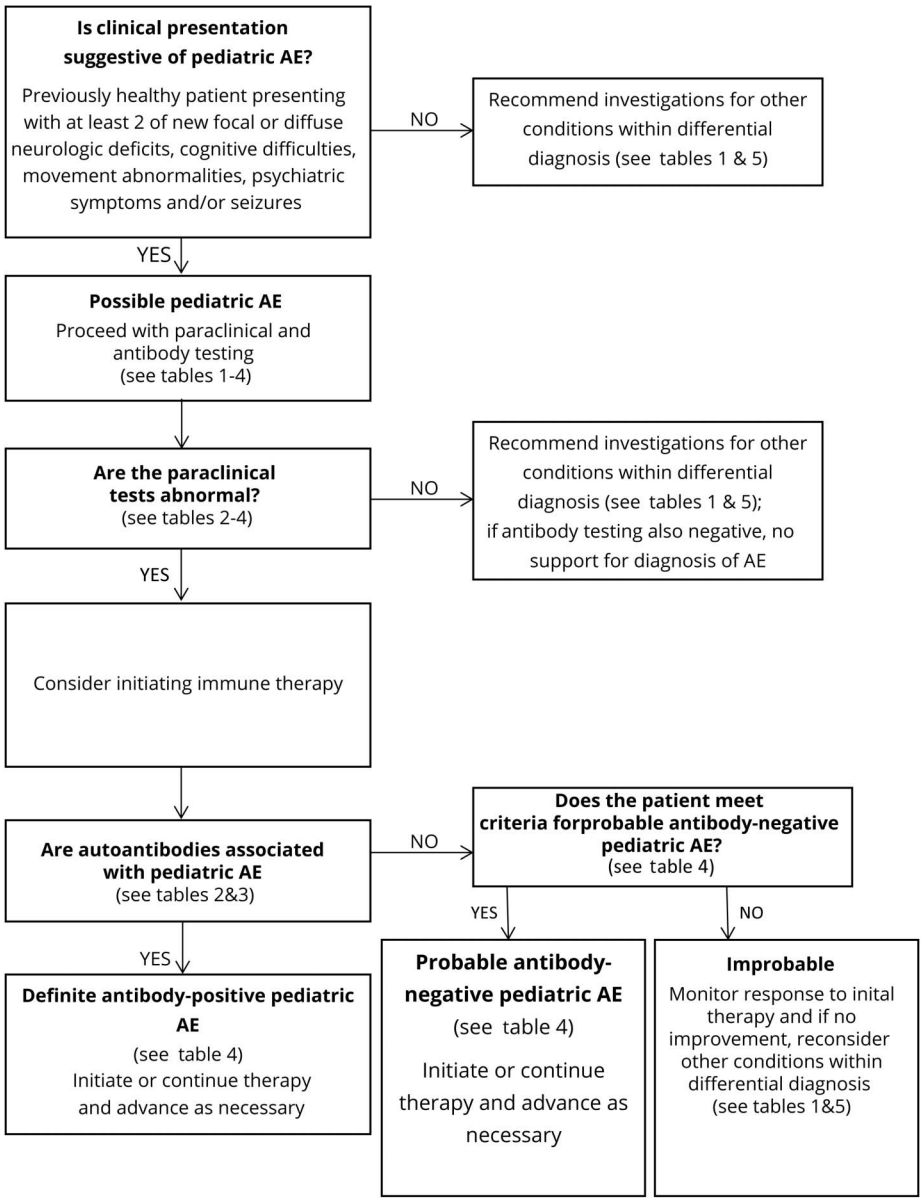
Neurol Neuroimmunol Neuroinflamm 2020;7;
DOI 10.1212/NXI.0000000000000663

CORRECTION

Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient

Neurol Neuroimmunol Neuroinflamm 2020;7:e730. doi:10.1212/NXI.0000000000000730

In the article "Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient" by Cellucci et al.,[1] first published online January 17, 2020, the text under the question in the top left box in figure 1 should read, "Previously healthy patient presenting with at least 2 of new focal or diffuse neurologic deficits, cognitive difficulties, movement abnormalities, psychiatric symptoms and/or seizures." The bolded header of the box directly below it should read, "Possible pediatric AE." The text in the 4th box down on the left should read, "Consider initiating immune therapy, if not already started." The corrected figure 1 appears below. The authors regret the errors.



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Acute ataxia in paediatric emergency departments: a multicentre Italian study

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Received 8 May 2018
Revised 20 February 2019
Accepted 21 February 2019
Published Online First 4 April 2019

ABSTRACT

Objectives To evaluate the causes and management of acute ataxia (AA) in the paediatric emergency setting and to identify clinical features predictive of an underlying clinically urgent neurological pathology (CUNP).

Study design This is a retrospective medical chart analysis of children (1–18 years) attending to 11 paediatric emergency departments (EDs) for AA in an 8-year period. A logistic regression model was applied to identify clinical risk factors for CUNP.

Results 509 patients (mean age 5.8 years) were included (0.021% of all ED attendances). The most common cause of AA was acute postinfectious cerebellar ataxia (APCA, 33.6%). Brain tumours were the second most common cause (11.2%), followed by migraine-related disorders (9%). Nine out of the 14 variables tested showed an OR >1. Among them, meningeal and focal neurological signs, hyporeflexia and ophthalmoplegia were significantly associated with a higher risk of CUNP (OR=3–7.7, p<0.05). Similarly, the odds of an underlying CUNP were increased by 51% by each day from onset of ataxia (OR=1.5, CI 1.1 to 1.2). Conversely, a history of varicella-zoster virus infection and vertigo resulted in a significantly lower risk of CUNP (OR=0.1 and OR=0.5, respectively; p<0.05).

Conclusions The most frequent cause of AA is APCA, but CUNPs account for over a third of cases. Focal and meningeal signs, hyporeflexia and ophthalmoplegia, as well as longer duration of symptoms, are the most consistent 'red flags' of a severe underlying pathology. Other features with less robust association with CUNP, such as seizures or consciousness impairment, should be seriously taken into account during AA evaluation.

What is already known on this topic?

- Ataxia is a relatively uncommon neurological emergency in childhood.
- Acute postinfectious cerebellar ataxia and intoxications are the most common causes of acute paediatric ataxia.

What this study adds?

- In Italy, acute postinfectious cerebellar ataxia is the most common cause of acute ataxia in children, and varicella zoster is the most frequently involved pathogen.
- Brain tumours are the second most common cause of paediatric acute ataxia.
- In acute ataxia assessment, focal neurological or meningeal signs, hyporeflexia, ophthalmoplegia, seizures, and longer duration of symptom evolution are associated with higher risk of severe underlying pathology.

INTRODUCTION

Ataxia consists of impaired coordination of motor activity. Children with ataxia classically present a wide-based gait, truncal instability, tremor, dysarthria and nystagmus.[1–4] Acute ataxia (AA) in childhood poses a diagnostic dilemma because of the broad differential diagnosis. While the most common causes are benign, AA can be due to potentially disabling or life-threatening conditions, requiring early diagnosis and prompt intervention.[1] Only few studies have described the different conditions that can be encountered in children presenting with AA, but conclusions were divergent due to different recruitment settings, small sample size and heterogeneous study designs.[5–8]

The first aim of our study was to describe the demographic and clinical features of children presenting to the paediatric emergency department (PED) for AA in a large, multicentre cohort, investigating the underlying aetiologies and analysing the management in an emergency setting. Given the critical importance of identifying patients requiring urgent investigations, our second aim was to identify clinical features associated with a higher risk of clinically urgent neurological pathology (CUNP).

MATERIALS AND METHODS

Study setting and participants

This retrospective, multicentre cohort study was carried out in the PED of 11 Italian hospitals (Turin,

To cite: Garone G, Reale A, Vanacore N, *et al*. *Arch Dis Child* 2019;**104**:768–774.

Table 1 Main demographic features and general information of the total cohort and the two subgroups

	Total cohort (n=509)	No CUNP (n=335)	CUNP (n=174)	P value
Age (years)				
Mean (median)±SD	5.8 (4.4)±4.0	5.9±4.1	5.6±3.9	NS
Time before symptom onset (days)				
Mean (median)±SD	3.8 (1.0)±5.4	2.4±3.4	6.4±7.2	<0.001
Sex (%)				
Male	53.6	52.8	55.2	NS
Female	46.4	47.2	44.8	
Triage code (%)				
Red	0.8	0.0	2.3	NS
Yellow	56.0	56.7	54.6	
Green	42.4	42.4	42.5	
White	0.8	0.9	0.6	
Hospitalisation (%)				
Discharge from ED	12.8	19.4	0.0	
Hospitalisation	85.2	77.3	100.0	
Hospitalisation refusal	2.0	3.0	0.0	
Length of stay (days)				
Mean (median)±SD	11.3 (9)±12.20	7.7±5	16.8±17	<0.001
Evolution of symptoms during follow-up (%)				
No information	27.1	31.9	17.8	<0.001
Improvement	63.9	67.5	56.9	
Stability	4.5	0.6	12.1	
Worsening	3.3	0.0	9.8	
Exitus	1.2	0.0	3.4	

The following triage codes were used: red (highly critical conditions), yellow (very urgent), green (urgent) and white (non-urgent).
P values are based on χ^2 and t-test results.
CUNP, clinically urgent neurological pathology; ED, emergency department.

Table 2 Neurological examination findings and reported symptoms in the total cohort and in the two subgroups

	Total cohort (%) (n=509)	No CUNP (%) (n=335)	CUNP (%) (n=174)	P value
Other cerebellar signs*	39.7	37.3	44.3	NS
Positive Romberg sign	37.3	41.2	29.9	0.012
Focal neurological signs	17.5	7.2	37.4	<0.001
Nystagmus	16.5	14.6	0.1	NS
Consciousness impairment	16.1	13.4	21.3	0.023
Hyporeflexia	15.7	8.7	29.3	<0.001
Ophthalmoplegia†	12.0	5.1	25.3	<0.001
Movement disorder	2.9	2.1	4.6	NS
Meningeal signs	2.6	0.6	6.3	<0.001
Papilloedema	2.4	0.0	6.9	<0.001
Seizures	2.0	0.6	4.6	0.004
≥1 associated symptom	80.7	79.7	82.8	NS
Nausea/Vomiting	38.5	37.9	39.7	NS
Headache	29.7	28.1	32.8	NS
Vertigo	24.2	29.0	14.9	<0.001
Fever	23.0	23.9	21.3	NS
Torticollis	2.4	0.9	5.2	0.003
Varicella	16.9	24.8	1.7	<0.001

P values are based on χ^2 test results.
*Dysarthria, tremor or dysmetria.
†Both internal and external.
CUNP, clinically urgent neurological pathology.

Pavia, Padua, Genoa, Bologna, Florence, Siena, L'Aquila, Catania and two centres in Rome). A retrospective medical chart analysis of all patients aged between 12 months and 18 years presenting to the participating PEDs in an 8-year period (January 2009–December 2016) was performed. We included patients with a history of impaired balance and gait incoordination with less than 30 days in duration in whom a clinical diagnosis of ataxia was made in the PED. Ataxia was the predominant sign, or it was clearly the first sign noted at the onset of symptoms. Patients already diagnosed with neurological disorders causing AA were excluded. Gait disorders due to pain, limb weakness, traumatic brain injury or epileptic seizures and patients with severely impaired consciousness were excluded.

Data collection

From each medical record, data on demographic features, clinical history, neurological examination findings, relevant investigations performed (both in the PED and during hospitalisation), hospital admission and length of stay (where applicable) were extracted. The aetiological diagnosis made at the end of the diagnostic work-up was used to classify the cause of AA .

Definitions and outcome measures

Some debate exists over the nosography of parainfectious or postinfectious cerebellar ataxias.[9] In this study, we classified as acute postinfectious cerebellar ataxia (APCA) all cases of postinfectious and parainfectious cerebellar dysfunction. Patients with transitory ataxia without history, signs, symptoms or laboratory

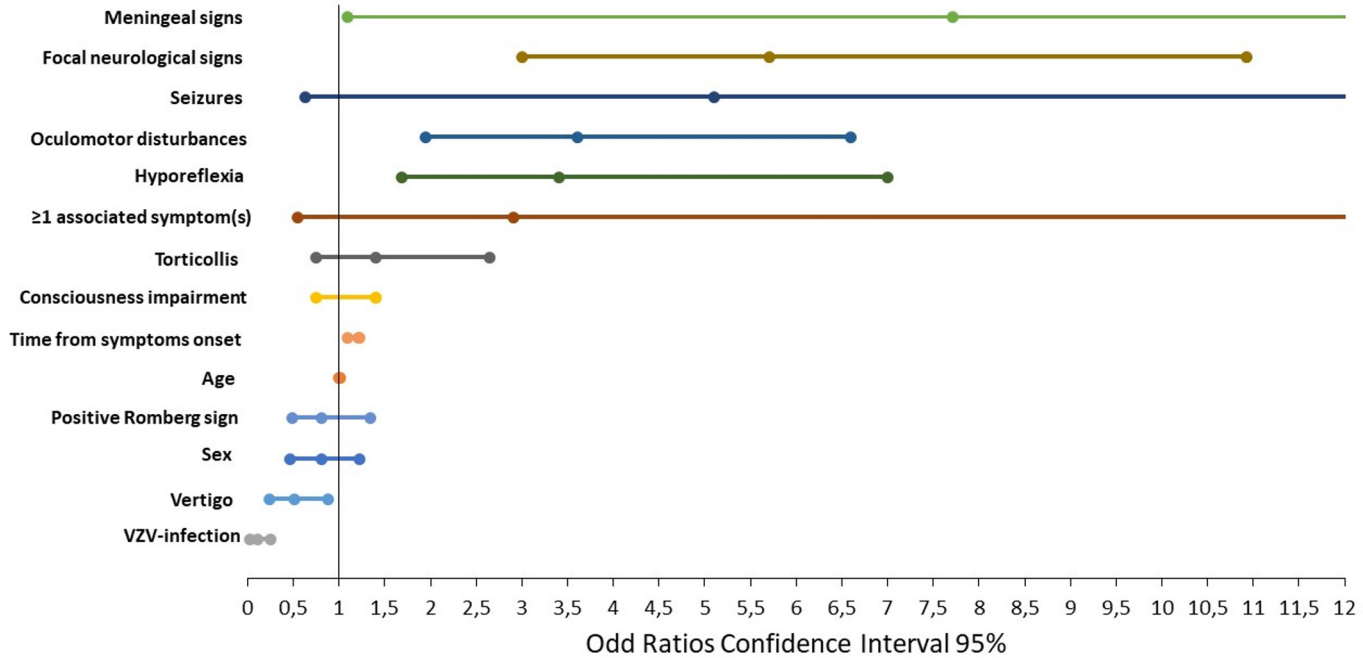

Figure 1 Multivariable regression analysis of predictors of clinically urgent neurological pathology in childhood acute ataxia. 95% CIs for each variable included in the logistic model are shown. Inclusion criteria of candidate clinical predictors are explained in the text. VZV, varicella-zoster virus.

findings of infectious illness were classified as transient undiagnosed ataxia (TUA). Considering that encephalitis, both infectious and autoimmune, may also present with an acute-onset cerebellar syndrome, this term has been reserved to patients developing severely impaired consciousness during the illness or showing widespread cerebral involvement on neuroimaging, diffuse electroencephalographic slowing or (in case of infectious encephalitis) microbiological evidence of direct infection of the central nervous system (CNS).

Psychogenic ataxia was diagnosed based on the presence of a phenomenology incongruent with an organic disorder, evidence of suggestibility, distractibility and/or variability of symptoms or inconsistent disability.

For the purposes of our study, CUNP was defined as any nervous system disorder requiring early diagnosis and prompt medical or surgical interventions to prevent disabling or life-threatening evolution, namely neoplastic, cerebrovascular and infectious CNS disorders, demyelinating diseases, acute neuropathies (AN), genetic or metabolic disorders, and CNS malformations requiring surgical treatment.

Statistical analysis

We described the clinical and demographic features of the overall cohort and of the two diagnostic subgroups (patients with and without CUNP). Each variable was tested to identify significant differences between the two subgroups. After reviewing for appropriateness, χ^2 and Student's t-tests were used for categorical and continuous variables, respectively.

We applied a logistic regression analysis model to assess the presence of any predictive variables associated with a higher risk of CUNP. Inclusion of variables in the model was based on clinical plausibility and significant or nearly significant differences on χ^2 and t-tests. Variables with extremely unbalanced distribution in the two groups (frequency of 0% in one group) were excluded. Adjusted OR and 95% CI were used as measures of effect. Statistical significance was set at $p<0.05$.

In addition, we performed a multivariable regression analysis to evaluate the clinical factors responsible for an increased physicians' attitude to request neuroimaging. Each clinical feature was tested for significant differences between patients who performed and did not perform neuroimaging. Mann-Whitney, χ^2 and Student's t-tests were used, where appropriate. All variables showing significant differences, together with sex and age, were included in the model.

Finally, to evaluate indication to perform neuroimaging, cerebrospinal fluid (CSF) sampling and nerve conduction study (NCS), selected clinical features were compared in patients with normal and abnormal findings. Mann-Whitney, χ^2 and Student's t-tests were used, where appropriate.

IBM SPSS Statistics V.24.0 software was used to perform all statistical analyses.

RESULTS

Main clinical and demographic features

During the study period, 2 426 030 children were admitted to the participating PEDs. A total of 509 patients with AA (male:female=1.16) were included, with a mean age of 5.81 years. The frequency of AA was of 1 case for every 4766 emergency department attendances (0.021%). The main demographic features and clinical findings of the total cohort and the two subgroups are summarised in tables 1 and 2, respectively. Investigations performed are illustrated in online supplementary table S1.

Associated symptoms and neurological exam findings

On admission, 80% of the patients reported some associated symptoms, mainly nausea or vomiting (38.5%) and vertigo (24.2%). Twenty-three per cent of the children reported febrile illness or were febrile on admission (table 2). On neurological examination, additional cerebellar signs were the most frequently reported neurological abnormalities (39.7%), followed by positive Romberg sign (37.3%).

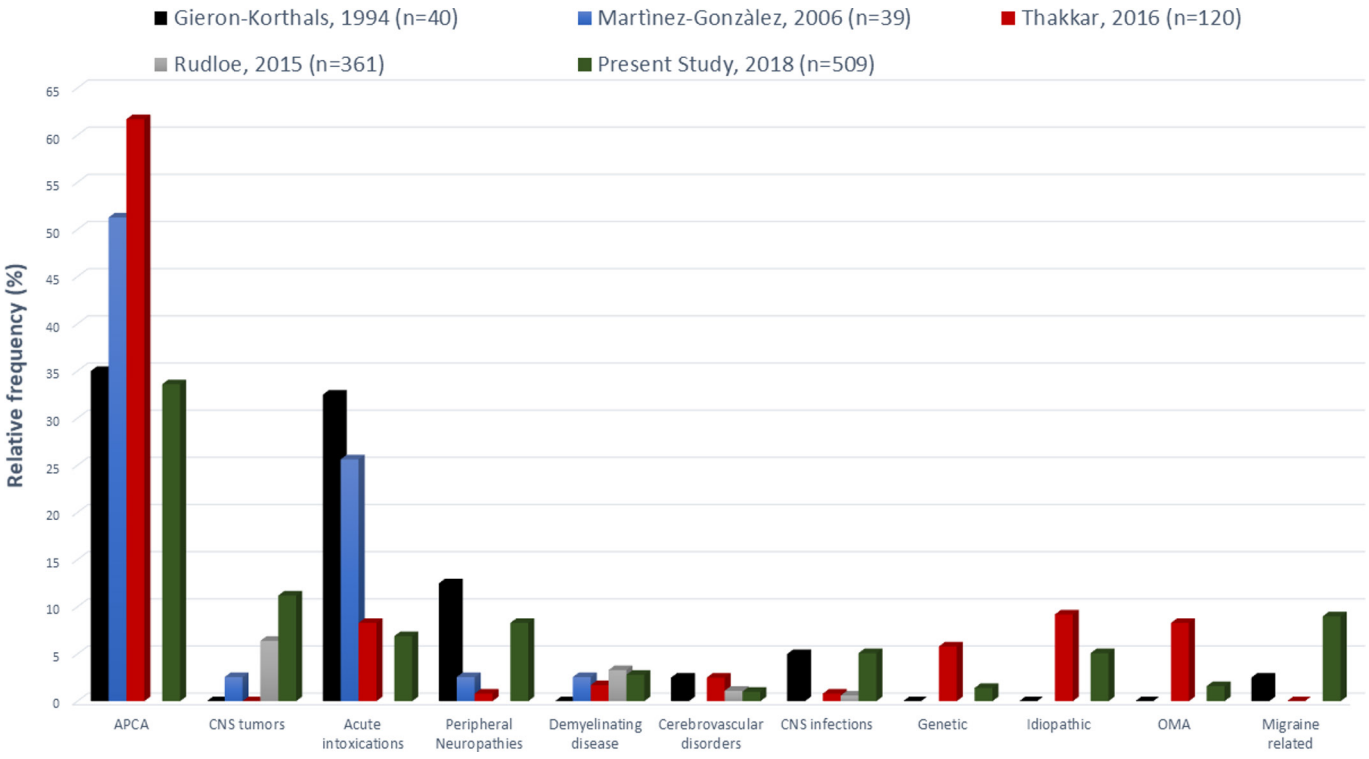

Figure 2 Comparative representation of distribution of the main causes of acute ataxia in the different cohorts reported in the literature. Due to the study design, only the frequency of disorders causing significant neuroimaging abnormalities was deducible from the study by Rudloe *et al*[6]. APCA, acute postinfectious cerebellar ataxia; CNS, central nervous system; OMA, opsoclonus-myoclonus-ataxia.

Ataxia causes

The most commonly identified cause of AA was APCA (33.6%) (online supplementary figure S2A), mainly due to varicella-zoster virus (VZV) infection (49.7%; online supplementary figure S2B,C). In the remaining cases, the triggering infection was isolated only in a minority of patients (29.1% of non-VZV-related APCA; online supplementary figure S2B). The second most common cause of AA was CNS tumours (57 cases, 11.2%).

Acute encephalitis was diagnosed in 30 children (5.9%), mostly infectious (23 cases), followed by autoimmune and paraneoplastic forms. ANs were found in 42 patients (8.3%).

Migraine-related disorders such as vestibular migraine and benign paroxysmal vertigo (BPV) were diagnosed in 46 patients (27 and 19 cases, respectively), representing the third most common group (9%). Psychogenic ataxia was recognised in 21 cases (4.1%), and 35 cases of acute intoxications due to drug overdose or substance abuse were found (online supplementary figure S4). Other less frequently encountered causes were vestibular disorders (5.3%), demyelinating diseases (2.8%), genetic-metabolic disorders (1.4%) and CNS malformations (0.8%; online supplementary figure S2A). Twenty-six patients (5.1%) were classified as TUA.

Logistic regression model

Based on the final diagnosis, 174 patients with CUNP were identified. Following comparison between patients with and without CUNP (tables 1–2), 14 variables were included in the model (figure 1, online supplementary table S2).

Papilloedema, the only finding appearing exclusively in CUNP patients, was excluded from the logistic analysis. Meningeal and focal neurological signs were associated with a higher risk of CUNP adjusting for other variables, followed by hyporeflexia and ophthalmoplegia. The odds of an underlying CUNP were increased by 51% by each day from onset of ataxia. Conversely, a history of VZV infection and vertigo resulted in a lower risk of CUNP. Adjusting for other variables, neither seizures nor consciousness impairment was significantly associated with CUNP.

Diagnostic investigations

Neuroimaging was performed in 351 children (69%), with abnormal findings in 129. Neuroimaging was more frequently requested in patients with other cerebellar signs, oculomotor deficits, nystagmus, focal signs, papilloedema and longer duration of symptoms (online supplementary table S3A), and less frequently performed in patients with history of VZV infection. Even when adjusting for other variables, the stronger predictors of neuroimaging use were the presence of other cerebellar signs, ophthalmoplegia and focal neurological signs. In addition to a history of varicella, longer duration of evolution of symptoms was also associated with a lower probability of being investigated with neuroimaging (online supplementary table S3B).

Among patients undergoing neuroimaging, abnormal results were significantly more frequent in patients with focal neurological signs, torticollis, consciousness impairment, papilloedema and ophthalmoplegia ($p<0.03$; online supplementary table S4). Conversely, they were less frequent in patients with varicella, vertigo or fever ($p<0.02$). Patients with abnormal neuroimaging showed longer time from symptom onset ($p<0.001$).

NCS was performed in 42 children; alterations were more common in children with hyporeflexia ($p<0.001$; online supplementary table S5). CSF samples, collected in 109 patients (21.4%), were significantly more frequently altered in children with hyporeflexia ($p=0.003$) and in those with focal neurological signs ($p=0.015$; online supplementary table S6). Conversely,

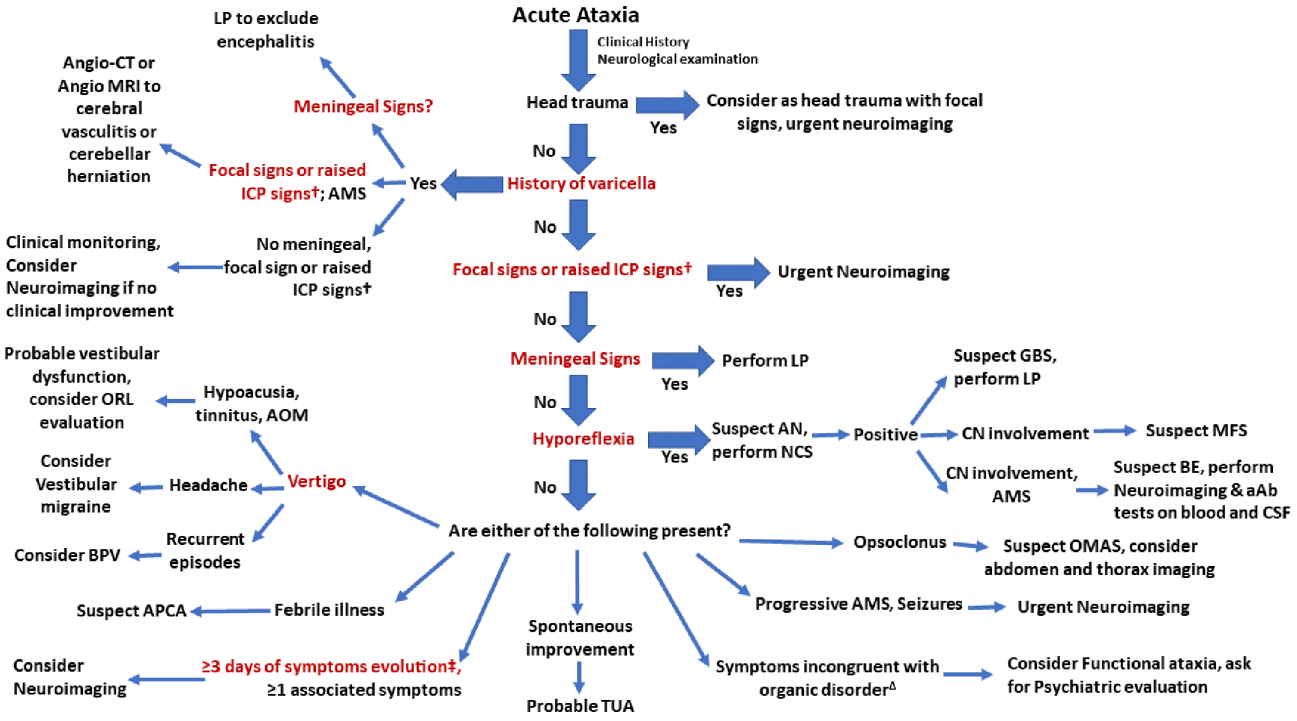

Figure 3 Flow-chart for the diagnostic evaluation of the acutely ataxic child. Signs and symptoms significantly associated with a higher risk of CUNP in our model are marked in red. †Raised ICP signs: papilledema, ophthalmoplegia, mydriasis, vomiting without nausea. ‡The cut-off of 3 days is indicated basing on the risk stratification model proposed by Rudloe *et al*.[6] ΔEvidence of suggestibility, distractibility and/or variability of symptoms or inconsistent disability. aAB, autoantibodies; AMS, altered mental status; AN, acute neuropathy; AOM, acute otitis media; APCA, acute post-infectious cerebellar ataxia; BE, Bickerstaff encephalitis; CSF, cerebrospinal fluid; CN, cranial nerve; GBS, Guillain Barré Syndrome; ICP, intracranial pressure; LP, lumbar puncture; MFS, Miller Fisher syndrome; NCS, nerve conduction study; OMAS, opsoclonus-myoclonus-ataxia syndrome; ORL, otorhinolaryngology; TUA, transient undiagnosed ataxia.

the presence of other cerebellar signs was associated with a lower frequency of CSF alterations (p=0.002).

DISCUSSION

AA epidemiology

Few data exist about the real incidence and prevalence of AA in childhood.[4] Our study represents the first, large multicentre study on AA conducted in a paediatric emergency setting, showing a frequency of 0.02% of all emergency department attendances, similar to previous PED-based studies.[5 6] Figure 2 shows the differences in frequency of the main causes of AA between our cohort and those previously reported.

APCA was the most frequent aetiology encountered. As previously described in the Italian milieu,[10] VZV is the predominantly involved infectious agent, probably because of the still poor, fluctuating and heterogeneous vaccination coverage all over the country (online supplementary figure S3[11]). Given that the spread of VZV vaccination is expected to diminish the incidence of VZV complications (including APCA[12]), the diagnostic approach to AA should be re-evaluated in light of an evolving immunisation context, as already suggested in the USA.[6]

Probably, the inclusion of children with up to 30 days of symptom evolution explains the relatively high frequency of CNS tumours and the low frequency of acute intoxications, compared with previous reports[5–8] (figure 2). Of note, almost one-third of acute intoxications were due to substance abuse, suggesting that it should always be suspected in otherwise unexplained AA, even in a paediatric setting.

In our cohort, we noted a high occurrence of vestibular migraine and BPV, almost absent in the previous studies.[5–8] The relationship between these two entities is yet unclear,[13] but they may be an increasingly recognised cause of AA in the future. Also AN was frequently encountered in our series (8.3%), with 36 cases of Guillain-Barré syndrome, suggesting that AA is a common presentation of this condition in children.

Noteworthy, a definite aetiology was not identified in a considerable proportion of patients with transient symptoms. The frequency of undiagnosed cases was highly variable in the previous studies, ranging from 9.2% to apparently no cases[5 7 8] The lack of undiagnosed cases in the smaller cohorts is largely imputable to chance. In addition, other factors probably play a role, such as the study setting (the higher the care level, the higher the proportion of undiagnosed patients due to the selection of rare causes) or the criteria applied for clinical diagnosis of several entities, namely APCA or psychogenic disorders (the stricter the criteria, the larger the number of unexplained cases).

Risk factors for urgent conditions

The second aim of our study was to determine the clinical features predictive of an underlying pathology requiring early intervention. Given its self-limiting evolution and good outcome, APCA was not considered as a CUNP. According to our model, children with a recent history of varicella or vertigo can be allocated to a low-risk category, these two features, respectively, pointing to VZV-related APCA and vestibular dysfunction. As expected, the presence of focal or meningeal signs, hyporeflexia and ophthalmoplegia is strongly suggestive of CUNP. A longer duration of symptoms before PED evaluation emerged as a significant risk factor for CUNP, accordingly

with the risk stratification model proposed by Rudloe *et al*[6] for identifying patients with intracranial pathology. This is probably explained by the insidious onset of some severe ataxia causes, such as brain tumours, showing how the emergency health service often intercepts patients with subacute and severe pathologies that require a high level of suspicion to avoid misdiagnosis. As cited above, papilloedema, a clear indication for neuroimaging, was not included in our model. Interestingly, extremely concerning findings such as consciousness impairment and seizures, despite their positive association with CUNP, did not reach significance. Several reasons can explain this finding. First, CUNP (although it is of interest for emergency physicians) is a broad and heterogeneous category, only defined by the urgent characteristics. Many urgent conditions presenting with ataxia do not cause consciousness impairment (eg, AN, posterior fossa tumours), and many non-urgent conditions (eg, migraine or functional disorders) may present with (or may mimic) an altered mental status. This weakens the association between consciousness impairment and CUNP. With regard to seizures, they are an infrequent event in patients with ataxia, its frequency probably being insufficient to reach significance in the multiple regression analysis. With the aim of a real-life application of our findings, we suggest that any child with a symptom or sign with an OR >1 should be appropriately investigated. On this basis, we developed a flow chart of a diagnostic approach to evaluating a child with AA (figure 3).

Diagnostic investigations in a child with ataxia

As expected, neuroimaging alterations are significantly more frequently found in patients with signs of CNS involvement (focal neurological signs, consciousness impairment, papilloedema, ophthalmoplegia, head tilt), but also in patients with longer evolution of symptoms. Noteworthy, most patients without CUNP underwent neuroimaging studies, configuring an overuse of diagnostic testing possibly exposing patients to unnecessary risks.[14] Hyporeflexia appears to be the most suggestive finding of AN.

Study limitations

The present study suffers from some limitations, mostly related to its retrospective nature. First, the accuracy of data is dependent on the physician's experience. In our study, neurological evaluation was performed by emergency physicians, who are not expected to be experienced in neurological assessment. Although neurologist consultation was requested in many cases (65.6%), the robustness of clinical assessment could have been partially limited. In addition, some clinical information may have not been reported correctly on emergency department records. Other limitations are due to exposure to some selection biases. In fact, some AA cases could have been misdiagnosed, underestimating their prevalence. By contrast, given the tertiary nature of most participating centres, the frequency of AA could have been overestimated at this care level. Finally, the CUNP category has been designed aiming to help clinicians in identifying patients with urgent needs, which is a primary concern in an emergency setting. However, it is not informative about the risk of a specific underlying condition.

CONCLUSIONS

Our study demonstrates that AA is an infrequent but concerning neurological emergency in childhood. The most frequent cause is APCA, but CUNPs account for over a third of the AA cases encountered in the PED. Focal and meningeal signs, hyporeflexia and ophthalmoplegia, as well as longer duration of symptoms, are the most consistent 'red flags' of a severe underlying pathology. Other features with less robust association with CUNP, such as seizures or consciousness impairment, should be seriously taken into account during AA evaluation.

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Acknowledgements We are grateful to the Società Italiana di Neurologia Pediatrica (SINP) for intellectual support to the study as part of the initiatives promoted by the SINP Study Group on Neurological Emergencies.

Contributors UR and GG conceptualised and designed the study, coordinated and supervised the data collection, interpreted the data, drafted the initial manuscript, provided critical review and revision of the manuscript, and wrote the final manuscript. NV performed the statistical analysis, interpreted the data, contributed to conceptualising the study and participated in the design of the study, and reviewed and revised the initial manuscript. ARe and PP contributed to conceptualising the study and participated in the design of the study, interpreted the data, and reviewed and revised the initial manuscript. CB, AS, GB, LC, DMC, SS, SG, FM, RF, AV, EB, CV, LDD, RM, SMas, LM, TF, AR, CG, SMar, CDP, LP, AFU and RR contributed to conceptualising the study, collected the data, and reviewed and revised the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The institutional ethics committee of each participating hospital approved the study protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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Acute hyperkinetic movement disorders in Italian paediatric emergency departments

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Received 9 November 2017
Revised 13 February 2018
Accepted 23 February 2018
Published Online First 8 March 2018

ABSTRACT

Introduction Limited data exist on epidemiology, clinical presentation and management of acute hyperkinetic movement disorders (AHMD) in paediatric emergency departments (pED).

Methods We retrospectively analysed a case series of 256 children (aged 2 months to 17 years) presenting with AHMD to the pEDs of six Italian tertiary care hospitals over a 2-year period (January 2012 to December 2013).

Results The most common type of AHMD was tics (44.5%), followed by tremors (21.1%), chorea (13.7%), dystonia (10.2%), myoclonus (6.3%) and stereotypies (4.3%). Neuropsychiatric disorders (including tic disorders, psychogenic movement disorders and idiopathic stereotypies) were the most represented cause (51.2%). Inflammatory conditions (infectious and immune-mediated neurological disorders) accounted for 17.6% of the cases whereas non-inflammatory disorders (including drug-induced AHMDs, genetic/metabolic diseases, paroxysmal non-epileptic movements and idiopathic AHMDs) accounted for 31.2%. Neuropsychiatric disorders prevailed among preschoolers and schoolers (51.9% and 25.2%, respectively), non-inflammatory disorders were more frequent in infants and toddlers (63.8%), whereas inflammatory conditions were more often encountered among schoolers (73.3%). In 5 out of 36 Sydenham's chorea (SC) cases, tics were the presentation symptom on admission to emergency department (ED), highlighting the difficulties in early diagnosis of SC. Inflammatory disorders were associated with a longer hospital stay and a greater need of neuroimaging test compared with other disorders.

Conclusions This study provides the first large sample of paediatric patients presenting to the ED for AHMDs, helping to elucidate the epidemiology, aetiology and clinical presentation of these disorders.

What is already known on this topic?

- Differential diagnosis of acute-onset hyperkinetic movement disorders is broad, with both inflammatory and non-inflammatory conditions reported as the most common aetiology.
- Psychogenic movement disorders account for a considerable proportion of acute movement disorders in childhood.
- Children are more prone than adults to extrapyramidal effects of antidopaminergic drugs.

What this study adds?

- Tics are the most frequently encountered movement disorder in the paediatric emergency department (44.5% in our cohort).
- Neuropsychiatric disorders are the leading cause of admission to emergency department for acute-onset hyperkinetic movement disorders.
- Autoimmune and inflammatory disorders are the most demanding forms regarding neuroimaging need and days of hospitalisation.

INTRODUCTION

Movement disorders (MD) are defined as either an excess (hyperkinesias) or a paucity (hypokinesias) of voluntary and automatic movements.[1 2] Hyperkinetic MDs can be further classified into tics, chorea, dystonia, tremor, myoclonus and stereotypies.[3 4] While most MDs are chronic neurological disturbances, some can develop acutely.[5] Since several MDs may be treatable, timely recognition and diagnosis is crucial.[6]

MDs are an uncommon cause of admission in paediatric emergency department (pED), almost exclusively presenting as acute hyperkinetic movement disorders (AHMD). The literature on AHMDs is very limited, with most of the studies being based on outpatient clinic and specialist neurology services data[7 8] or focusing on only one type of MD, such as dystonia.[9]

Paediatricians must differentiate benign forms from conditions potentially resulting in significant morbidity.

The aim of this study was to improve knowledge about epidemiology, clinical presentation and aetiology of AHMDs as a chief complaint in children presenting to pEDs, in order to provide support

To cite: Raucci U, Parisi P, Vanacore N, *et al*. *Arch Dis Child* 2018;**103**:790–794.

for the clinical management to emergency and primary care physicians.

MATERIALS AND METHODS

Study setting and participants

This retrospective, multicentre case series was collected in the pED of six Italian hospitals (Turin, Padua, Genoa, Florence, Rome and Catania).

Patients aged 2 months to 17 years presenting from January 2012 to December 2013 with a primary complaint of AHMD were systematically included. Gait disorders related to unilateral weakness, vestibular dysfunction, ataxia, pain and epilepsy were excluded. Moreover, we excluded patients already diagnosed with conditions causing AHMDs.

Data collection and definitions

The clinical records were extracted from emergency department (ED) databases and analysed. The following data were collected: age, gender, triage code, any prior disease, main symptoms, specialist consultations, neuroimaging studies (CT and MRI), other diagnostic tests, final diagnosis, hospital admission and duration of hospitalisation, where applicable.

AHMDs were classified basing on the phenomenology dominating the clinical presentation on pED admission, according to standard clinical classification criteria in childhood.[3 4]

Patients were subdivided into four age classes: (1) <3 years (infants/toddlers); (2) 3–6 years (preschoolers); (3) 6–12 years (schoolers); (4) >12 years (teenagers).

The following triage codes were used: red (highly critical conditions), yellow (very urgent), green (urgent), white (non-urgent).

Based on discharge diagnosis, patients were classified into three diagnostic categories previously established according to similar studies[7 8]: (1) neuropsychiatric disorders (NPD) (tics, stereotypies and psychogenic movement disorders (PMD)); (2) inflammatory disorders (ID) (Sydenham's chorea (SC), paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), autoimmune encephalitis and opsoclonus-myoclonus syndrome (OMS)); (3) non-inflammatory disorders (NID) (drug-induced AHMDs, metabolic/genetic disorders, tumours, paroxysmal non-epileptic movements, physiological or essential tremors).

Statistical analysis

We described the clinical and demographic features both of the overall sample and of the three diagnostic subgroups. The three groups were compared by means of the X^2 test for categorical variables and Student's t-test for continuous variables after reviewing for appropriateness. The statistical significance was set at $p<0.05$. SPSS software (V.24.0) was used to perform all statistical analyses.

RESULTS

Main clinical and demographic features

During the 2-year study period, among a total of 432.033 children admitted to the pEDs of the six hospitals involved, 256 subjects presented with AHMDs (5.9 visits per 10.000 ED attendances). Of the 256 patients, 149 were male (58.2%) and 107 were female (41.8%, M:F ratio=1.4), with a mean age of 76.6±50.7 months (range 2 months to 17 years). The age distribution was the following: infants/toddlers 27.3%; preschoolers 16.8%; schoolers 46.1%; teenagers 9.8%. On admission, 52 patients (20.3%) received a yellow code, 182 patients (71.1%) a green code and 22 patients (8.6%) a white one. Up to 204 patients (79.7%) were previously healthy, 25 children (9.8%) had a pre-existing neurological disease (migraine, epilepsy, cerebral palsy), 16 (6.3%) had a prior psychiatric disorder and 11 children (4.3%) were affected by other chronic disturbances.

With regard to pharmacological treatment, 17 patients (5.9%) were on neuroleptic or anticonvulsant drugs, 3 (1.2%) on antihistaminics and 5 (2.0%) on antiemetics.

Table 1 summarises the main demographic and clinical features of our sample.

Clinical presentation and final diagnosis

The most common AHMD was tics, seen in 114 patients (44.5%); tremors were reported in 54 patients (21.1%), chorea in 35 (13.7%), dystonia in 26 (10.2%), myoclonus in 16 (6.3%) and stereotypies in 11 (4.3%, table 1). At the time of the first clinical evaluation, 22.9% of patients had a normal neurological examination, while in 77.1% the presence of the AHMD referred at the time of triage was confirmed.

The frequency of the three AHMD subgroups significantly varied among the different age classes. Particularly, the IDs prevailed among schoolers (73.3%), the NIDs were more frequent in infants/toddlers (63.8%), while NPDs occurred more frequently both in schoolers and preschoolers (respectively 51.9% and 25.2%, table 1).

Table 2 summarises the clinical presentation and final diagnosis of our patients, in comparison with the cohorts described in the two previously published similar studies.[7 8]

Neuropsychiatric disorders

NPDs were the most frequent cause of AHMDs, identified in 131 (51.2%) patients, mostly simple or complex tic disorders (110 children), followed by PMDs (16) and stereotypies (5).

Inflammatory conditions

IDs were diagnosed in 45 patients (17.6%), Sydenham's was the only form of chorea encountered, diagnosed in 36 patients (14.2%). Remarkably, in 16 of them, a cardiac involvement was identified (44.4%). In addition, three cases of autoimmune encephalitis, two OMS (both secondary to neuroblastoma) and four cases of PANDAS were identified (table 2).

Non-inflammatory conditions

NIDs represented 31.2% (n=80) of AHMDs. Four patients had a metabolic/genetic disorder (two ceroidolipofuscinosis, one mucopolisacaridosis and one paroxysmal kinesigenic dystonia). Drug-induced AHMDs were documented in seven patients (2.7%), related to domperidone in three cases, to desloratadine in two, and to metoclopramide and haloperidol in the remaining two. In all of the children, complete remission occurred after treatment discontinuation.

In one patient, a pilocytic astrocytoma of basal ganglia was diagnosed. In 52 patients (20.3%), paroxysmal non-epileptic movements and essential or physiological tremors were diagnosed. Particularly, eight cases were classified as benign myoclonus of infancy and seven patients showed physiological tremors related to fever.

DISCUSSION

To date, few data are available about epidemiology, clinical phenotype and aetiology of children admitted to pED for AHMDs. Recently, two studies[7 8] investigated acute MDs in children; results were limited by the small cohort size and by

Table 1 Main demographic and clinical features of our sample

	Total n=256	Inflammatory conditions n=45 (17.6%)	Non-inflammatory conditions n=80 (31.2%)	Neuropsychiatric conditions n=131 (51.2%)	P value
Sex					
Female	107 (41.8%)	22 (48.9%)	46 (57.5%)	81 (61.8%)	NS (0.312)
Male	149 (58.2%)	23 (51.1%)	34 (42.5%)	50 (38.2%)	
Age (months; mean±SD (median))	76.6±50.7 (82.5)	99.9±31.8 (106)	47.8±57.6 (14.5)	86.2±43.5 (86)	0.0001
Age group					0.001
Infants/toddlers	70 (27.3%)	2 (4.4%)	51 (63.8%)	17 (13%)	
Preschoolers	43 (16.8%)	6 (13.3%)	4 (5%)	33 (25.2%)	
Schoolers	118 (46.1%)	33 (73.3%)	17 (21.3%)	68 (51.9%)	
Teenagers	25 (9.8%)	4 (8.9%)	8 (10%)	13 (9.9%)	
Triage code					0.007
White	22 (8.6%)	2 (4.4%)	3 (3.8%)	17 (13.0%)	
Green	182 (71.1%)	32 (71.1%)	53 (66.3%)	97 (74.0%)	
Yellow	52 (20.3)	11 (24.4%)	24 (30.0%)	17 (13.0%)	
Red	0	0	0	0	
MD type					0.0001
Tics	114 (44.5%)	8 (17.8%)	6 (7.5%)	100 (63%)	
Chorea	35 (13.7%)	31 (68.9%)	0	4 (3.1%)	
Tremors	54 (21.1%)	1 (2.2%)	38 (47.5%)	15 (11.5)	
Dystonia	26 (10.2%)	3 (6.7%)	20 (25%)	3 (2.3%)	
Myoclonus	16 (6.3%)	2 (4.4%)	12 (15%)	2 (4.4%)	
Stereotypies	11 (4.3%)	0	4 (5%)	7 (5.3%)	
Pre-existing disease					0.056
Not present	204 (79.7%)	39 (86.7%)	60 (75%)	105 (80.2%)	
Neurologic	25 (9.8%)	2 (4.4%)	14 (17.5%)	9 (6.9%)	
Psychiatric	16 (6.3%)	1 (2.2%)	3 (3.8%)	12 (9.2%)	
Other	11 (4.3%)	3 (6.7%)	3 (3.8%)	5 (3.8%)	
Specialist consultation	173 (67%)	32 (71%)	56 (70%)	85 (64.9%)	NS (0.63)
Neuroimaging					0.0001
Not done	202 (78.9%)	16 (35.6%)	66 (82.5%)	120 (91.6%)	
CT	8 (3.1%)	5 (11.1%)	1 (1.3%)	2 (1.5%)	
MRI	35 (13.7%)	20 (44.4%)	8 (10.0%)	7 (5.3%)	
CT plus MRI	11 (4.3%)	4 (8.9%)	5 (6.3%)	2 (1.5%)	
Outcome					
Discharged	168 (65.6%)	6 (13.3%)	56 (70.0%)	106 (80.9%)	0.0001
Hospitalised	88 (34.4%)	39 (86.7%)	24 (30.0%)	25 (19.1%)	
Length of hospital stay (days; mean±SD (median))	9.1±13.1 (6)	14±18.2 (10)	5.2±3.8 (4.5)	5.2±3.8 (4)	0.006

The different frequencies are compared by means of X^2 test.
MD, movement disorder; NS, not significant.

the study settings, referring mainly to child neurology services. Our study represents the first large, multicentre case series on AHMDs collected in pED.

The range of disorders causing AHMD is broad and the first diagnostic pitfall is the correct classification of the MD.[3] In fact, it can be difficult in children (especially in younger patients), also because of the overlapping features of different MDs.

The frequency of the different AHMDs in our series varied from previously reported data, likely because of the different setting of recruitment and the different inclusion criteria.

With regard to conditions causing AHMDs, NPDs were the most common aetiology, probably because of the inclusions of tic disorders in this subgroup, different from the previous studies where tics were excluded.[7 8]

Consequently, NPDs prevailed among patients aged 3–12 years, reflecting the high prevalence of tics during primary school.[10]

The different inclusion criteria are the consequence of the different setting of recruitment and explain the different composition of our series from those previously described.

IDs represented the second subgroup of AHMD causes. Particularly, SC represented the most common condition. Despite its lowering incidence in developed countries, SC remains the most common cause of chorea in children worldwide.[11 12] Consistent with published data,[11 13] girls were more often affected (F:M=1.6:1). The remarkable frequency of cardiac involvement highlights the importance of its prompt exclusion in any patient with acute-onset chorea.[6] Of note, in 5 out of 36 SC cases, tics were the presentation symptom on admission to pED. In fact, differential diagnosis between SC and tic disorders related to streptococcal infections can be difficult, particularly at onset.[14] On one hand, many patients with SC also have tics or psychological symptoms[6]; on the other hand, clinical distinction between

Table 2 Clinical presentation and final diagnosis of patients described in this study, compared with those reported by Dale *et al* and Goraya

	Dale *et al*[8]	Goraya[7]	Present study (2017)
Patients	52	92	256
Setting	Paediatric movement disorders service	Paediatric neurology service	Paediatric emergency department
Age	2 months to 15 years	5 days to 15 years	2 months to 17 years
Gender (M:F, ratio)	21:31; 0.67	63:29; 2.17	149:107; 1.39
Presenting AMD	**Hyperkinetic (n=59)**	**Hyperkinetic (n=92)**	**Hyperkinetic (n=256)**
	Tics (NC) Chorea (n=20) Dystonia (n=17) Tremors (n=12) Myoclonus (n=10)	Choreoathetosis (n=20) Dystonia (n=21) Tremors (n=15) Myoclonus (n=25) Tics (n=2) Tetany (n=5) Tetanus (n=2)	Tics (n=114) Chorea (n=35) Tremors (n=53) Dystonia (n=27) Myoclonus (n=16) Stereotypies (n=11)
	Hypokinetic (n=10)	**Hypokinetic (n=3)**	**Hypokinetic**
	Parkinsonism (n=10)	Parkinsonism (n=3)	NC
Aetiologies	**Inflammatory (n=22)**	**Inflammatory (n=32)**	**Inflammatory (n=45)**
	NMDA-R encephalitis (n=5) OMS (n=4) SC (n=3) SLE (n=3) ANE (n=3) Other encephalitis (n=3)	Encephalitis (n=11) OMS (n=7) SC (n=6) ADEM (n=3) Tetanus (n=3) Postinfectious tics (n=2) NMDA-R encephalitis (n=1)	AE including NMDA-R (n=3) SC (n=36) PANDAS (n=4) OMS (n=2)
	Non-inflammatory (n=18)	**Non-inflammatory (n=56)**	**Non-inflammatory (n=80)**
	Drug induced (n=7) Postpump chorea (n=5) Metabolic (n=3) Vascular (n=2)	Metabolic/nutritional (n=25) Physiological (n=17) Drug/toxins (n=4) Vascular (n=1) Traumatic brain injury (n=2) Benign paroxysmal torticollis (n=2) PAID (n=2) Cryptogenic (n=2) Ataxia-telangiectasia (n=1)	Primary dystonia (n=10) Physiological and essential tremors (n=30) Metabolic diseases (n=4) Undiagnosed myoclonus (n=6) Drug/toxins (n=7) PNED* (n=22) Cerebral tumour (n=1, pilocytic astrocytoma)
	Psychogenic (n=12)	**Psychogenic (n=4)**	**Neuropsychiatric (n=131)**
			Tic disorders (n=110) Isolated stereotypies (n=5) Psychogenic (n=16)

*PNED: benign myoclonus of infancy n=8, hypnic myoclonus n=1, jitteriness n=1, paroxysmal tonic upgaze n=1, Sandifer syndrome n=2, febrile myoclonus n=1, paroxysmal shuddering n=1, head nodding n=1, unspecified PNED n=6.
ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; AMD, acute movement disorder; ANE, acute necrotising encephalopathy; NC, not collected; NMDA-R, N-methyl-D-aspartate receptor; OMS, opsoclonus-myoclonus syndrome; PAID, paroxysmal autonomic instability with dystonia; PANDAS, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PNED, paroxysmal non-epileptic disorder; SC, Sydenham's chorea; SLE, systemic lupus erythematosus.

chorea and complex motor tics could be difficult in an emergency setting. Consequently, SC should always be considered in children presenting with acute-onset tics.

Of note, among 114 children presenting with acute-onset tics, only four fulfilled PANDAS diagnostic criteria. This finding suggests that PANDAS is an uncommon cause of acute-onset tics, according to previous reports.[15] Comprehensively, IDs represented the most concerning forms, requiring significantly longer hospitalisations and a wider use of neuroimaging.

Referring to NIDs, drug adverse reactions were a rare cause of AHMDs, in contrast with adult-based studies.[5] Neuroleptic drugs are a leading cause of iatrogenic MDs, with an increased risk in younger patients.[16 17] We encountered just one case of neuroleptic-related MD, probably because of the wider use of second-generation antipsychotics, which show a better tolerability profile, in the last years.[18] Similarly, although dystonic reactions have been frequently reported in children taking metoclopramide,[19] we found just one case of metoclopramide-induced dystonia. This low incidence in our series could be explained by the significant reduction of metoclopramide use in childhood since 2004, when in Italy its prescription was not recommended under the age of 16.

In contrast with literature data,[7 8] in our cohort no cases of postpump chorea were observed. This is obvious considering that postpump chorea only occurs in hospitalised patients undergoing cardiopulmonary bypass.[20]

The present study suffers from some limitations. First, AHMD diagnosis has been made by emergency physicians, who are not expected to be experienced in AHMD assessment. Although neurologist consultation was requested for a non-negligible group of patients (40%), the robustness of clinical diagnosis could have been partially limited. Other major limitations reside in the retrospective nature of the study and its exposure to some selection biases. In fact, some AHMDs could have been misdiagnosed, underestimating the prevalence of these conditions. Conversely, their prevalence could have been overestimated at a tertiary care level. Finally, some data (eg, time before symptoms onset) have not been collected because they were lacking from ED records. These factors are expected to partially limit the validity of our conclusions.

CONCLUSION

To our knowledge, this is the first study analysing AHMD presentation in pEDs, producing the most representative cohort available so far.

We highlighted the importance of NPDs as a leading cause of AHMD in children; conversely, the spread of atypical neuroleptics could explain the low prevalence of antipsychotic-induced AHMDs. Finally, IDs represent the most demanding forms in terms of diagnostic and therapeutic efforts. Given that most of the inflammatory AHMDs result from treatable conditions, a high level of suspicion is required to early recognise these potentially harmful disorders. Moreover, differentiating SC and tic disorders, especially secondary to streptococcal infections, can prove challenging, particularly at onset.

In conclusion, AHMDs are still a diagnostic challenge, especially in children, and further prospective studies are needed to provide robust evidence to guide their management.

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Acknowledgements We are grateful to the Italian Pediatric Neurology Society (Società Italiana di Neurologia Pediatrica-SINP) for intellectual support to the study as part of the initiatives promoted by the SINP Study Group on Neurological Emergencies.

Contributors UR and PP conceptualised and designed the study, coordinated and supervised data collection, interpreted the data, drafted the initial manuscript, provided critical review and revision of the manuscript, and wrote the final manuscript. NV performed statistical analysis, interpreted the data, contributed to conceptualising the study and participated in the design of the study, and reviewed and revised the initial manuscript. GG and VF contributed to conceptualising the study and participated in the design of the study, collected and interpreted the data, and reviewed and revised the initial manuscript. CB, AP, LC, AS, RF, AC, AFU, RT, AM, SS, PP, MM, FM, LI and MFP contributed to conceptualising the study, collected the data, and reviewed and revised the initial manuscript. AR contributed to conceptualising the study, provided study supervision, and reviewed and revised the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

Competing interests None declared.

Ethics approval The study was approved by the Local Ethical Committee of each participating centre.

Provenance and peer review Not commissioned; externally peer reviewed.

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Review of the new APLS guideline (2022): Management of the convulsing child

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Received 7 October 2021
Accepted 7 June 2022
Published Online First 22 June 2022

To cite: Bacon M, Appleton R, Bangalore H, *et al*. *Arch Dis Child Educ Pract Ed* 2023;**108**:43–48.

BACKGROUND

Convulsive status epilepticus (CSE) (box 1) is the most common childhood medical neurological emergency, with an incidence of approximately 20 per 100 000 per year in the developed world.[1 2]

CSE can be fatal, but mortality is lower in children than in adults—at about 2%–7%.[3]

Adverse neurological consequences following CSE consist of subsequent epilepsy, motor deficits, and learning and behavioural difficulties. The main determinant of outcome is the underlying aetiology (box 2). There is low risk of morbidity and mortality in children with unprovoked/prolonged febrile CSE. This risk increases significantly in cases with structural or genetic causes.

INFORMATION ABOUT THE CURRENT GUIDELINE

The Advanced Life Support Group (ALSG) who run the Advanced Paediatric Life Support (APLS) programme provides internationally renowned guidance on the emergency management of common childhood emergencies. The APLS programme is also endorsed by the Royal College of Paediatrics and Child Health. Together, a professional working group consisting of members of the ALSG, British Paediatric Neurology Association, Paediatric Intensive Care Unit, Royal College of Emergency Medicine, epilepsy nurses, ambulance representatives, pharmacists and a parent representative worked collaboratively to review and update the emergency management for generalised CSE in children aged 1 month old to 18 years old (see figure 1).

Management of non-CSE and super refractory status epilepticus are beyond the scope of this guideline. In certain circumstances, a child may have an individual emergency care plan which supersedes this guideline.

PREVIOUS GUIDELINE

The first APLS manual was published in 1997 and last updated in 2016.[4] Since then there have been significant changes in practice observed around the world on how to manage the convulsing child based on more recent research. This review aims to summarise key updates which will feature in the upcoming APLS seventh edition.

WHAT CAN I CONTINUE TO DO AS BEFORE?

Principles of treatment

Should the convulsion continue beyond t1 (5 min) there is a greater chance of it lasting longer than 30 min.[1]

Beyond this time point, it is unknown when exactly brain injury may occur and the longer the duration of the convulsion the harder it is to terminate. Together with effective resuscitation, early recognition and treatment of ongoing convulsion may affect outcome.

The aims of acute treatment are summarised in box 3.

Primary assessment and resuscitation

- It is important to obtain a brief history of events, current medication and allergies. A focused physical examination will help

Box 1 Definition of status epilepticus

Status epilepticus is a condition resulting either from failure of the mechanism responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point $t_{1\ at\ 5\ min}$).

It is a condition, which can have long-term consequences (after time point $t_{2\ after\ 30\ min}$) including neuronal death, neuronal injury and alteration of neuronal networks, depending on the type and duration of seizures.

identify the underlying cause. Simultaneously, acute resuscitation must be undertaken.

- The approach to resuscitation remains the same as for any seriously unwell child. Treatment of the convulsion should be assessed and treated only after the Airway, Breathing, Circulation, Disability (ABCD) have been assessed and managed.[4]

WHAT DO I NEED TO KNOW?

Emergency treatment of a convulsion

- The updated medical algorithm will continue to be provided in four steps, however with different time intervals. The new time intervals reflect current pharmacological understanding that allows enough time for treatment effect.
- There is an emphasis that while completing a step, the team should continually reassess ABCD and get ready for the next step to avoid any delays in treatment.
- Antiseizure medication doses are based on recommended dosing as per the *British National Formulary* for children and/or the most current available evidence.[5]

WHAT SHOULD I START DOING?

First-line treatment

Step 1

Benzodiazepines (BDZ) remain the first-line antiseizure medication of choice. The fact that BDZ can be given quickly and have a rapid onset of action supports their use as first line. There are also time-dependent GABA receptor changes that result in pharmacoresistance to BDZ, further supporting its early use. Studies have shown that the time from BDZ administration to seizure termination is between 2 min and 10 min.[6 7]

Respiratory depression is the most common and most clinically relevant side effect. The frequency of this adverse event is observed in up to 18% of children.[5 6]

The choice of BDZ will vary depending on local practices and availability.

In the UK, the BDZ readily available are buccal midazolam, rectal diazepam and intravenous lorazepam. Buccal midazolam is the least invasive option, can be administered quickly and more socially acceptable. From a practical perspective, the BDZ that can be given the quickest should be considered the BDZ of choice.

Given that most convulsions occur prehospital, a trained carer or paramedic is empowered to administer first-line treatment to avoid delay in initiating treatment.

Box 2 Common causes of status epilepticus

Known (ie, symptomatic)
Structural: Intracranial tumour, cerebrovascular disease, head injury, cortical dysplasia
Infectious: CNS infection (meningitis, encephalitis), tuberculosis, cerebral malaria
Metabolic: Metabolic disturbance (electrolyte imbalance, glucose imbalance, organ failure, etc), metabolic disorders, anoxic injury, mitochondrial disorders
Toxicity or drug-related: Low or high level of antiseizure medication, withdrawal of antiseizure medication, other drug/alcohol overdose, neurotoxins and poisons
Inflammatory: Autoimmune disorders, neurocutaneous disorders
Genetic: Dravet syndrome, ring chromosome 20, Angelman syndrome, fragile X syndrome, Rett syndrome, trisomy 21
Unknown (ie, cryptogenic)

Step 2

It is common practice to administer a second dose of BDZ if the convulsion has not stopped after 5 min from the first dose. However, the evidence to support this practice is limited.[2 6]

The risk of respiratory depression increases if more than two doses of BDZ are administered.[2 6] For this reason, the second dose of BDZ should be given in the presence of a trained health professional.

The main rationale for this step is that establishing intravenous/intraosseous access may invariably take time and thus a second dose of BDZ is commonly considered better than no treatment.[6]

Any prehospital doses should be counted and no more than two doses of BDZ administered.

The team should continuously monitor and support the child's airway and breathing.

Summary of first-line BDZ available in UK are provided in table 1.

Second-line treatment

Step 3

Levetiracetam, phenytoin, fosphenytoin, phenobarbital and sodium valproate are all considered to be equally effective second-line treatment for managing a convulsion that has not responded to initial BDZ.[8–10]

Intravenous levetiracetam is now considered the second-line antiseizure medication of choice in the UK.

One of several advantages of giving levetiracetam is that it can be given to any convulsing child without any contraindications and few side effects. The reason the recommended loading dose of levetiracetam is 40 mg/kg is to provide a margin of safety to those already on levetiracetam maintenance. It is easy to prepare, can

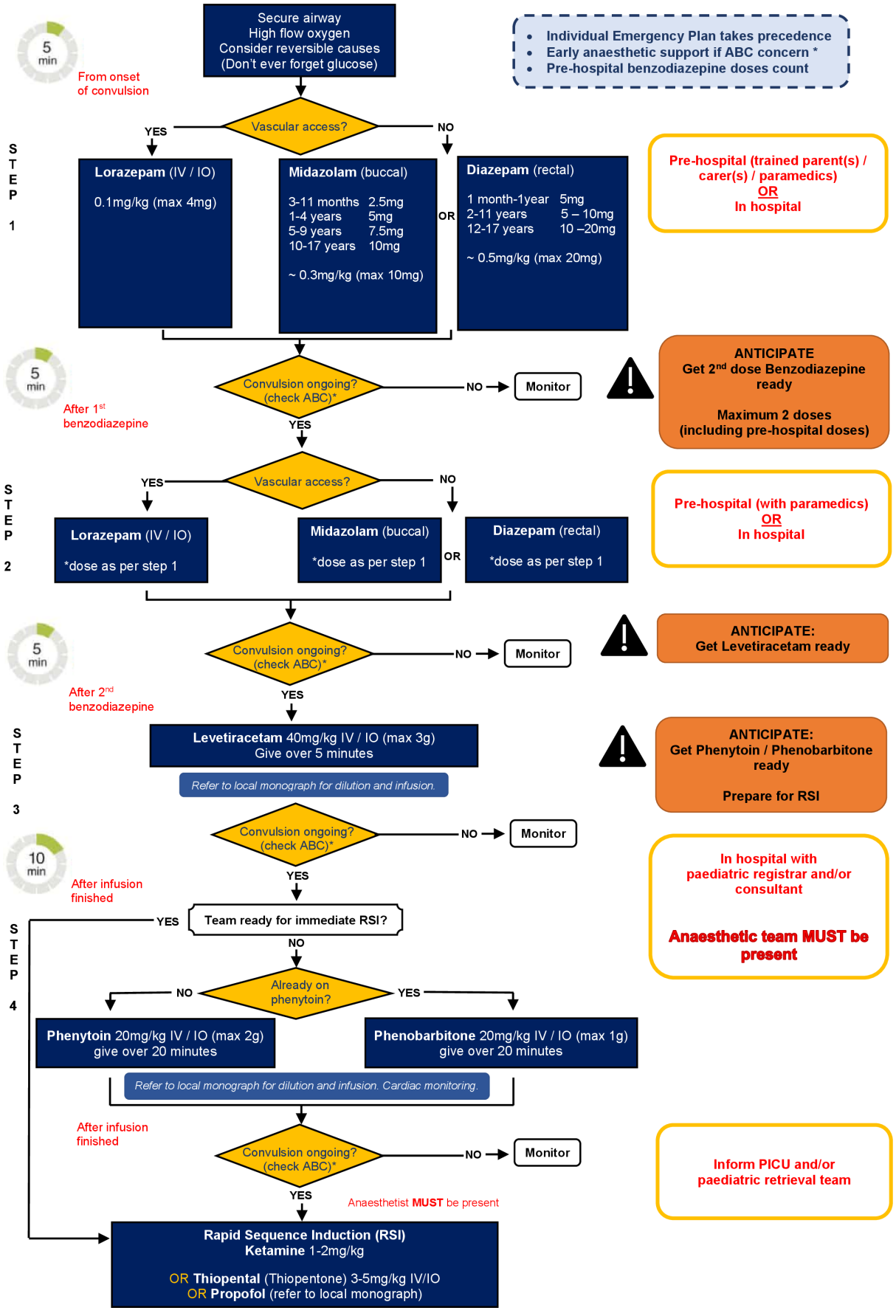

Figure 1 New Advanced Paediatric Life Support (APLS) algorithm on management of the convulsing child. ABC, airway, breathing, circulation; IV/IO, intravenous/intraosseous; RSI, rapid sequence induction; PICU, paediatric intensive care unit.

Box 3 Aims for acute treatment

- Support airway, breathing, circulation (ABC)
- Identify and treat life-threatening causes
- Termination of the convulsion
- Prevent reoccurrence of the convulsion
- Reduce risk of associated mortality and morbidity
- Avoid admission to intensive care

be given over 5 min and does not require any specific monitoring.

Step 4

At this stage of management there is no clear evidence that outlines what the next best step is. The treatment options are limited to either trying a further second-line antiseizure medication or to proceed with rapid sequence induction (RSI) with anaesthesia. The professional working group came to the consensus that a second-line antiseizure medication is a suitable interim step should the team not be ready to do an immediate RSI after step 3.

This decision is largely based on evidence from the ConSEPT Trial.[9] In the trial, 64% of patients who were given phenytoin and then levetiracetam had their seizures stop and 52% who had levetiracetam then phenytoin had their seizures stop without the need for RSI. This implies giving a further antiseizure medication can reduce the need for RSI and admission to intensive care, which is not without its own risks. Furthermore, recent research has shown that the total duration of the convulsion may not be associated with outcomes.[11]

This may be deemed enough to justify the new recommendation however there may be potential risks associated with this change. Although the evidence is suggestive that it may be reasonable to consider another antiseizure medication, the long-term implications of delaying RSI in children who would have perhaps had RSI earlier is unknown. For this reason, the group acknowledges there is a need for prospective surveillance of outcomes of children according to whether RSI was delayed or not as this will help guide future recommendations.

There is also potential that a larger proportion of children may have a delayed RSI because of the challenge teams will have in determining when they feel ready to proceed with RSI. Therefore it will be crucial for teams to anticipate and prepare ahead. It is recommended to concurrently activate a team to prepare for RSI after levetiracetam is administered while a further second line anti-seizure medication (phenytoin/phenobarbitone) is being prepared.

Phenytoin is licensed in the UK for paediatric use. Common side effects of phenytoin are that it can cause arrhythmia, hypotension and more rarely respiratory arrest.[5] Continuous cardiac monitoring is therefore recommended during its administration. If the child is already on maintenance phenytoin then phenobarbital could be considered.

Phenobarbital is licensed for use in the UK and is a reasonable alternative to phenytoin. Phenobarbital is associated with a greater incidence of side effects. Continuous cardiac monitoring is also recommended.

Table 2 provides a summary of the currently recommended second-line antiseizure medication.

There is little to no evidence which suggests one anaesthetic drug is superior to another when managing an ongoing convulsion at this stage. The drug of choice for RSI is largely influenced by the underlying aetiology, pharmacological evidence and the experience of the anaesthetic team. The advantages of ketamine are that it can be given in a haemodynamically unstable child who is not catecholamine deplete unlike thiopentone and propofol which may cause hypotension. In addition, there is rationale for using ketamine (with NMDA receptor antagonist action) in BDZ resistant CSE.

Box 4 Key updates

Steps 1 and 2
- Shorter 5-min interval between benzodiazepine doses.
- Prehospital treatment should count in the number of doses given. A maximum of two doses should be given.

Step 3
- Second-line drug is levetiracetam.

Step 4
- If the team is ready, they should proceed to rapid sequence induction (RSI) with either ketamine, thiopental or propofol.
- If the team is *not* ready either phenytoin or phenobarbital can be given and if immediately after completing this the child is still convulsing the team should proceed to RSI.

CRITICAL APPRAISAL BY RA

The management of any medical emergency should include a clear and unambiguous guideline and algorithm to maximise its clinical usefulness and patient benefit. This updated CSE guideline has four updates. The first is that if the child has received two (or more) doses of BDZ prior to attendance in A&E then no further BDZ will be given. This practice is similar to many European countries but in the USA additional doses of BDZ are permitted. The second is a shorter time interval (5 min, rather than 10 min) between steps 1 and 2 and between steps 2 and 3. Although this is not supported by any evidence, it is consistent with the '5 min' principle which states that an antiseizure medication should be given if a seizure has not stopped spontaneously after 5 min. This is appropriate to try and terminate CSE as soon as possible. The third update reflects important new evidence on the

Table 1 First-line antiseizure medication[2 5]

Drug	Route	Dose	Directions for administration	Pharmacokinetics	Adverse effects
Midazolam	Buccal	0.3 mg/kg (max 10 mg) 3–11 months 2.5 mg 1–4 years 5 mg 5–9 years 7.5 mg 10–17 years 10 mg	Prefilled syringe Administer liquid into the buccal cavity	Time to peak 30 min Plasma half-life 2–5 hours	Respiratory depression Sedation Hypotension
Diazepam	Per rectum	0.5 mg/kg (max 20 mg) 1 month to 1 year 5 mg 2–11 years 5–10 mg 12–17 years 10–20 mg	Prefilled rectal tube Administer liquid into the rectum	Time to peak 10–30 min Plasma half-life initially rapid distribution phase followed by a prolonged terminal elimination phase of 1–2 days	
Lorazepam	Intravenous/ intraosseous	0.1 mg/kg (max 4 mg)	Dilute with an equal volume of sodium chloride 0.9% give over 3–5 min Max. rate 50 µg/kg over 3 min	Time to peak: intravenous unknown Plasma half-life 12–18 hours	

second-line treatment when CSE has persisted after two doses of a BDZ (or the child's personal rescue treatment). Although levetiracetam was shown to be no more effective or better tolerated than phenytoin in three large randomised controlled trials[8–10] that involved over 750 children, its ease of preparation and administration and safety profile in not causing cardiac arrhythmias or severe hypotension, justifies its position as the preferred second-line anticonvulsant. Its rapid rate of infusion also means that another second-line anticonvulsant (phenytoin or phenobarbital) can be given if RSI and ventilatory support are not immediately available: this is the fourth update. The evidence justifying two sequential second-line drugs is far less robust and based on a single randomised controlled trial in which not all randomised children received

Table 2 Second-line antiseizure medication

Medication	Route	Dose	Directions for administration	Pharmacokinetics	Adverse effects	Special considerations
Levetiracetam	Intravenous/ intraosseous	40 mg/kg (max 3 g)	Dilute 1:1 with 0.9% sodium chloride (max 50 mg in 1 mL) and infused over 5 min	Time to peak 15 min Plasma half-life 7±1 hours	Somnolence, dizziness, possible psychosis (low risk)	None
Phenytoin	Intravenous/ intraosseous	20 mg/kg (max 2 g)	Dilute 1:1 with 0.9% sodium chloride to a minimum volume of 20 mL (maximum concentration 10 mg in 1 mL) and infused over 20 min Give through an in-line filter Rate of infusion should be no greater than 1 mg/kg/min (max. 50 mg/min)	Time to peak 30–60 min Plasma half-life 10–15 hours	Hypotension, arrhythmia, bradycardia, respiratory arrest Risk of intravenous extravasation injury	Do not use this if the child is on regular phenytoin Requires cardiac monitoring (ECG and blood pressure) Avoid if underlying cause is toxicity due to the increased risk of dysrhythmia
Phenobarbital	Intravenous/ intraosseous	20 mg/kg (max 1 g)	Dilute 1:1 with 0.9% sodium chloride to a minimum volume of 20 mL (max. 20 mg in 1 mL) and infused over 20 min Rate of infusion should be no greater than 1 mg/kg/min	Time to peak 30 min Plasma half-life 21–75 hours	Respiratory depression, hypotension, sedation	Requires cardiac monitoring (ECG and blood pressure)

two drugs. The use of two second-line drugs will inevitably prolong CSE prior to RSI and intubation. This mandates the importance of strictly adhering to the timelines in the algorithm and obsessional ABCD monitoring of the child throughout CSE. In summary, this updated CSE guideline reflects new evidence and should be commended.

CONCLUSION

CSE is a medical emergency associated with significant morbidity and mortality. Management of CSE is time critical. It is important that any recommendations on the emergency management of CSE in children and young people is regularly reviewed and reflects the emerging new evidence and medications available.

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Contributors The authors had multiple virtual meetings to create consensus for guideline. MB drafted the algorithm and article, other authors reviewed and edited. RA provided an independent critical appraisal of the guideline.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AM: GW Pharma - Personal payment, Honorarium; UCB - Honorarium; LivaNova - support to attend meeting; BPNA - Trustee and Professional Support Officer; Epilepsy Scotland - Co-opted Board Member; Ring 20 - Medical Advisory Board Member. NM: Veriton Supply training materials to NM's organisation including demonstration kits of midazolam oromucosal solution for use in training simulations. RFMC: GW Pharma – personal payment, Honorarium, support to attend meeting, local principal investigator in clinical trials; UCB- Honorarium; Eisai – Honorarium, personal payment, support to attend meetings; Zogenix - Honorarium, personal payment, support to attend meetings; Shares in Rize Medical Cannabis & Life Sciences. RA: Chairman of the Independent Data Safety Monitoring Committee for an NIHR HTA-funded study on mental health in children with epilepsy (the 'MICE' Study). 2019 – ongoing. Voluntary role.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Fifteen-minute consultation: Management of acute dystonia exacerbation and status dystonicus

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Received 30 March 2024
Accepted 19 May 2024
Published Online First 30 May 2024

To cite: Lumsden DE. *Arch Dis Child Educ Pract Ed* 2025;**110**:8–14.

ABSTRACT

Dystonia is a common disorder of movement and tone, characterised by sustained or intermittent muscle contractions causing abnormal movements, postures or both. Children and young people with dystonia can experience episodes of acute worsening tone, which require prompt treatment. When most severe, dystonia may become life-threatening—a state called 'status dystonicus'. This guide aims to provide a framework for how to approach the child with acutely worsening dystonia, following an 'ABCD' approach: Addressing the precipitant, Beginning supportive care, Calibrating sedation and Dystonia-specific medications.

INTRODUCTION

Dystonia is defined as 'a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both'.[1] Dystonia in childhood has many causes, the most common being cerebral palsy (CP).[2] Dystonic movements may be painful and can interfere with function and the delivery of daily care. Dystonia may occur in isolation, or as part of a more complex motor disorder. At worst, dystonia may become acutely life-threatening, a condition usually termed 'status dystonicus' (SD).[3] Precisely defining SD remains challenging, though a common definition is of 'increasingly frequent and severe episodes of generalised dystonia which had necessitated urgent hospital admission'.[4]

SD has been reported more often in children and young people (CAYP) than adults, with a trigger identified in around ~60% of cases.[5] While >300 episodes of SD have been reported to date, high-quality prospective studies are entirely lacking.[5 6] The true incidence of SD, or of episodes of worsening dystonia resulting in hospital admission, is unclear and very likely significantly underestimated. Around one in four CAYP experiencing SD fail to return to baseline following the episode, with a reported mortality of ~5%.[5] The risk of developing SD is present for all children with dystonia, though has been most frequently reported in CAYP with dyskinetic CP, pantothenate kinase-associated neurodegeneration and in GNAO1-related dystonia.[5] In the absence of a robust evidence base, this guide will focus on a pragmatic approach to the management of acute dystonia exacerbation.[7] For a more general approach to the diagnosis and management of dystonia in childhood, the reader is directed to the review by Forman and colleagues.[8]

GETTING THE RIGHT STATUS: DYSTONIA OR EPILEPSY?

The first challenge when faced in the emergency department (ED) with a CAYP experiencing severe dystonia is being confident that they are not experiencing an epileptic seizure. Prolonged generalised tonic–clonic seizures may be directly harmful to the brain if they continue after 30 min,[9] and in this situation, the aim of treatment is to *turn the seizure off*. In contrast, the aim of acute treatment for severe dystonia is to *turn the dystonia down*. Episodes of SD develop after a period of hours or days of worsening dystonia and lack a clear onset. It usually takes several hours, or even days, to entirely resolve the episode. Figure 1 outlines some of the ways in which status epilepticus (SE) and SD may be distinguished. CAYP will very often have received a dose of benzodiazepine prior to (or shortly following) arrival in the ED, which can impact on their responsiveness. If there is any question as to whether an episode is a seizure or not, encouraging families to record the movements for review later can be very beneficial. CAYP with dystonia often also

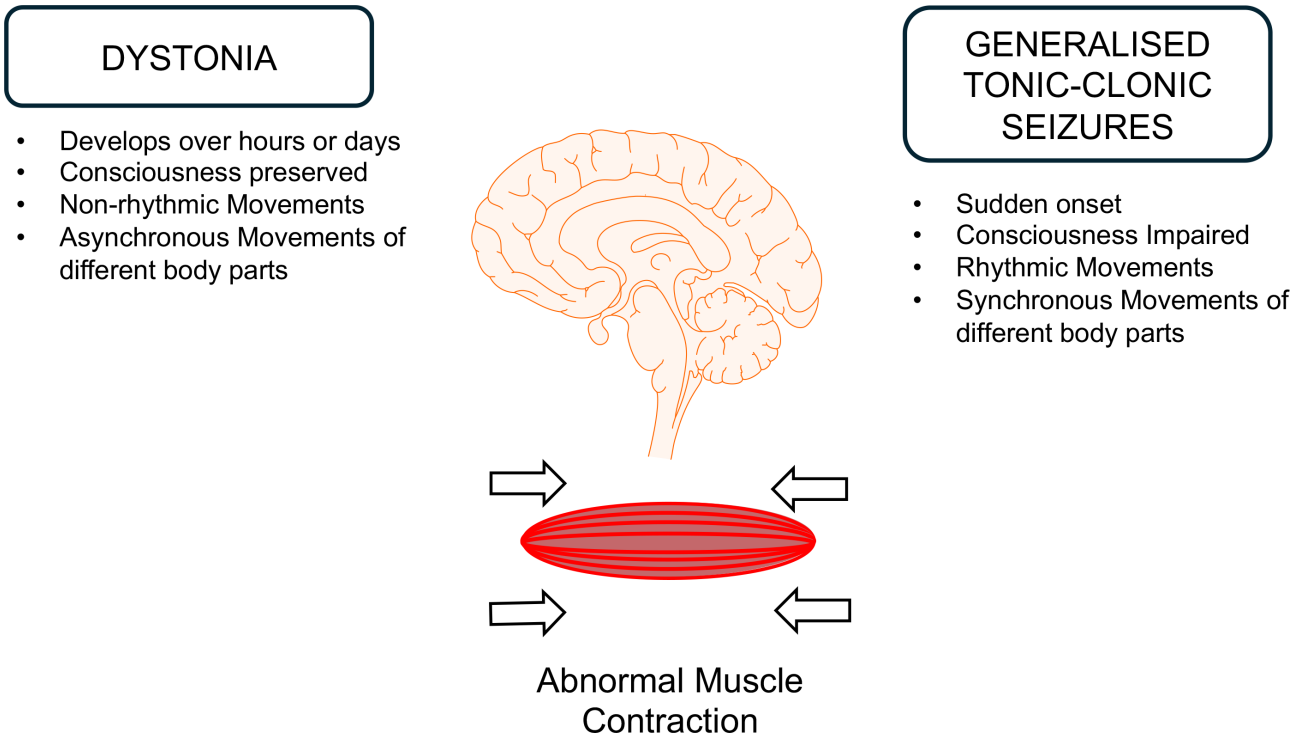

Figure 1 Differentiating episodes of 'status dystonicus' from 'status epilepticus'.

present with other hyperkinetic movement disorders—particularly chorea and myoclonus. These movements may also be exacerbated when dystonia worsens, which can further complicate differentiation from SE. Choreiform movements are typically non-rhythmic, random-appearing multiplanar non-purposeful movements. Myoclonic movements are brief, shock-like movements of a muscle group. Myoclonus may be epileptic (cortical myoclonus) or driven by subcortical mechanisms. Differentiation of the two at the bed side is difficult in practice, and an electroencephalogram recording is usually required.

MANAGING EPISODES OF ACUTE DYSTONIA EXACERBATION

A flow chart outlining an approach to managing episodes of acute dystonia exacerbation in CAYP is provided in figure 2. This emphasises an 'ABCD' approach. In contrast to the ABCD of Advanced Paediatric Life Support algorithms, these should be considered in parallel rather than sequentially. Grading the severity of dystonia for a CAYP is an important starting point, recognising that symptoms lie on a spectrum of severity, with SD at the most extreme. The Dystonia Severity Action Plan (DSAP) provides a simple 5-point scale for grading dystonia, which is useful for directing the urgency of intervention.[10] CAYP scoring 4 or 5 on this scale are in SD. Most children presenting acutely will be at DSAP grade 3, presenting an opportunity for intervention to prevent any further worsening of symptoms.

WHY HAS DYSTONIA WORSENED?—ADDRESSING THE PRECIPITANT

It is difficult to put a fire out if fuel keeps getting thrown onto it. Episodes of worsening dystonia will often (but not always) have a clear trigger, which is important to recognise and treat directly. Figure 3 provides a summary of common triggers for worsening dystonia, which should be considered for each CAYP. For frank SD, the common triggers differ between CAYP and adults,[5] and include intercurrent infection and changes to medications (either introductions or discontinuation). It is important for all presentations to specifically check if any new medications have been added or discontinued. Each CAYP should also be checked for an implanted device (deep brain stimulator or intrathecal baclofen pump). If one is present—the clinical team managing the device should be contacted urgently.

GENERAL MANAGEMENT—BEGINNING SUPPORTIVE CARE

As episodes of worsening dystonia take some time to improve, supportive care is required, as are treatments for any complications which may arise. This can include fluid management, pain relief and constipation management. An outline of supportive measures is provided in table 1, along with the complications acute dystonia exacerbation may cause to different organ systems. Depending on the severity of the episode, admission to a high dependency (CAYP at DSAP grade 4) or, less commonly, intensive care (CAYP at DSAP

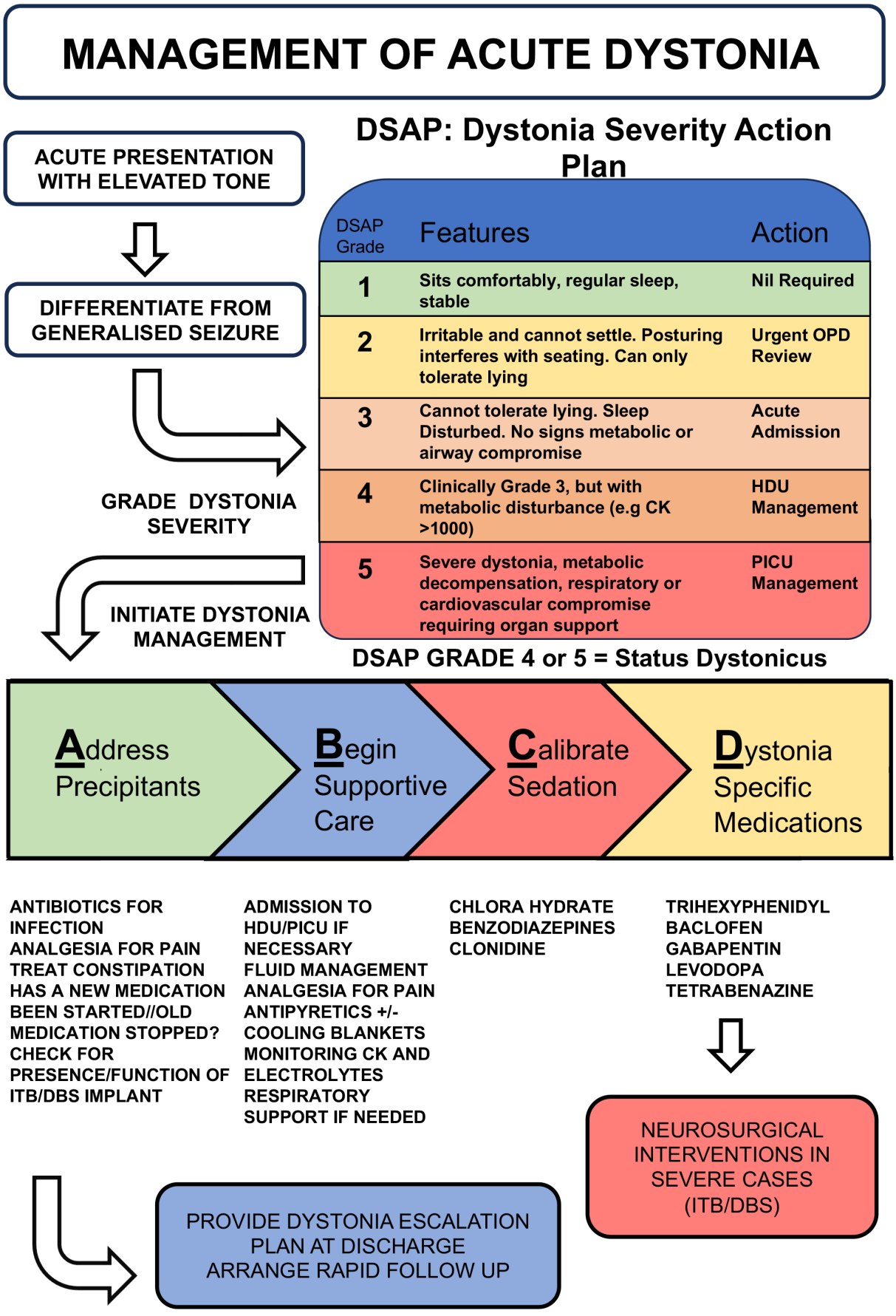

Figure 2 An approach to managing acute dystonia. CK, creatine kinase; DBS, deep brain stimulation; HDU, high-dependency unit; ITB, intrathecal baclofen; OPD, outpatient dystonia; PICU, paediatric intensive care unit.

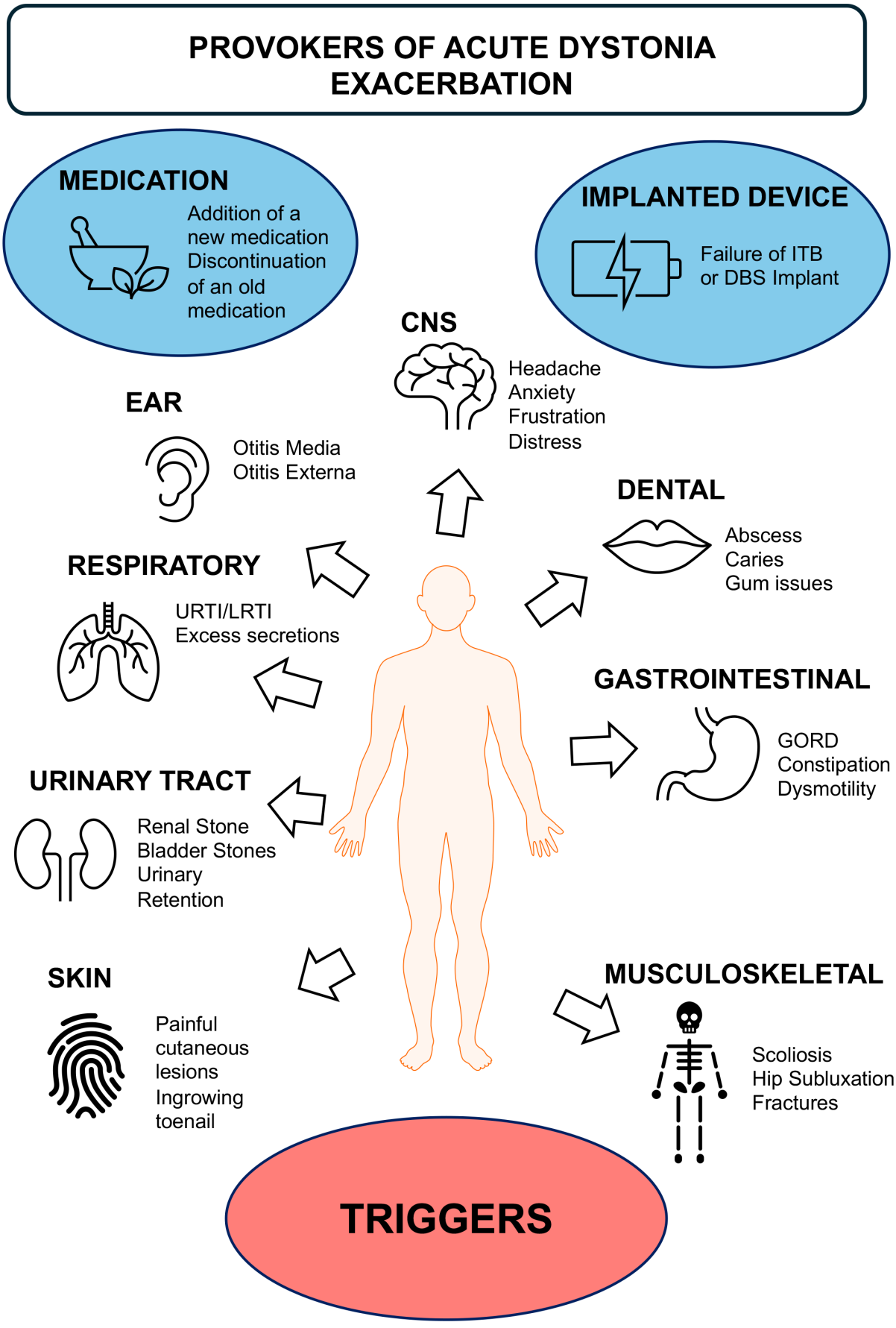

Figure 3 Triggering factors which may provoke worsening dystonia. CNS, central nervous system; DBS, deep brain stimulation; GORD, gastro-oesophageal reflux disease; ITB, intrathecal baclofen; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Table 1 Complications of status dystonicus and support required, organ system by organ system

System	Potential complications	Supportive measures
Respiratory	Airway compromise Bulbar dysfunction Aspiration Diaphragmatic compromise Exhaustion/poor respiratory effort	Airway adjuncts (may be poorly tolerated) Oxygen where necessary Intubation/ventilation (rarely required)
Renal/urinary tract	Acute kidney injury Urinary retention	Adequate hydration/hyperhydration Haemofiltration/renal replacement therapy (rarely required) Urethral catheterisation
Cardiovascular	Dehydration Dysautonomia	Adequate hydration
Gastrointestinal	Bulbar dysfunction GORD/gastric status Constipation	NG tube insertion Reflux treatment/gastric protection Laxatives
Musculoskeletal	Pain Fractures (rare)	Analgesia Support with positioning in bed and seating
Metabolic	Electrolyte disturbance Rhabdomyolysis Hyperpyrexia	Electrolyte replacement Hydration/hyperhydration Antipyretics Haemofiltration/renal replacement therapy (rarely required)
Psychological/emoting	Distress and anxiety PTSD symptoms longer term	Recognition that CAYP is alert and aware during episode (unless significantly sedated) Psychological support

CAYP, children and young people; GORD, gastro-oesophageal reflux disease; NG, nasogastric; PTSD, post-traumatic stress disorder.

grade 5) environment may be required. This may be due to the direct impact of dystonic movements, or the side effects of sedative and other medications (see below) required to control symptoms. One important risk with acute dystonia exacerbation is of rhabdomyolysis resulting in acute kidney injury, which in severe cases may result in the need for renal replacement therapy. While monitoring of plasma electrolyte and creatine kinase levels is necessary, frequency of blood sampling needs to be balanced against the disruptive impact of blood sampling itself on the CAYP. One of the goals of acute treatment is sedation—efforts which painful blood sampling will counteract. Severe dystonia places a significant energy demand on the body, and CAYP may rapidly become catabolic. Early placement of a nasogastric tube should be considered in CAYP without a surgical feeding tube already in place. The safety of a CAYP's swallow may be compromised by severe dystonia (particularly when this affects the head and neck), further compounded by the adverse effect of sedative medications.

TEMPORISING MEASURES—CALIBRATING SEDATION

While triggers are treated, and more dystonia-specific medications are changed (see below), a level of sedation is usually required to reduce distressing symptoms of dystonia. For mild episodes, this may be the very sparing use of a single agent, while for severe episodes of SD, a more complex regimen may be required. Table 2 provides some details of commonly used tone-reducing medications (TRMs), sedative and non-sedative. A number of different sedative medications have been described in the acute management of severe dystonia, including benzodiazepines, clonidine and chloral hydrate.[11] In all cases, care must be taken with regard to the risk of airway compromise and/or respiratory depression. For severe episodes of SD, particularly with concurrent rhabdomyolysis, intubation and ventilation may be required. In recent years, concerns have been raised about the use of chloral hydrate outside of the current UK licensing of short-term (not more than 2 weeks) treatment of insomnia in children with neurodevelopmental disorders. Consensus guidance has been produced to provide a framework for the use of this medication for CAYP with severe movement disorders.[12]

IMPROVING ABNORMAL TONE—DYSTONIA-SPECIFIC MEDICATIONS

Sedative strategies provide a period of symptom control while changes are made to background TRMs. A large number of TRMs have been described in the management of worsening dystonia and SD, with varying efficacy reported.[3 11] Table 2 provides details of some of the more commonly used medications, along with common side effects. Factors to consider when selecting a TRM are outlined in Box 1. For episodes of severe SD, the potential benefits of neurosurgical interventions such as deep brain stimulation (DBS) have been increasingly reported.[5 13] It remains unclear which CAYP are optimal candidates for DBS (or in some cases intrathecal baclofen) and at what time point during an episode of SD. All children admitted

Table 2 Tone-reducing medications (TRMs) used in the management of dystonia

Category	Medication	Mechanism of action	Main side effects
Acutely sedative TRM	Benzodiazepines (eg, midazolam, diazepam)	Enhances affinity of GABA-A receptors for agonists	Dependency and tolerance with longer-term use, respiratory depression, adverse cognitive effects
	Chloral hydrate	Hypnotic and sedative with similar action to barbiturates	Dependency and tolerance with longer-term use, GI upset
	Clonidine	Centrally acting adrenergic agent (α_2 adrenoreceptor agonist)	Dependency and tolerance with longer-term use, drowsiness, bradycardia, hypotension, dizziness (hypertension at very high doses)
Longer-term TRM	Baclofen	$GABA_B$ receptor agonist	Vomiting/GI upset, worsening airway secretions, impairing bulbar function, exacerbating axial hypotonia
	Trihexyphenidyl	Centrally acting anticholinergic (muscarinic) agent	Dry mouth, thicker secretions, pupil dilation, constipation
	Gabapentin	Disrupts regulatory action of $\alpha_2\delta$ calcium channel subunit (NOT gabanergic action, despite the name)	Tiredness, dizziness, GI upset, behavioural change, concerns about respiratory depression at high doses
	Levodopa	Precursor of the neurotransmitter dopamine	Vomiting/GI upset, potential for chorea with higher doses in children with dopamine deficit
	Tetrabenazine	Dopaminergic depletion (blocks synaptic release of dopamine)	Depression/low mood, Parkinsonism, neuroleptic malignant syndrome

GABA, gamma-aminobutyric acid; GI, gastrointestinal.

to an intensive care setting due to dystonia should be discussed early with a service which is experienced in the delivery of DBS to CAYP.

The evidence base for TRMs used in the management of dystonia is extremely limited,[14] and side effects limiting use are commonly experienced by CAYP.[15] During severe exacerbation of dystonia, it may be necessary to introduce or increase several TRMs, and it is important following an episode that there is close follow-up to try and rationalise ongoing medication use.

Box 1 Factors to consider when selecting tone-reducing medications (TRMs)

- TRMs the CAYP is already receiving.
- Background comorbidities which might be particularly worsened by the specific side effects of a given medication (eg, for a severely constipated child, an anticholinergic medication like trihexyphenidyl would be used with caution).
- The overall profile of the motor disorder for a CAYP (eg, co-incident spasticity would suggest potential benefits with the addition of baclofen).
- The speed at which symptom control is required (eg, a slow titration of trihexyphenidyl is required to limit the impact of anti-cholinergic side effects which may in term limit its use in a very acute situation).
- Whether a TRM could additionally help with treating a trigger (eg, gabapentin may have an additional analgesic effect in the CAYP with worsening dystonia due to pain from a subluxation of the hip).

CAYP, children and young people.

AFTER THE EPISODE: FOLLOW-UP AND AFTER CARE

CAYP experiencing an episode of worsening dystonia or SD will require close follow-up, for the reasons outlined in Box 2. Unfortunately, CAYP who have experienced an episode of worsening dystonia are at risk of experiencing further such episodes in the future. Given this risk, and the lack of standardised guidelines for the management of worsening dystonia, all children who have experienced an episode of worsening dystonia necessitating hospital admission should be provided with a personalised plan for dystonia management, providing (a) guidance on medication

Box 2 Reasons for close follow-up after an episode of worsening dystonia

- To consider if and when doses of TRMs increased during the episode of worsening dystonia can be reduced.
- To monitor for significant side effects from elevated doses of TRM.
- To ensure completed treatment/management of the trigger for an episode (if one has been identified).
- To monitor any complications encountered during the episode of worsening tone.
- To enable assessment of changed needs for the CAYP and family/carers if dystonia does not return to baseline.
- To provide support for the well-being of the CAYP and their family after what will typically have been a difficult episode.

CAYP, children and young people; TRM, tone-reducing medication.

changes to be made if dystonia acutely worsens, (b) advice on how to manage medications if CAYP are made nil by mouth and (c) the contact details for the team responsible for managing a CAYP's dystonia. The British Paediatric Neurology Association provides blank dystonia passports which can be adapted to an individual CAYP, along with guidance as to how these forms should be completed.[16] These plans should be documented in patient notes, with a copy provided to parents/carers to carry.

CONCLUSION

Episodes of acute worsening of symptoms are not uncommon in children with dystonia. A systematic approach is required to treatment, with a particular focus on identifying and treating triggers. Following discharge, CAYP require close follow-up and should be provided with guidance to support the management of any future episodes experienced.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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	Transverse myelitis	Guillain-Barre syndrome	Spinal cord compression
Onset	Acute (1-2 days)	Sub-acute Worsens over 2 weeks	Acute /Sub-acute
Possible Trigger	Infection	Infection	Trauma, malignancy
Typical first symptom	Back pain	Leg pain	Back pain
Motor	Paraparesis or quadriparesis, often asymmetrical. Initially hypotonia and hyporeflexia followed by hypert onia and hyperreflexia.	Symmetrical ascending motor weakness, usually starting in legs Hypotonia Areflexia	Complete vs incomplete lesions Level of motor weakness Initially hypotonia and hyporeflexia followed by hypertonia and hyperreflexia.
Sensory	Sensory level	No sensory level but mild sensory loss and sensory disturbances (pain, numbness, tingling) common	Sensory level Loss of anal tone
Cranial nerves	No central neuro involvement	Facial, bulbar weakness and ophthalmoplegia common.	No central neuro involvement
Other findings	Autonomic instability Bladder and bowel symptoms Systemic illness (fever, lethargy, malaise) common	Autonomic instability Bladder and bowel symptoms Breathing may be affected	Autonomic instability Bladder and bowel symptoms. Breathing may be affected
Investigati ons	Urgent MRI whole spine with contrast	Neurophysiology LP: raised CSF protein	Urgent MRI whole spine

DISEASES OF UMN:
acute spinal cord disorders

Type of Lesion	Tracts Involved	Clinical Signs	Causes
complete	all	Pyramidal, sensory, autonomic below lesion	Trauma, ATM
anterior	AHCs, corticospinal tracts, spinothalamic & autonomic	Acute bilateral flaccid weakness, loss of pain & temp and sphincter/autonomic function Preservation of dorsal columns (JPS, VIB)	Anterior spinal artery occlusion
Central			Syrinx, NMO
Conus medullaris	Autonomic outflow & sacral nerves	Sphincter dysfunction, sacral sensory loss	Post viral myelitis
Cauda	Spinal nerve	Often asymm flaccid leg weakness	Compressio

NMJ disorders:
Presynaptic disorders Botulism

- ingestion of spoiled preserved (canned) foods
- *Clostridium botulinum* multiplies in the intestines and releases botulinum toxin, passes into the bloodstream, reaching the neuromuscular junction -> irreversibly blocks release of acetylcholine at nerve terminal
- Clinical onset:

constipation, hypotonia and cephaloparesis

later generalized hypotonia, ptosis, ophthalmoparesis, facial diplegia, generalized weakness with hyperreflexia and respiratory failure may appear in severe cases

- diagnosis is confirmed by isolating *Clostridium botulinum* in cell cultures, and/or detection of the botulinum toxin in stool
- EMG incremental pattern response to repetitive nerve stimulation at high frequencies helpful
- no specific treatment other than supportive care. Prognosis very good, clinical improvement after a 15–90-day period.

MUSCLE DISEASES

- **Familial periodic paralysis**
- AD genetic diseases that affect the Na/K pump of the muscle cells
- Cc: type 1 (CACNA1S mutation)
- type 2 (SCN4A mutation)
- acute muscle weakness associated with hypokalemia (less than 2 mEq/l), which appears hours after the initial triad: history of exercise, high intake of carbohydrates and subsequent sleep- most episodes occur on waking in early morning.
- hyperkalemic paralysis (SCN4A mutation), associated with myotonia, produces short-term weakness only, with a duration of minutes in some cases.

Off legs - functional

- Diagnosis of FND should be made on basis of positive features O/E, NOT on the absence of disease: this is a positively identifiable condition with positive criteria:
- Positive physical signs in functional disorders that can be shared with patient to explain the diagnosis: workshop
- Hoover's sign- hip extension weakness that returns to normal with contralateral hip flexion against resistance
- Hip abductor sign: hip abduction weakness that returns to normal with contralateral hip abduction against resistance
- Global pattern of weakness, affecting extensors and flexors equally
- Evidence of inconsistency: eg weakness of plantar flexion on bed but able to walk on tip toes

Differentials for GBS

CNS:
Brainstem encephalitis- MOG, sarcoid, Bickerstaff
Spinal cord inflammation-ATM, MOG
Compression of brainstem or spinal cord
Malignancy- leptomeningeal metastases, neurolymphomatosis
Brainstem stroke

PNS:
AHC- AFP
Nerve roots- CMV, EBV, HIV, VZV, Lyme
Peripheral nerves- CIDP, porphyria, toxins, vit def (E, B12 and 1)
NMJ: MG
Muscles- periodic paralysis, acute rhabdomyolysis, inflammatory myositis,

Functional disorder

OPEN

EVIDENCE-BASED GUIDELINES

Diagnosis and management of Guillain–Barré syndrome in ten steps

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Abstract | Guillain–Barré syndrome (GBS) is a rare, but potentially fatal, immune-mediated disease of the peripheral nerves and nerve roots that is usually triggered by infections. The incidence of GBS can therefore increase during outbreaks of infectious diseases, as was seen during the Zika virus epidemics in 2013 in French Polynesia and 2015 in Latin America. Diagnosis and management of GBS can be complicated as its clinical presentation and disease course are heterogeneous, and no international clinical guidelines are currently available. To support clinicians, especially in the context of an outbreak, we have developed a globally applicable guideline for the diagnosis and management of GBS. The guideline is based on current literature and expert consensus, and has a ten-step structure to facilitate its use in clinical practice. We first provide an introduction to the diagnostic criteria, clinical variants and differential diagnoses of GBS. The ten steps then cover early recognition and diagnosis of GBS, admission to the intensive care unit, treatment indication and selection, monitoring and treatment of disease progression, prediction of clinical course and outcome, and management of complications and sequelae.

Guillain–Barré syndrome (GBS) is an inflammatory disease of the PNS and is the most common cause of acute flaccid paralysis, with an annual global incidence of approximately 1–2 per 100,000 person-years[1]. GBS occurs more frequently in males than in females and the incidence increases with age, although all age groups can be affected[1]. Patients with GBS typically present with weakness and sensory signs in the legs that progress to the arms and cranial muscles, although the clinical presentation of the disease is heterogeneous and several distinct clinical variants exist. Diagnosis of GBS is based on the patient history and neurological, electrophysiological and cerebrospinal fluid (CSF) examinations[2–4]. Other diseases that have a similar clinical picture to GBS must be ruled out[4]. Electrophysiological studies provide evidence of PNS dysfunction and can distinguish between the subtypes of GBS: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN)[5]. Disease progression can be rapid, and most patients with GBS reach their maximum disability within 2 weeks. About 20% of patients with GBS develop respiratory failure and require mechanical ventilation. Cardiac arrhythmias and blood pressure instability can occur owing to involvement of the autonomic nervous system[6]. This involvement of the autonomic nervous system contributes to mortality, which is estimated at 3–10% for patients with GBS even with the best medical care available[7–9]. After the initial progressive phase, patients with GBS reach a plateau phase that can last from days to weeks or months, after which they start to recover, and 60–80% of patients with GBS are able to walk independently 6 months after disease onset, with or without treatment[10,11]. GBS is a monophasic illness, although some patients can deteriorate after first stabilizing or improving on therapy — a phenomenon that is referred to as a treatment-related fluctuation (TRF). Relapses of GBS can occur in 2–5% of patients[10,12–15].

GBS is thought to be caused by an aberrant immune response to infections that results in damage to peripheral nerves, although the pathogenesis is not fully understood. In a subgroup of patients with GBS, serum antibodies are found against gangliosides, which reside

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https://doi.org/10.1038/s41582-019-0250-9

Key points

- Classic Guillain–Barré syndrome (GBS) is an acute-onset ascending sensorimotor neuropathy, but the disease can present atypically or as a clinical variant.
- Abnormal results in electrophysiological studies and a combination of an increased protein level and normal cell count in cerebrospinal fluid are classic features of GBS, but patients with GBS can have normal results in both tests, especially early in the disease course.
- Respiratory function should be monitored in all patients as respiratory failure can occur without symptoms of dyspnoea.
- Intravenous immunoglobulin and plasma exchange are equally effective in treating GBS; no other treatments have been proven to be effective.
- The efficacy of repeat treatment in patients who have shown insufficient clinical response is uncertain; nevertheless, this practice is common in patients who show deterioration after an initial treatment response.
- Clinical improvement is usually most extensive in the first year after disease onset and can continue for >5 years.

at high densities in the axolemma and other components of the peripheral nerves[16,17]. Complement activation, infiltration of macrophages and oedema are typical characteristics of affected peripheral nerves and nerve roots in patients with GBS[16].

The incidence of GBS can increase during outbreaks of infectious illnesses that trigger the disease[18]. Most recently, the Zika virus epidemics in French Polynesia in 2013 and in Latin America and the Caribbean in 2015–2016 were linked to an increase in individuals being diagnosed with GBS[19–21].

The Zika virus outbreaks brought to light the lack of globally applicable guidelines for the diagnosis and management of GBS. Such guidelines are necessary because the diagnosis of GBS can be challenging owing to heterogeneity in clinical presentation, an extensive differential diagnosis, and the lack of highly sensitive and specific diagnostic tools or biomarkers. Guidance for the treatment and care of patients with GBS is also needed because disease progression can vary greatly between patients, which complicates an entirely prescriptive approach to management. In addition, treatment options are limited and costly, and many patients experience residual disability and complaints that can be difficult to manage.

Availability of globally applicable clinical guidelines for GBS is especially important as new outbreaks of pathogens that trigger GBS are likely to occur in the future. To generate this globally applicable clinical guideline for GBS, the ten most important steps in the management of GBS, covering diagnosis, treatment, monitoring, prognosis and long-term management, were identified by a group of international experts on GBS (FIG. 1). For each step, recommendations were provided on the basis of evidence from the literature and/or expert opinion, and consensus was sought for each recommendation to finalize the guideline. These recommendations are intended to assist providers in clinical decision-making; however, the use of the information in this article is voluntary. The authors assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Methods

Following the outbreak of Zika virus and its association with an increase in the incidence of GBS, the European Union-funded Zika Preparedness Latin American Network (ZikaPLAN) was established[22]. Our new guideline was initially prepared by participants of the ZikaPLAN network, comprising experts on GBS from the Netherlands (S.E.L., M.R.M. and B.C.J.), Brazil (F.d.A.A.G. and M.E.D.) and the United Kingdom (H.J.W.). These members brought specific clinical and research expertise to the guideline from their leading roles in large international projects on GBS (such as the International GBS Outcome Study (IGOS)), along with direct experience in managing the large increases in GBS cases in Zika virus-affected regions of Latin America[23]. To develop the preliminary guidelines, a series of in-person meetings were held between lead authors on the writing committee (S.E.L., M.R.M., B.C.J. and H.J.W.), along with smaller individual meetings with colleagues in Latin America (S.E.L., F.d.A.A.G. and M.E.D.) and continuous e-mail correspondence to review drafts and receive input. On the basis of their expert opinion and through consensus, this group identified ten of the most important steps in the diagnosis and management of GBS.

For each step, structured literature searches were performed in October 2018 by members of the writing committee (S.E.L and M.R.M), using PubMed and Embase, and the results of these searches provided the basis for the first draft of the guideline. The main inclusion criterion for the literature searches was any study, trial, review or case report published from 2015 onwards that provided detail on the diagnosis, treatment, management or prognosis of patients with GBS. Publications on the pathogenesis of GBS, or those with a focus on diseases not related to GBS, along with publications written in

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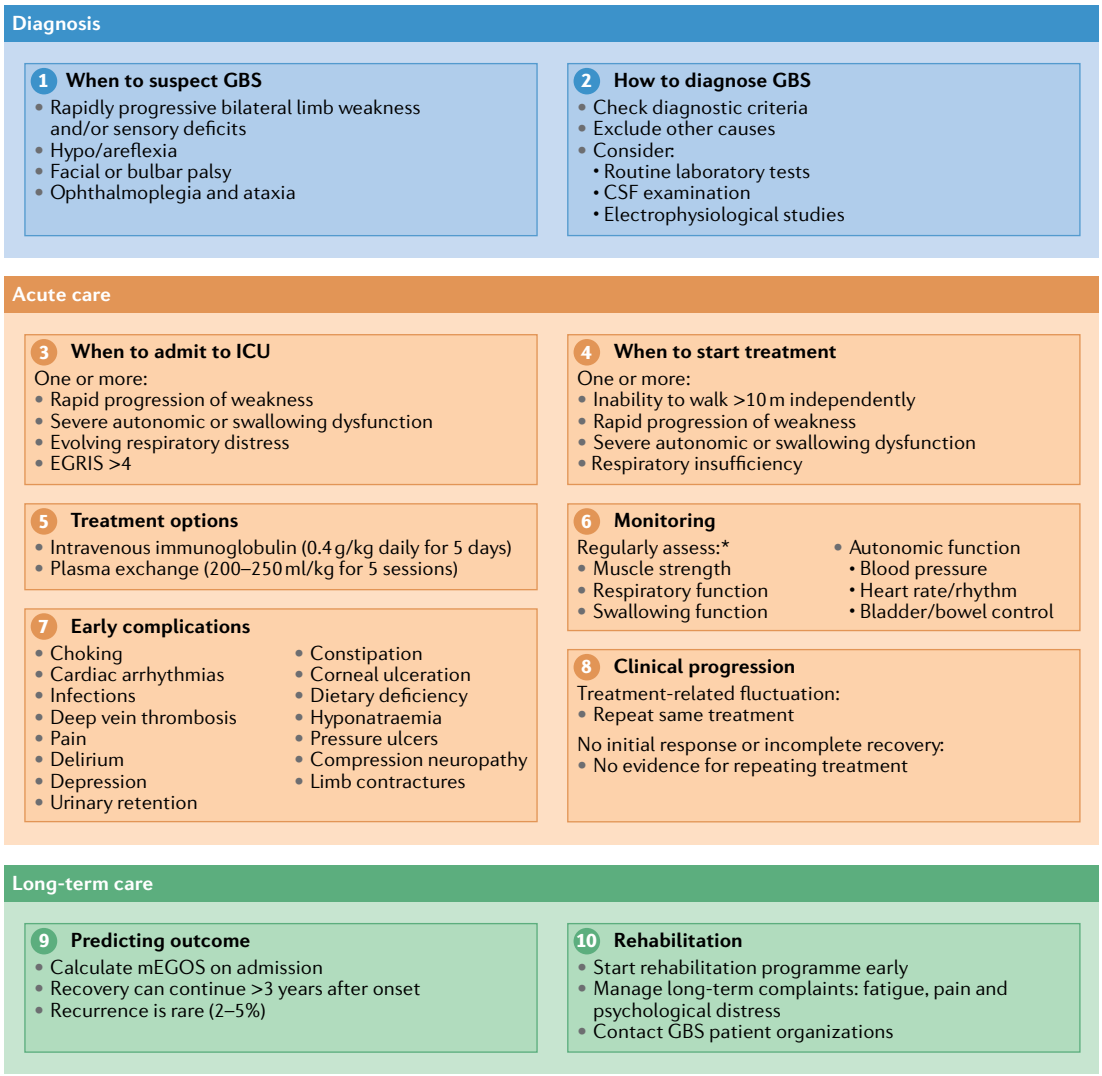

Fig. 1 | **Ten-step approach to the diagnosis and management of Guillain–Barré syndrome.** This bullet point summary provides an overview of each of the ten steps described in the guideline. *Frequency of monitoring is dependent on the clinical picture and should be assessed in individual patients. CSF, cerebrospinal fluid; EGRIS, Erasmus GBS Respiratory Insufficiency Score (BOX 3); GBS, Guillain-Barré syndrome; ICU, intensive care unit; mEGOS, modified Erasmus GBS Outcome Score (Supplementary Table 3).

a language other than English or Dutch were excluded from the review. Keywords used in the search strategy included the following Medical Subject Headings (MeSH) terms: "Guillain–Barré syndrome" AND ["diagnosis" OR "therapeutics" OR "treatment outcome" OR "prognosis"]. To obtain literature for more specific topics, additional MeSH terms were combined with primary search keywords, including "intravenous immunoglobulins", "plasma exchange", "intensive care units", "pregnancy", "Miller Fisher syndrome" and "HIV". Following this review of the most recent literature, landmark studies published prior to 2015 were identified for inclusion by the writing committee (S.E.L., M.R.M., B.C.J. and H.J.W.), along with additional papers selected by screening the reference lists of already included manuscripts and consultation with the authors. Where possible, our recommendations regarding treatment were based on systematic reviews. Expert opinion from the authors was sought for recommendations when more limited evidence (for example, cohort studies or case–control studies) was available, for instance on topics regarding the differential diagnosis or rehabilitation of GBS.

In consideration of the global variation in healthcare context and variants of GBS, this first draft was subsequently reviewed by an international group of experts on GBS from Argentina (R.R.), Australia (E.M.Y.), Bangladesh (B.I.), Brazil (M.L.B.F. and C.S.), China (Y.W.), Colombia (C.A.P.), Japan (S.K.), Malaysia (N.S.), the Netherlands (P.A.v.D.), Singapore (T.U.), South Africa (K.B.), the United States (D.R.C. and J.J.S.) and the United Kingdom (R.A.C.H). In total, seven rounds of review were held to reach a consensus. To consider the perspective of patients with GBS on the management of the disease, the GBS/CIDP Foundation International, a non-profit organization that provides support, education, research funding and advocacy to patients with GBS or chronic inflammatory demyelinating polyneuropathy (CIDP) and their families, reviewed

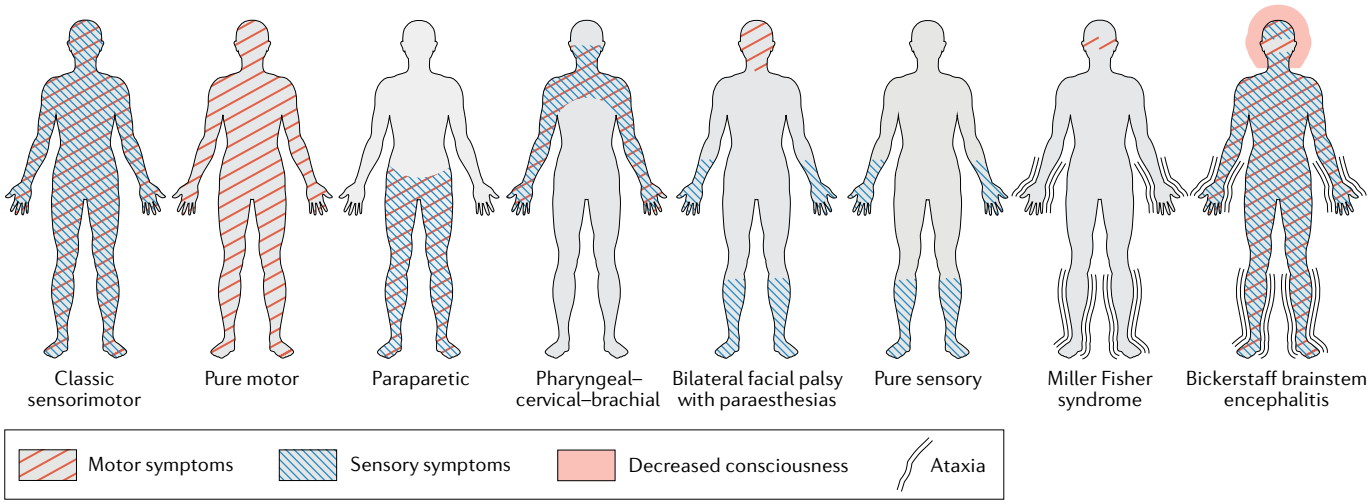

Fig. 2 | **Pattern of symptoms in variants of Guillain–Barré syndrome.** Graphic representation of the pattern of symptoms typically observed in the different clinical variants of Guillain–Barré syndrome (GBS). Symptoms can be purely motor, purely sensory (rare) or a combination of motor and sensory. Ataxia can be present in patients with Miller Fisher syndrome and both decreased consciousness and ataxia can be present in patients with Bickerstaff brainstem encephalitis. Symptoms can be localized to specific regions of the body, and the pattern of symptoms differs between variants of GBS. Although bilateral facial palsy with paraesthesias, the pure sensory variant and Miller Fisher syndrome are included in the GBS spectrum, they do not fulfil the diagnostic criteria for GBS. Adapted with permission from REF.[113],

the manuscript and provided comment during the development of the guideline.

Step 1: when to suspect GBS

Typical clinical features

GBS should be considered as a diagnosis in patients who have rapidly progressive bilateral weakness of the legs and/or arms, in the absence of CNS involvement or other obvious causes. Patients with the classic sensorimotor form of GBS present with distal paraesthesias or sensory loss, accompanied or followed by weakness that starts in the legs and progresses to the arms and cranial muscles. Reflexes are decreased or absent in most patients at presentation and in almost all patients at nadir[10,24]. Dysautonomia is common and can include blood pressure or heart rate instability, pupillary dysfunction, and bowel or bladder dysfunction[25]. Pain is frequently reported and can be muscular, radicular or neuropathic[26]. Disease onset is acute or subacute, and patients typically reach maximum disability within 2 weeks[11]. In patients who reach maximum disability within 24 h of disease onset or after 4 weeks, alternative diagnoses should be considered[2,3]. GBS has a monophasic clinical course, although TRFs and relapses occur in a minority of patients[12,13].

Atypical clinical presentation

GBS can also present in an atypical manner. Weakness and sensory signs, though always bilateral, can be asymmetrical or predominantly proximal or distal, and can start in the legs, the arms or simultaneously in all limbs[6,26]. Furthermore, severe and diffuse pain or isolated cranial nerve dysfunction can precede the onset of weakness[26]. Young (<6 years old) children in particular can present with nonspecific or atypical clinical features, such as poorly localized pain, refusal to bear weight, irritability, meningism, or an unsteady gait[27,28]. Failure to recognize these signs as an early presentation of GBS might cause delay in diagnosis[28]. In a minority of patients with atypical GBS, particularly those with only motor signs (pure motor variant) and an AMAN subtype on electrophysiological examination, normal or even exaggerated reflexes might be observed throughout the disease course[29].

Variants

Some patients have a distinct and persistent clinical variant of GBS that does not progress to the classic pattern of sensory loss and weakness. These variants include: weakness without sensory signs (pure motor variant); weakness limited to the cranial nerves (bilateral facial palsy with paraesthesias), upper limbs (pharyngeal–cervical–brachial weakness) or lower limbs (paraparetic variant); and the Miller Fisher syndrome (MFS), which in its full manifestation consists of ophthalmoplegia, areflexia and ataxia[6,30,31] (FIG. 2 and TABLE 1). In general, GBS variants are rarely 'pure' and often overlap in part with the classic syndrome or show features that are typical of other variant forms[32].

Besides the variants listed above, pure sensory ataxia, Bickerstaff brainstem encephalitis (BBE) and a pure sensory variant are often included in the GBS spectrum because they share clinical or pathophysiological features with GBS. However, the inclusion of these clinical variants is subject to debate as they do not fulfil the diagnostic criteria for GBS[2,3,31] (BOX 1). The pure sensory variant shares clinical features with the classic sensorimotor form of GBS, with the exception of the presence of motor symptoms and signs[31,33]; pure sensory ataxia and MFS have overlapping clinical profiles, and patients with BBE

usually present with symptoms resembling MFS and subsequently develop signs of brainstem dysfunction, including impaired consciousness and pyramidal tract signs[30–32,34–36]. Similar to patients with MFS, individuals with sensory ataxia or BBE can exhibit IgG antibodies to GQ1b or other gangliosides in their serum[30,34]. However, whether pure sensory GBS, pure sensory ataxia and BBE are variants of GBS and/or an incomplete form of MFS is subject to debate, and careful diagnostic work-up is required when these variants are suspected[31,33,35] (BOXES 1 and 2).

Preceding events

About two-thirds of patients who develop GBS report symptoms of an infection in the 6 weeks preceding the onset of the condition[11]. These infections are thought to trigger the immune response that causes GBS[6]. Six pathogens have been temporally associated with GBS in case–control studies: *Campylobacter jejuni*, cytomegalovirus, hepatitis E virus, *Mycoplasma pneumoniae*, Epstein–Barr virus and Zika virus[18,20,37]. It has been suggested that other pathogens are linked to GBS on the basis of evidence from case series or epidemiological studies, but their role in the pathogenesis of GBS is uncertain[38–43]. In general, the absence of an antecedent illness does not exclude a diagnosis of GBS, as putative infections or other immunological stimuli can be subclinical.

Vaccines were first linked to GBS in 1976 when a 7.3-fold increase in the risk of GBS was observed among nonmilitary individuals in the United States who had received the 'swine' influenza vaccine[44]. The epidemiological link between other vaccines and GBS has been examined many times since, but only two further studies showed a relationship between GBS and influenza vaccines[45,46]. These studies suggested an increase of approximately one additional GBS case per one million vaccinations, which is several orders of magnitude lower than that observed for the 1976 influenza vaccine[47,48]. No other vaccines have been convincingly linked to GBS[15].

A relationship between administration of immunobiologicals (for example, tumour necrosis factor antagonists, immune checkpoint inhibitors or type I interferons) and GBS has been reported on the basis of case series information and biological plausibility[49]. Other events, including but not limited to surgery and malignancy, have been temporally related to GBS, but these relationships lack a clear biological rationale and the epidemiological evidence is limited[50,51].

Step 2: how to diagnose GBS

In the absence of sufficiently sensitive and specific disease biomarkers, the diagnosis of GBS is based on clinical history and examination, and is supported by ancillary investigations such as CSF examination and electrodiagnostic studies. The two most commonly used sets of diagnostic criteria for GBS were developed by the National Institute of Neurological Disorders and Stroke (NINDS) in 1978 (revised in 1990)[2,3] (BOX 1) and the Brighton Collaboration in 2011 (REF[4]) (Supplementary Table 1). Both sets of criteria were designed to investigate the epidemiological association between GBS and vaccinations but have since been used in other clinical studies and trials. We consider the NINDS criteria to be more suited to the clinician as they present the clinical features of typical and atypical forms of GBS, although the criteria from the Brighton Collaboration are also

Table 1 | **Variants of Guillain–Barré syndrome**

Variant	Frequency (% of GBS cases)[a]	Clinical features	Refs
Classic sensorimotor GBS[b]	30–85	Rapidly progressive symmetrical weakness and sensory signs with absent or reduced tendon reflexes, usually reaching nadir within 2 weeks	11,24,114,115
Pure motor[c]	5–70	Motor weakness without sensory signs	5,11,24
Paraparetic	5–10	Paresis restricted to the legs	10,24,115
Pharyngeal–cervical–brachial	<5	Weakness of pharyngeal, cervical and brachial muscles without lower limb weakness	10,114,115
Bilateral facial palsy with paraesthesias[d]	<5	Bilateral facial weakness, paraesthesias and reduced reflexes	114–116
Pure sensory[d]	<1	Acute or subacute sensory neuropathy without other deficits	117,118
Miller Fisher syndrome	5–25	Ophthalmoplegia, ataxia and areflexia. Incomplete forms with isolated ataxia (acute ataxic neuropathy) or ophthalmoplegia (acute ophthalmoplegia) can occur[31]. Overlaps with classical sensorimotor GBS in an estimated 15% of patients	11,24,114,116–119
Bickerstaff brainstem encephalitis[d]	<5	Ophthalmoplegia, ataxia, areflexia, pyramidal tract signs and impaired consciousness, often overlapping with sensorimotor GBS	114,115

[a]Estimated frequencies, with percentages displayed to the nearest 5%, based on nine (primarily adult) cohort studies in various geographical regions[10,11,24,114–119]. Frequencies differ by region and study, contributing to the variability. Most studies are biased owing to exclusion of some of the variants. [b]The sensorimotor form is seen in an estimated 70% of patients with GBS in Europe and the Americas, and in 30–40% of cases in Asia[11]. [c]The pure motor variant is reported in 5–15% of patients with GBS in most studies, but in 70% cases in Bangladesh[11,120]. [d]Does not fulfil commonly used diagnostic criteria for GBS, which require the presence of bilateral limb weakness or fulfilment of the criteria for Miller Fisher syndrome[3,4]. GBS, Guillain–Barré syndrome.

important, widely used, and can help the clinician to classify cases with (typical) GBS or MFS according to diagnostic certainty. Various differential diagnoses must also be kept in mind when GBS is suspected, and some symptoms should raise suspicion of alternative diagnoses (BOXES 1 and 2). The role of ancillary investigations in confirming a GBS diagnosis is described in more detail in the following section.

Laboratory investigations

Laboratory testing is guided by the differential diagnosis in individual patients, but in general all patients with suspected GBS will have complete blood counts and blood tests for glucose, electrolytes, kidney function and liver enzymes. Results of these tests can be used to exclude other causes of acute flaccid paralysis, such as infections or metabolic or electrolyte dysfunctions (BOX 2). Further specific tests may be carried out with the aim of excluding other diseases that can mimic GBS (BOX 2). Testing for preceding infections does not usually contribute to the diagnosis of GBS, but can provide important epidemiological information during outbreaks of infectious diseases, as was seen in previous outbreaks of Zika virus and *C. jejuni* infection[19,52]. The diagnostic value of measuring serum levels of anti-ganglioside antibodies is limited and assay-dependent. A positive test result can be helpful, especially when the diagnosis is in doubt, but a negative test result does not rule out GBS[53]. Anti-GQ1b antibodies are found in up to 90% of patients with MFS[17,54] and therefore have greater diagnostic value in patients with suspected MFS than in patients with classic GBS or other variants. When GBS is suspected, we advise not to wait for antibody test results before starting treatment.

Cerebrospinal fluid examination

CSF examination is mainly used to rule out causes of weakness other than GBS and should be performed during the initial evaluation of the patient. The classic finding in GBS is the combination of an elevated CSF protein level and a normal CSF cell count (known as albumino-cytological dissociation)[55]. However, protein levels are normal in 30–50% of patients in the first week after disease onset and 10–30% of patients in the second week[10,11,24,56]. Therefore, normal CSF protein levels do not rule out a diagnosis of GBS. Marked pleocytosis (>50 cells/μl) suggests other pathologies, such as leptomeningeal malignancy or infectious or inflammatory diseases of the spinal cord or nerve roots. Mild pleocytosis (10–50 cells/μl), though compatible with GBS, should still prompt clinicians to consider alternative diagnoses, such as infectious causes of polyradiculitis[10,11] (BOX 2).

Electrodiagnostic studies

Electrodiagnostic studies are not required to diagnose GBS. However, we recommend that these studies are performed wherever possible as they are helpful in supporting the diagnosis, particularly in patients with an atypical presentation. In general, electrophysiological examination in patients with GBS will reveal a sensorimotor polyradiculoneuropathy or polyneuropathy, indicated by reduced conduction velocities, reduced sensory and motor evoked amplitudes, abnormal temporal dispersion and/or partial motor conduction blocks[6,57]. Typical for GBS is a 'sural sparing pattern' in which the sural sensory nerve action potential is normal while the median and ulnar sensory nerve action potentials are abnormal or even absent[6,57]. However, electrophysiological measurements might be normal when performed early in the disease course (within 1 week of symptom onset) or in patients with initially proximal weakness, mild disease, slow progression or clinical variants[5,58,59]. In these patients, a repeat electrodiagnostic study 2–3 weeks later can be helpful. In patients with MFS, results of electrodiagnostic studies are usually normal or demonstrate only a reduced amplitude of sensory nerve action potentials[4,60].

Box 1 | **Diagnostic criteria for Guillain–Barré syndrome**

This box lists the diagnostic criteria for Guillain–Barré syndrome (GBS) developed by the National Institute of Neurological Disorders and Stroke (NINDS)[3] and subsequently modified in a review paper[6]. We have added some features that cast doubt on the diagnosis, which were not mentioned in the original criteria[2,3,6], and have made some adaptations to improve readability. These criteria are not applicable to some of the specific variants of GBS, as described in TABLE 1.

Features required for diagnosis

- Progressive bilateral weakness of arms and legs (initially only legs may be involved)[a]
- Absent or decreased tendon reflexes in affected limbs (at some point in clinical course)[a]

Features that strongly support diagnosis

- Progressive phase lasts from days to 4 weeks (usually <2 weeks)
- Relative symmetry of symptoms and signs
- Relatively mild sensory symptoms and signs (absent in pure motor variant)[a]
- Cranial nerve involvement, especially bilateral facial palsy[a]
- Autonomic dysfunction
- Muscular or radicular back or limb pain[b]
- Increased protein level in cerebrospinal fluid (CSF); normal protein levels do not rule out the diagnosis[b]
- Electrodiagnostic features of motor or sensorimotor neuropathy (normal electrophysiology in the early stages does not rule out the diagnosis)[b]

Features that cast doubt on diagnosis

- Increased numbers of mononuclear or polymorphonuclear cells in CSF ($>50 \times 10^6$/l)
- Marked, persistent asymmetry of weakness
- Bladder or bowel dysfunction at onset or persistent during disease course[b]
- Severe respiratory dysfunction with limited limb weakness at onset[b]
- Sensory signs with limited weakness at onset[a]
- Fever at onset
- Nadir <24 h[b]
- Sharp sensory level indicating spinal cord injury[a]
- Hyper-reflexia or clonus[b]
- Extensor plantar responses[b]
- Abdominal pain[b]
- Slow progression with limited weakness without respiratory involvement
- Continued progression for >4 weeks after start of symptoms[b]
- Alteration of consciousness (except in Bickerstaff brainstem encephalitis)[b]

Minor adaptations were made by the authors to a simplified version of the original NINDS criteria[6]. [a]Statements in NINDS criteria that were adapted by authors to improve readability. [b]Additional features which were not included in the NINDS. Note: for clarity, we have omitted 'Features that rule out the diagnosis' from the original NINDS criteria for this adapted version.

Box 2 | **Differential diagnosis of Guillain–Barré syndrome**

The differential diagnosis of Guillain–Barré syndrome is broad and highly dependent on the clinical features of the individual patient. Here, we present an overview of the most important differential diagnoses categorized by location in the nervous system.

CNS

- Inflammation or infection of the brainstem (for example, sarcoidosis, Sjögren syndrome, neuromyelitis optica or myelin oligodendrocyte glycoprotein antibody-associated disorder)[a]
- Inflammation or infection of the spinal cord (for example, sarcoidosis, Sjögren syndrome or acute transverse myelitis)
- Malignancy (for example, leptomeningeal metastases or neurolymphomatosis)
- Compression of brainstem or spinal cord
- Brainstem stroke
- Vitamin deficiency (for example, Wernicke encephalopathy[a], caused by deficiency of vitamin B1, or subacute combined degeneration of the spinal cord, caused by deficiency of vitamin B12)

Anterior horn cells

- Acute flaccid myelitis (for example, as a result of polio, enterovirus D68 or A71, West Nile virus, Japanese encephalitis virus or rabies virus)

Nerve roots

- Infection (for example, Lyme disease, cytomegalovirus, HIV, Epstein–Barr virus or varicella zoster virus)
- Compression
- Leptomeningeal malignancy

Peripheral nerves

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Metabolic or electrolyte disorders (for example, hypoglycaemia, hypothyroidism, porphyria or copper deficiency)
- Vitamin deficiency (for example, deficiency of vitamins B1 (also known as beriberi), B12 or E)
- Toxins (for example, drugs, alcohol, vitamin B6, lead, thallium, arsenic, organophosphate, ethylene glycol, diethylene glycol, methanol or N-hexane)
- Critical illness polyneuropathy
- Neuralgic amyotrophy
- Vasculitis
- Infection (for example, diphtheria or HIV)

Neuromuscular junction

- Myasthenia gravis
- Lambert–Eaton myasthenic syndrome
- Neurotoxins (for example, botulism, tetanus, tick paralysis or snakebite envenomation)
- Organophosphate intoxication

Muscles

- Metabolic or electrolyte disorders (for example, hypokalaemia, thyrotoxic hypokalaemic periodic paralysis, hypomagnesaemia or hypophosphataemia)
- Inflammatory myositis
- Acute rhabdomyolysis
- Drug-induced toxic myopathy (for example, induced by colchicine, chloroquine, emetine or statins)
- Mitochondrial disease

Other

- Conversion or functional disorder

[a]Differential diagnosis for Bickerstaff brainstem encephalitis.

Electrodiagnostic studies can also differentiate between the three electrophysiological subtypes of classical GBS: AIDP, AMAN, and AMSAN. Several sets of electrodiagnostic criteria exist that aim to classify patients into these different electrophysiological subtypes on the basis of the presence of specific electrodiagnostic characteristics in at least two motor nerves. International consensus is yet to be reached on which set of criteria best defines the electrophysiological subtypes[5,52,61]. However, about one-third of patients with GBS do not meet any of these criteria and are labelled 'equivocal' or 'inexcitable'. Studies have demonstrated that repeating electrodiagnostic studies 3–8 weeks after disease onset might aid electrodiagnostic classification by allowing classification of cases that were initially unclassifiable, or reclassification of cases that were initially classified as AIDP, AMAN or AMSAN, although this practice is controversial[62–64].

Imaging

MRI is not part of the routine diagnostic evaluation of GBS, but can be helpful, particularly for excluding differential diagnoses such as brainstem infection, stroke, spinal cord or anterior horn cell inflammation, nerve root compression or leptomeningeal malignancy (BOX 2). The presence of nerve root enhancement on gadolinium-enhanced MRI is a nonspecific but sensitive feature of GBS[65] and can support a GBS diagnosis, especially in young children, in whom both clinical and electrophysiological assessment can be challenging[66]. In light of recent outbreaks of acute flaccid myelitis in young children, the clinical presentation of which can mimic GBS, the potential use of MRI to distinguish between these two diagnoses should be given special attention[67,68]. However, clinicians should be mindful that nerve root enhancement can be found in a minority of individuals with acute flaccid myelitis[69].

A new potential diagnostic tool in GBS is ultrasound imaging of the peripheral nerves, which has revealed enlarged cervical nerve roots early in the disease course, indicating the importance of spinal root inflammation as an early pathological mechanism[70,71]. This technique might, therefore, help establish a diagnosis of GBS early in the disease course, although further validation is required.

Step 3: when to admit to the ICU

Reasons to admit patients to the intensive care unit (ICU) include the following: evolving respiratory distress with imminent respiratory insufficiency, severe autonomic cardiovascular dysfunction (for example, arrhythmias or marked variation in blood pressure), severe swallowing dysfunction or diminished cough reflex, and rapid progression of weakness[72,73]. A state of imminent respiratory insufficiency is defined as clinical

signs of respiratory distress, including breathlessness at rest or during talking, inability to count to 15 in a single breath, use of accessory respiratory muscles, increased respiratory or heart rate, vital capacity <15–20 ml/kg or <1 l, or abnormal arterial blood gas or pulse oximetry measurements.

As up to 22% of patients with GBS require mechanical ventilation within the first week of admission, patients at risk of respiratory failure must be identified as early as possible[74]. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) prognostic tool was developed for this purpose and calculates the probability (1–90%) that a patient will require ventilation within 1 week of assessment[74] (BOX 3).

Risk factors for prolonged mechanical ventilation include the inability to lift the arms from the bed at 1 week after intubation, and an axonal subtype or unexcitable nerves in electrophysiological studies[75]. Early tracheostomy should be considered in patients who have these risk factors.

Step 4: when to start treatment

Immunomodulatory therapy should be started if patients are unable to walk independently for 10 m (REFS[76,77]). Evidence on treatment efficacy in patients who can still walk independently is limited, but treatment should be considered, especially if these patients display rapidly progressive weakness or other severe symptoms such as autonomic dysfunction, bulbar failure or respiratory insufficiency[78–80]. Clinical trials have demonstrated a treatment effect for intravenous immunoglobulin (IVIg) when started within 2 weeks of the onset of weakness and for plasma exchange when started within 4 weeks[76,77]. Beyond these time periods, evidence on efficacy is lacking.

Box 3 | **Erasmus GBS Respiratory Insufficiency Score**

The Erasmus Guillain–Barré syndrome (GBS) Respiratory Insufficiency Score (EGRIS) calculates the probability that a patient with GBS will require mechanical ventilation within 1 week of assessment and is based on three key measures. Each measure is categorized and assigned an individual score; the sum of these scores gives an overall EGRIS for that patient (between 0 and 7). An EGRIS of 0–2 indicates a low risk of mechanical intervention (4%), 3–4 indicates an intermediate risk of mechanical intervention (24%) and ≥5 indicates a high risk of mechanical intervention (65%). This model is based on a Dutch population of patients with GBS (aged >6 years) and has not yet been validated internationally. Therefore, it may not be applicable in other age groups or populations. An online resource that automatically calculates the EGRIS for a patient based on answers to a series of questions has been made available by the International GBS Outcome Study (IGOS) consortium (see Related links). The Medical Research Council (MRC) sum score is the sum of the score on the MRC scale for: muscle weakness of bilateral shoulder abduction; elbow flexion; wrist extension; hip flexion; knee extension; and ankle dorsiflexion. A higher MRC sum score denotes increased disability, up to a maximum score of 60.

Measure	Categories	Score
Days between onset of weakness and hospital admission	>7 days	0
	4–7 days	1
	≤3 days	2
Facial and/or bulbar weakness at hospital admission	Absent	0
	Present	1
MRC sum score at hospital admission	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤20	4
EGRIS	NA	0–7

NA, not applicable. Adapted with permission from REF.[74], Wiley-VCH.

Step 5: treatment options

Treatment strategies

IVIg (0.4 g/kg body weight daily for 5 days) and plasma exchange (200–250 ml plasma/kg body weight in five sessions) are equally effective treatments for GBS[76,80]. IVIg and plasma exchange carry comparable risks of adverse events, although early studies showed that plasma exchange was more likely than IVIg to be discontinued[76,81]. As IVIg is also easier to administer and generally more widely available than plasma exchange, it is usually the treatment of choice. Besides IVIg and plasma exchange, no other procedures or drugs have been proven effective in the treatment of GBS. Although corticosteroids would be expected to be beneficial in reducing inflammation and, therefore, disease progression in GBS, eight randomized controlled trials on the efficacy of corticosteroids for GBS showed no significant benefit, and treatment with oral corticosteroids was even shown to have a negative effect on outcome[82]. Furthermore, plasma exchange followed by IVIg is no more effective than either treatment alone and insufficient evidence is available for the efficacy of add-on treatment with intravenous methylprednisolone in IVIg-treated patients[82,83]. In clinical settings where resources are limited, small-volume plasma exchange might be an economical and relatively safe alternative to conventional plasma exchange, but this approach cannot be recommended for general use until its efficacy has been established in further trials[84].

Antimicrobial or antiviral treatment can be considered in patients with GBS who have an ongoing infection; however, preceding infections have usually resolved before the onset of weakness.

Specific patient groups

GBS variants. Patients with pure MFS tend to have a relatively mild disease course, and most recover completely without treatment within 6 months[85]. Therefore, treatment is generally not recommended in this patient group but patients should be monitored closely because a subgroup can develop limb weakness, bulbar or facial palsy, or respiratory failure[32,80]. The severity of the disease course of BBE justifies treatment with IVIg or plasma exchange, although evidence for the efficacy of treatment in this context is limited[34,85]. For the other clinical variants, no evidence regarding treatment is currently available, although many experts will administer IVIg or plasma exchange[86].

Pregnant women. Neither IVIg nor plasma exchange is contraindicated during pregnancy. However, as plasma exchange requires additional considerations and monitoring, IVIg might be preferred[87–89].

Table 2 | **Important complications of Guillain–Barré syndrome**

Complication	When to be alert
Choking	Bulbar palsy
Cardiac arrhythmias	All patients
Hospital-acquired infections (e.g., pneumonia, sepsis or urinary tract infection)	Bulbar and facial palsy, immobility, bladder dysfunction, mechanical ventilation
Pain and tactile allodynia	Limited communication
Delirium	Limited communication
Depression	Limited communication
Urinary retention	All patients
Constipation	Immobility
Corneal ulceration	Facial palsy
Dietary deficiency	Bulbar and facial palsy
Hyponatraemia	All patients
Pressure ulcers	Immobility
Compression neuropathy	Immobility
Limb contractures and ossifications	Severe weakness for prolonged period of time

Important complications of Guillain–Barré syndrome (GBS)[72]. Most of these complications can occur in any patient with GBS, at any time, but the second column shows when they are most likely to occur and/or when to be especially alert.

Children. There is no indication that it is necessary to deviate from standard adult practice when treating children with GBS[76,78,90]. Evidence on the relative efficacies of plasma exchange and IVIg in children is limited[90]. However, as plasma exchange is only available in centres that are experienced with its use and seems to produce greater discomfort and higher rates of complications than IVIg in children, IVIg is usually the first-line therapy for children with GBS[91]. Although some paediatric centres administer IVIg as 2 g/kg (body weight) over 2 days, rather than the standard adult regimen of 2 g/kg (body weight) over 5 days, one study indicated that TRFs were more frequent with a 2-day regimen (5 of 23 children) than with the 5-day regimen (0 of 23 children)[78].

Step 6: monitoring disease progression

Regular assessment is required to monitor disease progression and the occurrence of complications. First, routine measurement of respiratory function is advised, as not all patients with respiratory insufficiency will have clinical signs of dyspnoea. These respiratory measurements can include usage of accessory respiratory muscles, counting during expiration of one full-capacity inspiratory breath (a single breath count of ≤19 predicts a requirement for mechanical ventilation), vital capacity, and maximum inspiratory and expiratory pressure[73,92]. Clinicians should consider using the '20/30/40 rule', whereby the patient is deemed at risk of respiratory failure if the vital capacity is <20 ml/kg, the maximum inspiratory pressure is <30 cmH_2O or the maximum expiratory pressure is <40 cmH_2O (REF[93]). Second, muscle strength in the neck, arms and legs should be assessed using the Medical Research Council grading scale or a similar scale, and functional disability should be assessed on the GBS disability scale (Supplementary Table 2), a widely used tool for documenting GBS disease course[94]. Third, patients should be monitored for swallowing and coughing difficulties. Last, autonomic dysfunction should be assessed via electrocardiography and monitoring of heart rate, blood pressure, and bowel and bladder function.

The nature and frequency of monitoring depends on the rate of deterioration, the presence or absence of autonomic dysfunction, the phase of the disease, and the healthcare setting, and should be carefully assessed in each individual patient. Up to two-thirds of the deaths of patients with GBS occur during the recovery phase and are mostly caused by cardiovascular and respiratory dysfunction[6,7,11]. We therefore advise clinicians to stay alert during this phase and monitor the patient for potential arrhythmias, blood pressure shifts, or respiratory distress caused by mucus plugs. This monitoring is especially important in patients who have recently left the ICU and in those with cardiovascular risk factors.

Step 7: managing early complications

Complications in GBS can cause severe morbidity and death[95]. Some of these complications, including pressure ulcers, hospital-acquired infections (for example, pneumonia or urinary tract infections) and deep vein thrombosis, can occur in any hospitalized bed-bound patient, and standard-practice preventive measures and treatment are recommended. Other complications are more specific to GBS, for example, the inability to swallow safely in patients with bulbar palsy; corneal ulceration in patients with facial palsy; and limb contractures, ossification and pressure palsies in patients with limb weakness (TABLE 2). Pain, hallucinations, anxiety and depression are also frequent in patients with GBS, and caregivers should specifically ask patients whether they are experiencing these symptoms, especially if patients have limited communication abilities and/or are in the ICU. Recognition and adequate treatment of psychological symptoms and pain at an early stage is important because these symptoms can have a major impact on the wellbeing of patients. Caregivers should also be aware that patients with GBS, even those with complete paralysis, usually have intact consciousness, vision and hearing. It is important, therefore, to be mindful of what is said at the bedside, and to explain the nature of procedures to patients to reduce anxiety. Adequate management of complications is best undertaken by a multidisciplinary team, which might include nurses, physiotherapists, rehabilitation specialists, occupational therapists, speech therapists and dietitians.

Step 8: managing clinical progression

Insufficient response to treatment

About 40% of patients treated with standard doses of plasma exchange or IVIg do not improve in the first 4 weeks following treatment[80,82]. Such disease progression does not imply that the treatment is ineffective, as progression might have been worse without therapy[6]. Clinicians may consider repeating the treatment or changing to an alternative treatment, but at present no evidence exists that this approach will improve the outcome[96,97]. A clinical trial investigating the effect of administering a second IVIg dose is ongoing[98].

Treatment-related fluctuations

TRFs are observed in 6–10% of patients with GBS and are defined as disease progression occurring within 2 months following an initial treatment-induced clinical improvement or stabilization[12,13]. TRFs should be distinguished from clinical progression without any initial response to treatment. The general view is that a TRF indicates that the treatment effect has worn off while the inflammatory phase of the disease is still ongoing. Therefore, patients with GBS who display TRFs might benefit from further treatment, and repeating the full course of IVIg or plasma exchange in these patients is a common practice, although evidence to support this approach is lacking[80].

CIDP

In ~5% of patients with GBS, repeated clinical relapses suggest a more chronic disease process, and the diagnosis is changed to acute-onset CIDP[12]. Acute-onset CIDP typically presents with three or more TRFs and/or clinical deterioration ≥8 weeks after disease onset[12].

Step 9: predicting outcome

Most patients with GBS, even those who were tetraplegic at nadir or required mechanical ventilation for a long period of time, show extensive recovery, especially in the first year after disease onset[11,99]. About 80% of patients with GBS regain the ability to walk independently at 6 months after disease onset[11]. The probability of regaining walking ability can be calculated in individual patients using the modified Erasmus GBS outcome score (mEGOS) prognostic tool[100] (Supplementary Table 3).

Despite the generally positive prospects for patients with GBS, death occurs in 3–10% of cases, most commonly owing to cardiovascular and respiratory complications, which can occur in both the acute and the recovery phase[7–9]. Risk factors for mortality include advanced age and severe disease at onset[7]. Long-term residual complaints are also common and can include neuropathic pain, weakness and fatigue[101–103]. However, recovery from these complaints may still occur >5 years after disease onset[103].

Recurrent episodes of GBS are rare, affecting 2–5% of patients, but this percentage is still higher than the lifetime risk of GBS in the general population (0.1%)[14,15]. Many vaccines carry a warning about GBS, although prior GBS is not a strict contraindication for vaccination. Discussion with experts might be useful for patients who were diagnosed with GBS <1 year before a planned vaccination or who previously developed GBS shortly after receiving the same vaccination. In these patients, the benefits of vaccination for specific illnesses (for example, influenza in elderly individuals) must be weighed against the small and possibly only theoretical risk of a recurrent GBS episode[14].

Step 10: planning rehabilitation

Patients with GBS can experience a range of long-term residual problems, including incomplete recovery of motor and sensory function, as well as fatigue, pain and psychological distress[103]. Before the patient is discharged, these possible long-term effects of GBS should be considered and managed[104,105].

Physical function

Arranging a rehabilitation programme with a rehabilitation specialist, physiotherapist and occupational therapist is a crucial step towards recovery. Programmes should aim to reduce disability in the early stages of recovery and later to restore motor and sensory function and physical condition to predisease levels[106]. Exercise programmes for patients with GBS, which include range-of-motion exercises, stationary cycling, and walking and strength training, have been shown to improve physical fitness, walking ability and independence in activities of daily living[106]. However, the intensity of exercise must be closely monitored as overwork can cause fatigue[106].

Fatigue

Fatigue, unrelated to residual motor deficits, is found in 60–80% of patients with GBS and is often one of the most disabling complaints[107,108]. Other causes should be considered before concluding that fatigue in a patient is a residual result of GBS. As with recovery of physical function, a graded, supervised exercise programme has been shown to be useful in reducing fatigue[109].

Pain

Severe pain is reported in at least one-third of patients with GBS 1 year after disease onset and can persist for >10 years[14,26]. Chronic pain in GBS is characterized by muscle pain in the lower back and limbs, painful paraesthesias, arthralgia, and radicular pain. Although the pathogenesis of this pain is not fully understood, muscle pain and arthralgia might be attributable to immobility, and neuropathic pain might be caused by regeneration of, or persistent damage to, small nerve fibres[26]. Management strategies include encouraging mobilization and administering drugs for neuropathic or nociceptive pain[104].

Psychological distress

Rapid loss of physical function, often in previously healthy individuals, can be severely traumatic and may cause anxiety and/or depression. Early recognition and management of psychological distress is important in patients with GBS, especially as mental status can influence physical recovery and vice versa; referral to a psychologist or psychiatrist might be beneficial for some patients[110]. Providing accurate information to patients on the relatively good chance of recovery and low recurrence risk (2–5%) can help reduce their fear[11,14]. Connecting patients with others who have had GBS can also help guide them through the rehabilitation process. The GBS/CIDP Foundation International — the international patient association for GBS — and other national organizations can help establish these networks.

Conclusions

GBS can be a complex disorder to diagnose and manage as the clinical presentation is heterogeneous and the prognosis varies widely between patients. Managing GBS can be especially challenging during outbreaks triggered by infectious disease, as was most recently seen during the Zika virus epidemic. In the absence of an international clinical guideline for GBS, we have

developed this consensus guideline for the diagnosis and management of GBS. This guideline was developed by a team of clinical neurologists from around the world and is designed for general applicability in all clinical environments, irrespective of specialist capabilities or availability of resources. The step-by-step design was used to focus attention on the most important issues in GBS and to make the guideline easy to use in clinical practice.

As the field of GBS research develops, and ongoing studies aim to improve diagnostics, treatment and prognostic modelling, this guideline will need to be updated regularly. For example, ultrasound imaging of the peripheral nerves is emerging as a potential diagnostic tool and might require further comment in future versions of this guideline. In relation to treatment, the efficacy of complement inhibitors, IgG-cleaving enzymes and a second course of IVIg is being investigated[78,111,112]. Little is known about how to measure and predict long-term outcome in patients with GBS, and validation studies of known prognostic models (for example, mEGOS and EGRIS) and research into new outcome measures are needed. We intend to seek feedback on this guideline and provide updates based on results from ongoing studies and future research.

To further improve the worldwide management of GBS, we aim to use this consensus report as a basis for the development of online information resources, training material and teaching courses. These resources will be directed towards healthcare workers, including clinical neurologists, as well as patients with GBS and their relatives.

Published online 20 September 2019

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Acknowledgements

The authors thank Lisa Butler (Executive Director, GBS/CIDP Foundation International) for her contribution in reviewing the manuscript. C.A.P., C.S., M.L.B.F., M.R.M., and S.E.L. are supported by a grant from the European Union (Horizon 2020, ZikaPLAN Grant Agreement No. 734584). H.J.W. is supported by a grant from the European Union (Horizon 2020, ZikaPLAN Grant Agreement No. 734584) and by the Wellcome Trust Foundation. B.C.J. is supported by a grant from the European Union (Horizon 2020, ZikaPLAN Grant Agreement No. 734584) and has received funding from Prinses Beatrix Spierfonds and GBS/CIDP Foundation International. F.d.A.A.G. is supported by a grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico. D.R.C. is on the

Board of Directors for the Peripheral Nerve Society. P.A.v.D. received a grant from the Prinses Beatrix Foundation for the SID-GBS randomized controlled trial. S.K. is supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grants-in-Aid for Scientific Research, 18H02745) and the Ministry of Health, Labour and Welfare of Japan (Health and Labour Sciences Research Grant). N.S. is supported by grants from the Malaysian Ministry of Education (FP043-2018A) and ALS Association. T.U. is supported by a grant from the GBS/CIDP Foundation International. E.M.Y. is supported by a grant from the National Health and Medical Research Council of Australia (Early Career Fellowship).

Author contributions

All authors made substantial contributions to the discussion of article content and edited the manuscript before submission. B.C.J., S.E.L. and M.R.M. conceptualized and designed the article structure, researched data for the article, and wrote the first draft of the manuscript.

Competing interests

B.C.J. has received funding from Annexon Biosciences, Baxter, CSL Behring, Hansa Biopharma and Grifols. D.R.C. has received consultancy honoraria from Annexon Biosciences, argenx, Biotest Pharmaceuticals, Cigna Health Management, CSL Behring, DP Clinical, Grifols, Hansa Biopharma, New Enterprise Associates, Octapharma, Pharnext SAS, Polyneuron Pharmaceuticals, Seattle Genetics, Stealth BioTherapeutics, and Syntimmune. D.R.C is also on a data safety monitoring board for Pfizer, Sanofi, Alnylam Pharmaceuticals, PledPharma, and Momenta Pharma. Johns Hopkins University has licensed technology to AstraZeneca Pharmaceuticals, Genentech, Levicept, Seattle Genetics, Merrimack Pharmaceuticals, Levicept and Disarm Therapeutics, for which D.R.C. receives royalties. P.A.v.D. received a grant from Sanquin Blood supply for the SID-GBS randomized controlled trial, and a grant from Grifols to conduct the I-SID GBS study. R.A.C.H. has received consultancy honoraria from Laboratoire Francais du Fractionnement et des Biotechnologies (LFB S.A.). S.K. has received speaker honoraria from Teijin Pharma, Nihon Pharmaceutical and Japan Blood Products Organization, and research support from Nihon Pharmaceutical and Japan Blood Products Organization. R.R. is supported by a grant from CSL Behring. N.S. receives research support from Hovid Berhad. The other authors declare no competing interests.

Reviewer information

Nature Reviews Neurology thanks Antonino Uncini and the other, anonymous, reviewers for their contribution to the peer review of this work.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/s41582-019-0250-9.

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Neurological gait disorders in childhood

Martin Smith
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Abstract

There are an enormous number of neurological illnesses that can manifest with gait disturbance in childhood. Whilst experience and clinical acumen are helpful in diagnosing these disorders, some basic principles in assessment and diagnosis are helpful in determining the phenomenology, time course, and neuro-anatomical localisation. In this review we focus on some of the more common movement disorders resulting in inserted postures (including spasticity and dystonia), inserted movements (including chorea and myoclonus), and impairment of motor control (including ataxia and neuro-muscular disorders). A number of case studies are included to illustrate the factual descriptions.

Keywords ataxia; chorea; dystonia; gait disorders in childhood; myoclonus; spasticity

Case study: a 14-year-old female is referred with a gait disorder. She was born prematurely, at 28 weeks gestation, but attained her motor milestones within the normal range. She has high functioning autistic spectrum disorder and anxiety. There is no relevant family history.

Examination reveals unequivocal upper motor neuron signs, predominantly in the lower limbs. MRI scan reveals white matter abnormalities adjacent to the lateral ventricles, consistent with white matter injury of prematurity.

Genetic testing revealed a mutation in the *KIF5A* gene, associated with Hereditary Spastic Paraparesis type 10. The history of prematurity and PVL was incidental to her gait disorder.

Introduction

Although many other neurological impairments can be a far greater barrier to independence, gait disorders remain an important group of presentations in child neurology. It is useful to be able to recognise the key features in presentation, to guide strategies for diagnosis and therapy.

The neurological building blocks of successful ambulation include strength, balance and planning of complex movement. Sensory input including vision, vestibular and proprioceptive feedback are also integral. It follows that ambulation can be threatened by weakness, poor balance, poor motor planning and control, and sensory impairments. These difficulties can be continually present, or episodic.

In this article, we focus primarily on some of the more common movement disorders resulting in inserted postures (including spasticity and dystonia), inserted movements (including chorea and myoclonus), and impairment of motor control (including ataxia and neuro-muscular disorders), which can overlap in many individuals. A number of case studies are included to illustrate the factual descriptions.

Spasticity

Spasticity is defined as a velocity-dependent increase in muscle tone. It typically results in co-contraction of antagonist muscle pairs, with a bias towards greater involvement of the upper limb flexors and lower limb extensor muscle groups. Spasticity of the lower limbs tends to lead to hip extensor tightness, reduced knee flexion during swing through, and equinus posture due to excessive contraction of gastrocnemius. This results in forefoot contact, and the so-called waddling gait as circumduction of the hip compensates to allow swing through. Spasticity may occur following lesions to the brain or spinal cord (pyramidal tract lesions), but can also occur in non-lesional disorders such as hereditary spastic paraparesis.

Investigations should always include imaging of the brain and spinal cord, and if normal may require further investigations e.g. metabolic investigations, and genetic screen for hereditary spastic paraparesis.

There are many therapeutic options to reduce spasticity in specific or wider muscle groups. These include drugs (e.g. oral Baclofen), localised neuromuscular blockade (Botulinum neuro-toxin), and neurosurgical procedures (e.g. selective dorsal rhizotomy and intra-thecal Baclofen delivery). Physiotherapy is at least as important as all these options, and the absence of physiotherapy renders the medical interventions nearly futile.

Whenever these treatments are employed it is important to have clear functional goals, and always remember that spasticity is one part of the upper motor neuron syndrome, along with weakness and poor motor planning. Spasticity reduction in itself may not always lead to improved function, and may even worsen function, particularly in the context of underlying weakness/instability.

Dystonia

Dystonia has similarities to spasticity, in leading to co-contraction of antagonistic muscle groups. However, the velocity-dependent element is absent, the disorder is more fluctuant with variability in tone, can be task specific, and more likely to lead to twisting postures.

Gait disorders in dystonia may appear at times frankly bizarre, due to the predominance of extensor activity and twisting postures. As a general rule, the ankles will demonstrate equinovarus posture, but there is a greater range of abnormalities than seen in spasticity. Moreover, the task specific element can be a source of confusion in distinguishing between dystonia

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and functional gait disorders. For example, it is entirely possible for an individual with dystonia to be unable to walk forward without assistance, but able to walk backwards unaided, or even ride a bicycle.

Dystonia is typically associated with lesions of the thalami and basal ganglia (extra-pyramidal tracts) but can also occur in non-lesional, usually genetic, disorders e.g. DYT1 and DYT5 (dopa-responsive dystonia).

The investigation of dystonia should be targeted to the clinical context. An MRI brain scan is invariably required, and further investigations may include:

- Copper and caeruloplasmin (Wilson's disease)
- Blood film (for acanthocytes)
- TSH, T3 and T4 (Allan-Hernon Dudley syndrome)
- Urate (Lesch-Nyhan syndrome)
- Paired blood and CSF glucose (GLUT1 deficiency)
- CSF neurotransmitters (disorders of dopamine/serotonin synthesis, metabolism or transport) and lactate (mitochondrial disorders)
- Other metabolic tests — plasma lactate, manganese, biotinidase, very long chain fatty acids, lysosomal screen, vacuolated lymphocytes, acylcarnitine profile, transferrin isoelectric focussing
- Urine organic acids, creatine to creatinine ratio
- CGH microarray (for copy number variants, deletions and duplications encompassing disease-causing genes) and multigene panels for monogenic dystonia (e.g. DYT1, DYT11, *PANK2*/*PLA2G6* and other disorders of neurodegeneration with brain iron accumulation, *KMT2B* and other genes causing complex dystonia phenotypes)
- Neurophysiology should not be required to diagnose pure dystonia, but some disorders demonstrate a mixed pattern of dystonia and lower motor neuron signs

Therapeutic options to manage dystonia include medication (e.g. Trihexyphenidyl, Gabapentin, Clonidine), Botulinum toxin, ITB and deep brain stimulation. The latter is particularly effective in primary dystonia with normal imaging, but also offers some degree of benefit in secondary dystonia, notably Pantothenate Kinase Associated Neurodegeneration. The ketogenic diet may be considered in individuals with GLUT1 deficiency. A trial of Levodopa can significantly ameliorate or even abolish motor symptoms in patients with Segawa's disease (DYT5-dystonia) and other dopa-responsive disorders, and should be considered first line in patients with dystonia of undetermined aetiology.

Some forms of dystonia may be intermittent, and can be characterised as either movement related (kinesogenic), not-related to movement (non-kinesogenic), or specifically related to sustained exercise (Lance type). Paroxysmal kinesogenic dystonia is triggered by sudden movement, and episodes are short lasting on average, approx. 1 minute. They are associated with mutations in the *PRRT2* gene, and typically respond very well to low dose Carbamazepine. Non-kinesogenic dystonic episodes tend to last much longer (up to several hours), and may be triggered by caffeine or alcohol. They respond less well to Carbamazepine, but may respond to benzodiazepines. Exercise induced dystonia show mixed responses to these medications.

Case study: a 6-year-old girl is referred for advice on the management of cerebral palsy. On closer questioning she was born at term following an uneventful pregnancy, in good condition, and did not display any feature of neonatal encephalopathy. She had never walked unaided, but had been able to walk with the help of one from 3 years of age. MRI brain and spine were normal. Examination findings were suggestive of bilateral lower limb spasticity, although plantar responses were flexor (downgoing).
The specific question parents asked is "why doesn't she have cerebral palsy in the morning, doctor?".
The history of fluctuation, together with the unremarkable neonatal history and normal imaging, suggested the diagnosis of dopa-responsive dystonia (Segawa disease or DYT5). She was given an empirical trial of low dose L-Dopa (2 mg/kg/day), and was walking normally within one week. Subsequent genetic testing revealed a mutation in the *GCH1* gene. Neurotransmitters were not measured, but would be expected to show low neopterin, low BH4, low HVA, low/normal 5-HIAA, although for some patients, the CSF profile can be (near) normal.
She remained with near normal mobility until transition to adult services. The only residual abnormality was very mild ankle varus. However, she was susceptible to anxiety and depression (which is reported in this condition, and possibly related to cerebral serotonin deficiency) which was not corrected by L-Dopa replacement.

Case study: a 9-year-old girl is referred with in-turning of the left ankle. Over the following 12 months this progresses, with involvement of all four limbs. She becomes non-ambulant. Her facial muscles are spared. MRI scan and baseline metabolic investigations are normal. Genetic testing reveals the heterozygous common mutation (GAG deletion) in the *TOR1A* (DYT1) gene.
She proceeds to implantation of a deep brain stimulator, with bilateral electrodes positioned in the globus pallidus interna. Initial improvement is modest, but over 6 months she regains entirely normal function, which is maintained at last follow up over a decade later.

Case study: a 15-year-old male is referred with walking difficulties. For 6 months previously he had had some personality change attributed to teenage moodiness. Examination revealed generalised dystonia. MRI scan revealed high signal with the basal ganglia. There was no obvious Kayser-Fleisher ring to routine inspection. However, he was found to have low values of serum copper and caeruloplasmin, and a mutation in the *ATP7B* gene, confirming the diagnosis of Wilson's disease.
He was treated with chelation therapy with Trientene and Zinc, with satisfactory gradual reduction in urinary copper values. However, his dystonia continued to progress and he became non-ambulant.
Comment: Early diagnosis is crucial in Wilson's disease, although chelation therapy is not always effective in preventing further deterioration of physical signs.

Case study: a 6-year-old male is referred with a gait disorder superimposed on mild global developmental delay. Examination findings are non-specific, but appear to be a mixed picture of extra-pyramidal signs and weakness. MRI brain revealed cerebellar atrophy.
Whole exome sequencing identifies bi-allelic mutations in the *PLA2G6* gene. Over the following 3 years he becomes non-ambulant, with cortical visual impairment and worsening cognitive ability. DBS is considered but declined, and he is listed for an ITB pump to manage worsening dystonia.

Case study: a 14-year-old male is referred with an intermittent gait disorder. He was playing as goalkeeper for a football team, but has recently stopped as he would become frozen or locked when he needed to rush out towards on oncoming attacker.
Routine neurological examination was unremarkable, but when asked to stand and run suddenly he developed generalised dystonia lasting approx. 1 minute.
The diagnosis of paroxysmal kinesogenic dystonia led to the prescription of low dose Carbamazepine (5 mg/kg/day), on which he became entirely asymptomatic. Subsequent genetic testing identified a mutation in the *PRRT2* gene.

Chorea and athetosis

Chorea produces involuntary, random-appearing, high frequency inserted movements. Athetosis is similar, but of lower intensity, almost writhing, and can be likened in some respects to a cat's tail in the relatively languid appearance of the movements.

The gait manifestations seen in chorea are primarily due to the breakdown of co-ordinated movement, although can be exacerbated by co-existing dystonia and weakness.

Relatively common causes include neonatal hypoxic-ischaemic injury (sometimes labelled as dyskinetic cerebral palsy), hyperbilirubinaemia, para-infectious or post-streptococcal syndromes, and rare but increasingly recognised disorders such as NMDA receptor antibody encephalitis. Benign hereditary chorea, is associated with mutations in the *NKX2-1* gene which encodes the Thyroid Transcription Factor 1 (TITF1).

ADCY-5 related dyskinesias typically present with axial hypotonia and delayed motor and/or language milestones during infancy, associated with early onset chorea with a generalised distribution, classically also involving the facial muscles and peri-oral region.

Mutations in *GNAO1* were initially reported in association with early infantile epileptic encephalopathy. Subsequently the recognised phenotype has widened to include a hyperkinetic movement disorder, with exacerbations triggered by fever and other intercurrent illness.

Treatment may be targeted against the underlying disorder (e.g. plasma exchange for NMDAR Ab encephalitis), but medication to suppress chorea may include Levetiracetam, Tetrabenazine, Sodium Valproate and Sulpiride.

Deep brain stimulation has proven to be partially effective in some conditions. For example, bilateral GPi DBS can substantially improve the frequency and severity of life-threatening exacerbations in individuals with *GNAO1* mutations, although the baseline movement disorder is largely unchanged.

Case study: a 14-year-old female presented to hospital with headaches and a first seizure. GCS was 15, with no focal neurology. A routine CT scan was normal. CSF examination revealed 55 white cells, no red cells, and PCR was positive for herpes simplex. She was treated with 3 weeks of iv acyclovir. After 2 weeks she deteriorated substantially, developing a choreiform movement disorder. She became encephalopathic, and required tube feeding. She was incontinent.
Immunological testing revealed antibodies against NMDA receptors. Ovarian teratoma and other neoplastic lesions were not found. She was treated with high dose steroids, IVIG, and plasma exchange. She improved only very slowly, but by 9 months she was able to be discharged home. She returned to school 12 months after the onset of her illness, and subsequently achieved 10 GCSE qualifications.

Myoclonus

Myoclonus is the fastest of the movement disorders, typically producing "electric shock" type movements or jerks (positive myoclonus) of 10–50 ms duration, although spinal or brain stem myoclonus may last up to 200 ms. Negative myoclonus refers to sudden, brief relaxation of muscles, and may result in drop attacks.

It can be caused by lesions within widely dispersed parts of the central nervous system, including the cortex, sub-cortex, brain stem and spinal cord. Important features to extract in the history and examination include whether it occurs at rest, during action, or is stimulus driven, and whether it is irregular or rhythmic.

As with chorea, the gait manifestations seen in myoclonus are primarily due to the interruption of smooth co-ordinated movement, although can be exacerbated by co-existing dystonia etc.

Myoclonus can be benign, but is sometimes a feature of progressive neurodegenerative disorders. A key distinction is between epileptic and non-epileptic myoclonus, which is relatively simple by means of ictal EEG. Epilepsy syndromes with myoclonus include juvenile myoclonic epilepsy, myoclonic absence and myoclonic astatic epilepsy. Progressive myoclonic epilepsy is a feature of neuronal ceroid lipofuscinosis, mitochondrial disease, Unverricht-Lundborg disease, sialidosis and Lafora body disease.

Non-epileptic myoclonus is seen in dystonia-myoclonus syndrome (DYT11), and opsoclonus-myoclonus syndrome. Non-epileptic myoclonus is often pharmaco-resistant, but options can include piracetam, levetiracetam, and topiramate.

Case study: a 5-year-old girl is seen in clinic with a several years history of hand tremor and a mild gait disorder. Her paternal grandmother had suffered a persistent tremor since childhood, attributed to meningitis in infancy. The child's father was healthy.
Examination revealed marked pectoral myoclonus, with mild dystonic posturing of the outstretched hands. Her gait was only mildly abnormal, with only a hint of dystonia.
Genetic testing confirmed a pathogenic heterozygous mutation in the *epsilon-sarcoglycan* gene (DYT11) in all three family members.
There was no benefit in the upper limb tremor from oral medication (including levetiracetam, piracetam, and trihexyphenidyl). Deep brain stimulation was considered but declined by the family.
Comment: DYT11 commonly displays the phenomenon of genomic imprinting, with inactivation of the maternal allele. When inherited from the mother, the disease manifests in only 5—10% of individuals. When inherited from the father, approx. 90% will be affected.

Ataxia

Ataxia is defined as an inability to generate a normal or expected voluntary movement trajectory that cannot be attributed to weakness or involuntary muscle activity about the affected joints. Typically this manifests as a broad based gait disorder due to impaired balance and co-ordination, and may be due to pathology affecting cerebellar motor control or impaired proprioception. MRI brain imaging is mandatory in all new onset cases.

Ataxia can be classified by acute, or chronic onset, and whether or not it is stable, progressive or episodic. Examples of acute non-progressive ataxia include acute cerebellitis (which is typically para or post infectious, and may follow Herpes Zoster), and Guillain-Barre syndrome (including the Miller Fisher variant). Chronic progressive disorders include ataxia telangiectasia, and Friedreich's ataxia.

Ataxia telangiectasia (AT) is important to recognise early, to avoid un-necessary exposure to ionising radiation. However, the characteristic ocular telangiectasia are rarely evident in preschool years. It is therefore important to measure serum alpha-feto protein levels in a child with unexplained ataxia or dystonia.

Ataxia with oculomotor apraxia type 1 has a similar neurological phenotype to AT, although the AFP is not elevated. Most cases are related to mutations in the *APTX* gene. AOA types 2 and 3 are also described.

The cardinal features of Friedreich's ataxia are the combination of gait ataxia, axonal neuropathy, areflexia, extensor plantar responses, cardiomyopathy and diabetes. There is no currently effective treatment, although Idebenone is often used empirically.

Other rare causes of ataxia which are potentially amenable to treatment, include ataxia with vitamin E deficiency, abetalipoproteinaemia, cerebrotendinous xanthomatosis, Refsum's disease, and Hashimoto encephalopathy.

There are two well described forms of episodic ataxia, although advances in genetic technologies have resulted in an increasing number of reported genetic episodic ataxias. In type 1, the ataxia is usually brief, lasting seconds to minutes. Myokymia may be present between ataxic episodes. Triggers can include anxiety, excitement and fever. Most cases are related to heterozygous mutations in *KCNA1*. Acetazolamide may be helpful, but benefit is not always sustained.

In EA type 2 episodes may last hours to days, although some children will present with chronic progressive ataxia. Most cases are related to mutations in the *CACNA1A* gene. In type 2, the episodes can last hours to days, and may also respond to Acetazolamide.

Mutations in *ATP1A3* are associated with cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensori-neural hearing loss (CAPOS syndrome). ATP1A3 variants are also reported in both rapid-onset dystonia parkinsonism, and alternating hemiplegia of childhood.

Case study: a 2-year-old boy is referred with motor delay and speech delay. He has recently started to walk but with a persisting broad-based gait. Both parents appear fit and well, but on closer questioning father admits to episodic difficulties with balance. On occasions, he has been refused entry to pubs as he appeared drunk, even before he had consumed any alcohol. He has always attributed this to tiredness, and had never sought medical advice.
Genetic investigations identified that both father and son have mutations in the *CACNA1A* gene. Both were offered a trial of acetazolamide. Father reported complete resolution of his symptoms, but unfortunately the child did not show any improvement on the maximum dose tolerated.

Neuromuscular weakness

It is always important to bear in mind that disorders of the peripheral nervous system may impair gait, whether by weakness and/or impaired sensation.

Anatomically they can be considered disorders affecting the anterior horn cell (e.g. spinal muscular atrophy), peripheral nerve (e.g. Charcot-Marie-Tooth syndrome), neuromuscular junction (e.g. myasthenia gravis), or muscle (e.g. Duchenne muscular dystrophy). Typically these disorders will demonstrate weakness, wasting, and reduced or absent reflexes. Romberg's sign may be positive if the dorsal columns are involved.

The classical picture of a high stepping gait, due to weakness of ankle dorsiflexion, is commonly seen in peripheral neuropathies. This can often be heard as well as seen, with a slapping sound as the foot makes contact with the ground.

Investigations will usually include creatinine phosphokinase, nerve conduction studies and EMG, and more detailed genetic investigations targeted at the specific concerns.

Functional gait disorders

This important group of disorders, sometimes also known as medically unexplained or psychogenic illness, commonly present to both Paediatric and Adult Neurology services. Most experienced clinicians will make an early diagnosis based on features that include fluctuation and inconsistencies, pattern and distribution of the movement disorder, in the absence of any plausible neuro-anatomical basis. However, a reasonable number of baseline investigations are usually required to reassure the child and family.

Whilst it is sensible to remain open-minded, it is important to be honest and open with the young person and family when the disorder appears unlikely to have an organic explanation. Detailed investigations for implausible diagnoses may delay or erode the prospects of recovery.

Many young people will respond to a holistic rehabilitation regime, which should ideally include a clinical psychologist. However, a significant minority can remain entrenched in a medical model of long term neurodisability.

Summary

There are an enormous number of neurological illnesses that can manifest with gait disturbance. In this review we have attempted to describe some of the more common disorders. There is no substitute for experience in diagnosing these disorders, but basic principles in assessment and diagnosis include a careful history and examination to understand the phenomenology, time course, and neuroanatomical localisation. Investigations will almost always include imaging of the brain and spinal cord, with further investigations targeted appropriately towards the differential diagnosis.

A proportion of disorders will be either self-limiting or amenable to a range of medical interventions, but many will prove to be chronic or progressive disorders, which require a holistic approach to caring for the young person and family. ◆

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Practice points

- History and examination are vital in establishing an accurate diagnosis in movement disorders
- Dystonia, in particular, represents a significant diagnostic challenge as symptoms may vary considerably and appear initially inconsistent
- When assessing a child with a neurological gait disorder, it is helpful to carefully characterise both the positive and negative factors. The latter may often produce greater impairment. Examples of positive factors leading to excessive muscle contraction include inserted postures (e.g. dystonia), and inserted movements (e.g. myoclonus or chorea). Examples of negative factors including weakness and ataxia.

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Cite this as: *BMJ* 2020;371:m3745
http://dx.doi.org/10.1136/bmj.m3745
Published: 21 October 2020

PRACTICE POINTER

Recognising and explaining functional neurological disorder

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What you need to know

- Functional neurological disorder (FND) is associated with considerable distress and disability. The symptoms are not faked
- Diagnose FND positively on the basis of typical clinical features. It is not a diagnosis of exclusion
- FND can be diagnosed and treated in presence of comorbid, pathophysiologically defined disease
- Psychological stressors are important risk factors but are neither necessary nor sufficient for the diagnosis

Functional disorders are conditions whose origin arises primarily from a disorder of nervous system functioning rather than clearly identifiable pathophysiological disease—such as irritable bowel syndrome, fibromyalgia, and functional neurological disorder (FND)—they are the second commonest reason for new neurology consultations.[1] FND is common in emergency settings,[2] stroke,[3] and rehabilitation services.[4] It causes considerable physical disability and distress, and often places an economic burden both on patients and health services.[5] Many clinicians have had little formal clinical education on the assessment and management of these disorders, and patients are often not offered potentially effective treatments.

In practice, FND should be diagnosed by someone with specific expertise in the diagnosis of neurological conditions. Our recommendation is to refer all patients with a suspected diagnosis of FND to secondary care. However, the diagnosis may be raised as a possibility with the patient in primary care, and knowledge of how the diagnosis is confirmed greatly aids subsequent management.

In this article we offer evidence based advice to generalists on how to recognise FND, based on clinical diagnostic and prognostic studies. Although the focus of this paper is on recognising FND, we have included a short box on management to make readers aware that there are good treatments available for FND and that some patients can get better.

Sources and selection criteria

We conducted a PubMed search of evidence for diagnosis of functional neurological disorder (FND) until June 2020, especially systematic reviews.[14 30 31] We also relied on author research paper archives, and a recent international comprehensive textbook on FND (JS and AC were co-editors).[32] The article was reviewed and improved by representatives from five patient organisations: FND Hope, FND Hope UK, FND Action, FND Dimensions, and FND Friends.

What is functional neurological disorder?

FND describes a disorder of the voluntary motor or sensory system with genuine symptoms including paralysis, tremor, dystonia, sensory disturbance (including visual loss), speech symptoms, and seizures. The hallmark is that such symptoms can be positively identified as internally inconsistent or incongruent with recognised pathophysiological disease.

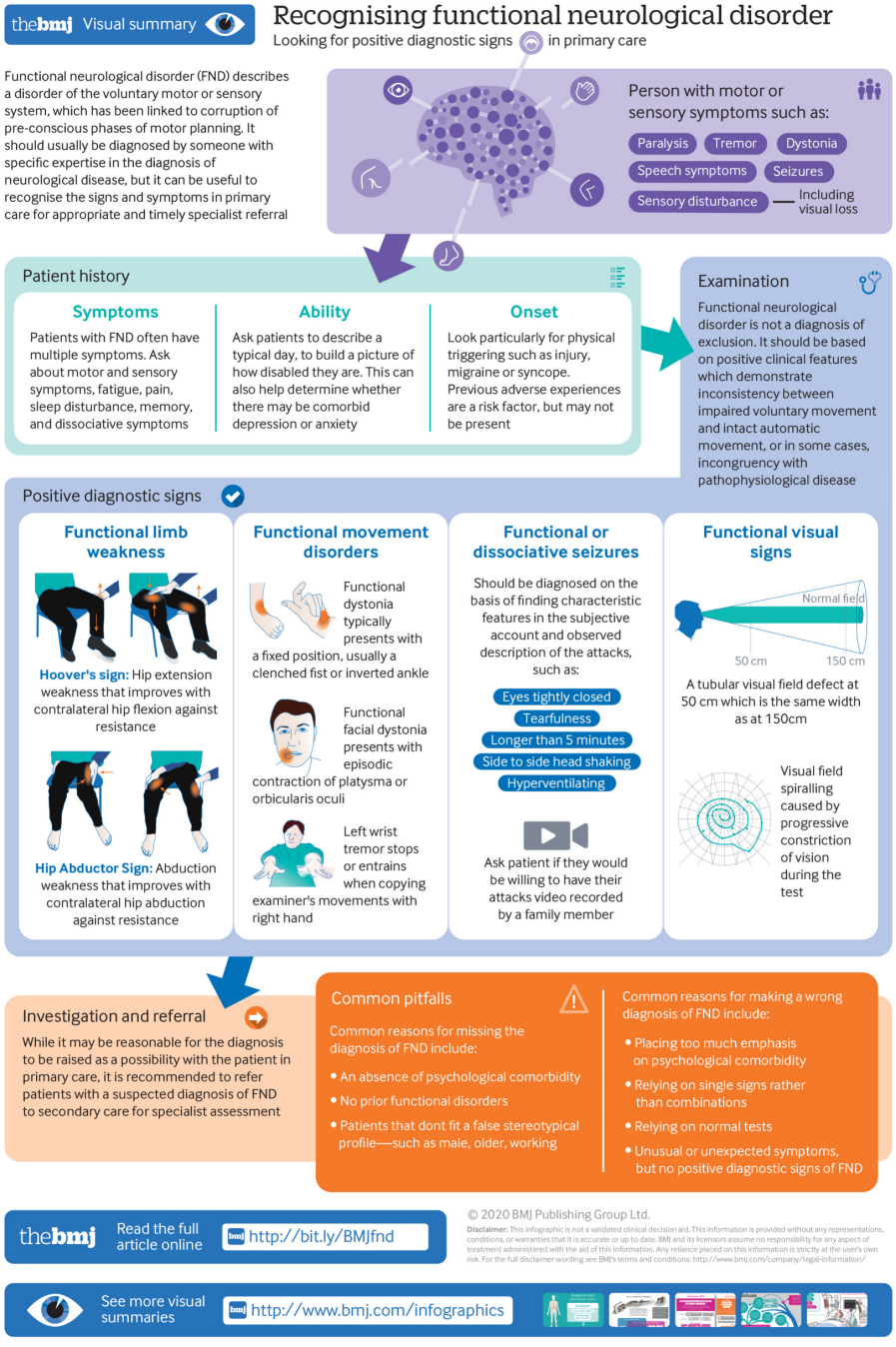
It is not a diagnosis of exclusion

Commonly used synonyms are dissociative neurological symptoms, psychogenic neurological symptoms, and conversion disorder. The DSM-5 definition of FND requires the presence of positive diagnostic features and not just the exclusion of other conditions. In DSM-IV, one of the diagnostic requirements for FND was a recent psychological stressor; however, this was removed in recognition that many patients do not have identifiable stressors.

FND often coexists with other persistent physical symptoms such as dizziness, pain, and fatigue. Patients may also have other functional disorders such as irritable bowel syndrome, fibromyalgia, or chronic pelvic pain.

What are the new concepts in the mechanism and aetiology of functional neurological disorder?

In the past 20 years, developments in the application of neuroscience and the availability of more detailed clinical studies has led to a shift in how we consider the aetiology and mechanism of FND. Previously, FND was always considered to be a consequence of adverse life events such as recent stress or childhood experience. Newer models take account of motor physiology and predictive coding theories. Growing evidence supports the notion that in FND the early pre-conscious phases of motor planning are corrupted by a combination of abnormal involuntary brain-generated predictions about bodily states and interference from more emotionally orientated brain networks such as the limbic system and amygdala.[6-8] For example, signs such as tubular visual field loss (see infographic) can be explained by considering the brain as a largely "predictive" organ which makes and tests predictions about the body rather than constructing perceptions from scratch. In FND it is thought that the brain prioritises excessively strong predictions based on what the brain expects to "see" (such as "tunnel vision") or be able to do (leg weakness) over the actual incoming sensory input.[9]



Such models acknowledge that previous adverse experiences are a risk factor for the development of FND,[10] but they also explain how symptoms are formed, allow for symptom development in patients who have not had adverse experiences, and help explain why symptoms are often triggered by minor physical trauma or pathophysiological events such as migraine or panic attacks.[11] These models challenge outdated ones that are dependent on a dualistic separation of mind and brain. They present FND as a disorder of a dynamic, plastic brain that constantly modifies its structure and function through interactions with the environment and its interoceptive relationship with the body.[6]

How is a positive diagnosis of functional neurological disorder made?

Diagnosis is based on positive clinical features which typically demonstrate impaired voluntary movement or sensation in the presence of intact automatic movement or sensation, or in some cases, incongruency with pathophysiological disease.

Patient history

Some helpful features of history taking in FND include:

- *List the symptoms*—Patients with FND often have multiple symptoms. As well as asking about motor and sensory symptoms,

ask about fatigue, pain, sleep disturbance, and memory, and offer patients time to list their physical symptoms.[1]

- *Describe a typical day*—This helps build a picture of how disabled the person is and can help determine whether there may be comorbid depression or anxiety. Asking about good days and bad days can help assess variability.
- *Ask about onset and course,* looking particularly for physical triggering such as injury, migraine, or syncope that may help explain why a particular symptom developed. For example, migraine aura can trigger functional limb weakness, or an unexpected syncope can trigger subsequent dissociative attacks.
- *Ask about dissociative symptoms* such as depersonalisation (a feeling of being disconnected from your own body) and derealisation (a feeling of being disconnected from the world around you).[12] These are common symptoms and can occur at the onset or as part of a dissociative attack. It may be a relief to a patient to discover that their strange experiences have a medical name and are shared by many other people.
- *Use of home video*—For episodic symptoms such as seizures or paroxysmal movement, mobile phone videos (with patient consent) can be helpful for diagnosis.[13]
- *Ideas, concerns, and expectations*—Ask the patient what they and their family or carers think might be wrong, about the experiences they have had with healthcare professionals, and what they think it would be helpful for doctors to do at this point.
- *Asking about stress and adverse life events*—See box 1.

Box 1: Should you ask about adverse life events?

Adverse recent and childhood life events such as abuse are common in the general population and in a range of medical and psychiatric disorders. A systematic review and meta-analysis of 34 case-control studies of functional neurological disorder (FND) found that adverse events are more common in FND than in the general population (with an odds ratio of 2-4), but are certainly not always present, and their presence is not useful diagnostically.[10]

Exploring past traumatic life events may help with individual formulation of aetiology and future treatment, but doing so may also cause distress. Patients with FND who have not had these events may have been sensitised by previous encounters to consider this line of questioning an intrusion into their privacy and an inappropriate search for a psychological cause. Patients with FND who have had adverse experiences may feel they are being blamed for their symptoms by an authority figure, which can recapitulate the traumatising event. If necessary, or if encouraged by the patient, inquire about adverse life events with sensitivity at a pace that is suitable to the patient. It can often wait until follow-up visits.

Clinical features

The diagnosis of FND rests on the demonstration of one or more (usually a combination) of positive physical clinical features, with examples listed below[14]:

Functional limb weakness

- *Hoover's sign* describes weakness of hip extension which returns transiently to normal during contralateral hip flexion against resistance (see fig 1 and infographic). It can be done sitting or lying.
- *The hip abductor sign* describes a similar sign in relation to weakness of hip abduction that returns to normal with contralateral movement (fig 1 and infographic).

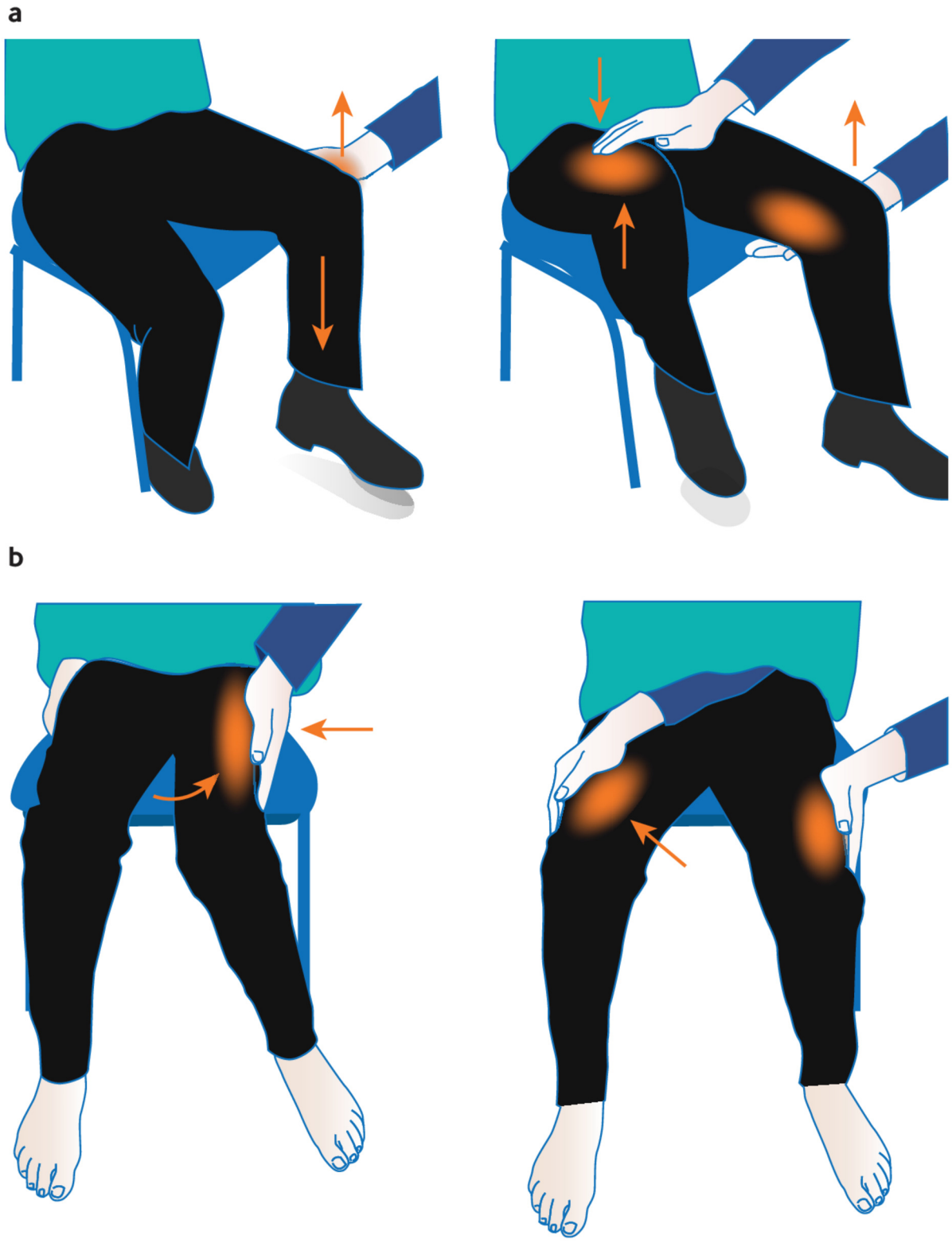


Fig 1 | (a) Hoover's sign of functional leg weakness in functional neurological disorder (FND): hip extension is weak to direct testing (left), but hip extension strength becomes normal with contralateral hip flexion against resistance (right) (adapted from Stone[15]). (b) Hip abductor sign of functional leg weakness in FND: hip abduction is weak to direct testing (left), but strength becomes normal with contralateral hip abduction against resistance (right) (adapted from Stone et al[16])

Functional movement disorders

- *Functional tremor* is diagnosed by looking for evidence of distractibility with the "entrainment test." Ask the patient to copy rhythmic movements of varying frequency made by the examiner between thumb and forefinger using one hand and then observe the response in the other hand. Cessation of the tremor, "entrainment" to the same rhythm, or inability to copy the movement suggest functional tremor. See fig 2 and infographic.

Fig 2 | Tremor entrainment test of functional tremor in functional neurological disorder. The patient copies the examiner making variable rhythmic pincer movements of thumb and forefinger with their better (right) side. The patient's left sided functional tremor stops during the entrainment task, showing that its distractible (adapted from Roper et al[17]). If the tremor entrains to the same rhythm as the examiner or the patient cannot copy the movement the test is also positive

- *Functional dystonia* typically presents with a fixed position, usually a clenched fist or inverted ankle (see fig 3 and infographic). This is different to other types of dystonia which are usually mobile.
- *Functional facial dystonia* usually presents with episodic contraction of platysma or orbicularis, resulting in a typical appearance (see fig 3 and infographic).

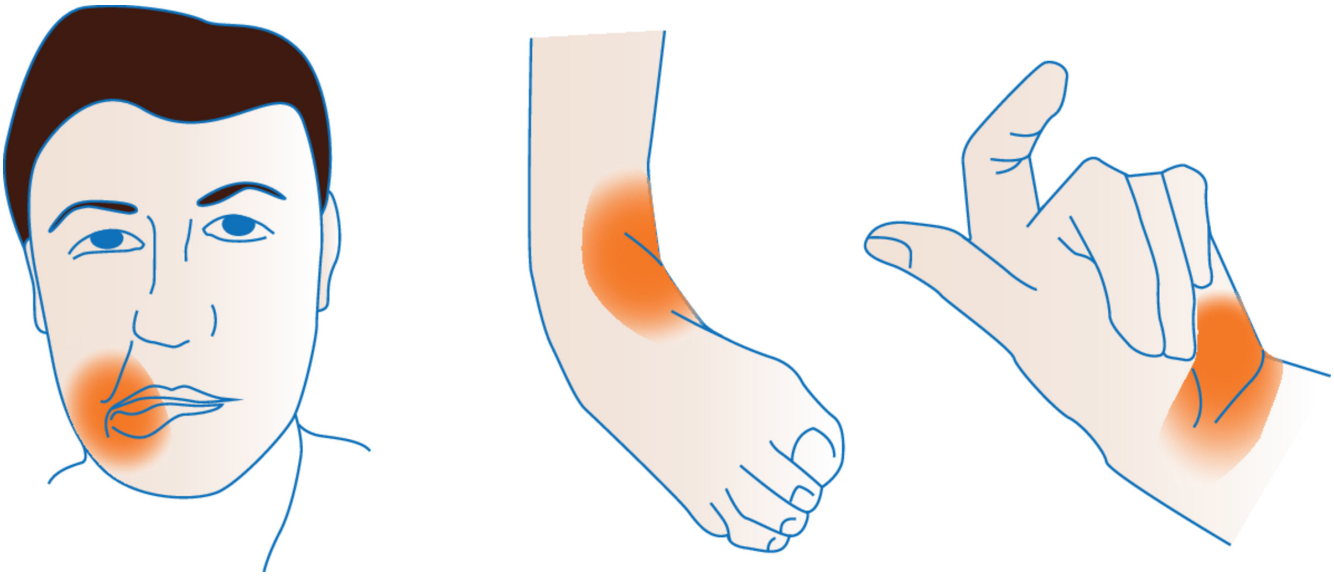


Fig 3 | Functional dystonia typically presents with facial spasm in which there is jaw deviation to one side and contraction of platysma or orbicularis, or a fixed posture with a clenched fist or inverted plantarflexed ankle. Orange shading shows areas of fixed muscular contraction

Functional or dissociative seizures

These are diagnosed on the basis of characteristic features in the subjective account and observed description of the attacks.

Subjective descriptions often include symptoms of autonomic arousal such as palpitations, warmth, and sweating, as well as dissociative experiences (with or without fear). These often only last seconds and are often not recalled; they are not diagnostic of functional seizures, but knowledge of them can help guide management. For example, a person might be dissociating as a conditioned response to unpleasant autonomic arousal, and learning distraction techniques to gain control (in a similar way to panic attacks) can be helpful.

Objective features—demonstrated in a systematic review of the specificity and sensitivity of various clinical signs of functional seizures versus epilepsy in 34 studies—include the eyes being tightly closed, tearfulness, duration more than 5 minutes, hyperventilation during a seizure, and side to side head shaking (see table 1 and infographic).[18] Around 30% of patients have events that look like syncope.[19] The combination of sudden motionless unresponsiveness with eyes closed for more than 2 minutes is rarely due to another cause. Making a clinical diagnosis requires experience of the range of presentation of epileptic seizures and syncope which may co-exist.

Table 1 | Clinical features that help separate functional seizures in functional neurological disorder (FND) from epilepsy (based on Avbersek et al 2010[18]). Syncope usually lasts less than 30 seconds and with eyes open. Clinical features usually need to be assessed in combination. A smartphone video taken by a friend or family member with consent may help

Clinical feature	Common in FND and rare in epilepsy or syncope	Common in epilepsy and rare in FND	May be present in either
Eyes Closed during event	Yes	—	—
Resistance to eyelid opening	Yes	—	—
Duration longer than 2 minutes	Yes	—	—
Hyperventilation during episode	Yes	—	—
Crying after the event	Yes	—	—
Guttural Cry at onset	—	Yes	—
Stertorous (snoring) breathing after the event	—	Yes	—
Synchronous EEG evidence of epilepsy	—	Yes (although interictal EEG often normal)	—
Report of tongue biting	—	—	Yes
Urinary incontinence	—	—	Yes

EEG = electroencephalogram.

Functional visual loss.

Characteristic features include tubular (rather than conical) vision, so visual field at 150 cm distance is the same width as at 50 cm. The laws of physics mean that the diameter of a field should increase conically with distance (see fig 4 and infographic). Patients may also demonstrate visual field "spiralling" on Goldmann perimetry (fig 4 and infographic)—the longer the test goes on, the more constricted the person's visual field becomes

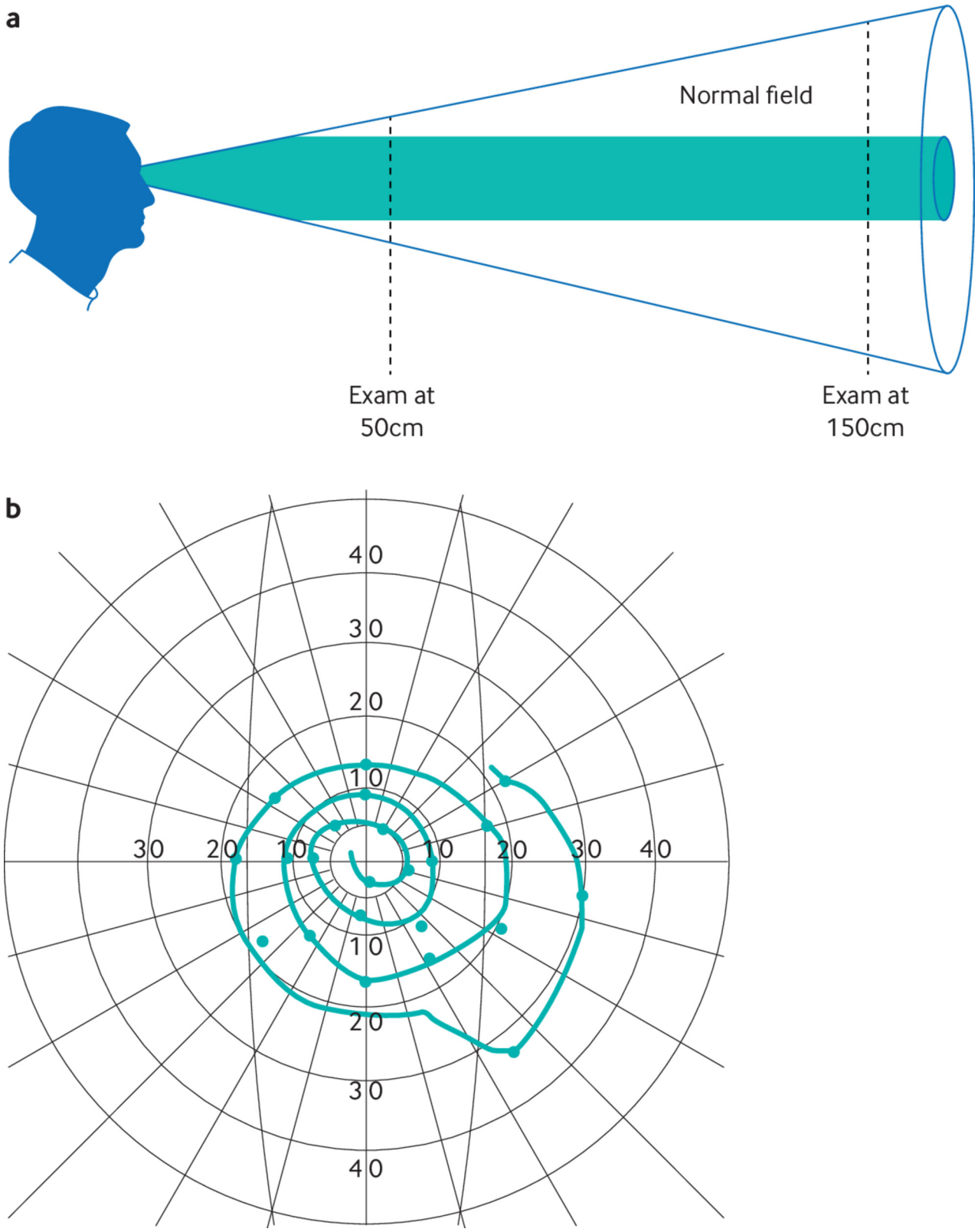


Fig 4 | (a) Functional visual loss can be detected at the bedside by finding a tubular visual field defect at 150 cm which is the same width as at 50 cm. (b) Spiralling of visual fields on Goldmann perimetry occurs when the subject's vision becomes more constricted the longer the test goes on

When are investigations for pathophysiological disease comorbidity necessary?

Always consider whether patients with signs and symptoms of FND could also have pathophysiological disease, and be willing to make two diagnoses if appropriate. For example, someone may have multiple sclerosis, but their disability may be coming predominantly from FND.[20] Other contributing neurological and medical problems such as vitamin B12 or thyroid deficiency, migraine, hypermobility spectrum disorders, or carpal tunnel syndrome are also common, and around 20% of patients with functional seizures as part of FND also have epilepsy.[21] Therefore, routine blood tests and assessment for some of these common disorders may be helpful when waiting for a neurological review.

FND can be a relapsing remitting condition, but other new conditions can occur at any stage. If new neurological symptoms develop in someone with diagnosed FND, consider whether they are likely to be related to the FND diagnosis or if they are unrelated. Offer an unbiased assessment and ask for a neurological review when there is doubt.

Arrange appropriate laboratory, radiological, or neurophysiological investigations even when there is clear evidence of FND; however, remain aware that, in asymptomatic individuals undergoing cranial neuroimaging, one in six individuals has an incidental abnormality, the discovery of which may cause more harm and worry.[22] Incidental findings on spinal imaging, such as disc prolapse, in asymptomatic individuals occur at a percentage similar to a patient's age.[23] Therefore, to reduce patient concern, when FND is clinically the most likely diagnosis, consider informing patients in advance that tests for pathophysiological disease are likely to be negative or might show these incidental changes.

Video electroencephalography, especially with an induction protocol, allows a video recording of typical features and helps to exclude epilepsy occurring in addition to functional seizures.

Avoid diagnosing FND on the basis that investigations for other conditions are negative and consider that FND may still be present even when investigations for other conditions are positive.

What are the diagnostic pitfalls of functional neurological disorder?

A systematic review showed that the mean proportion of patients receiving an incorrect diagnosis of FND in studies between 1970 and 2003 was 4%,[24] which is similar to most neurological and psychiatric disorders. Furthermore, it seems to be just as common for FND to be misdiagnosed as neurological disease[25]; this is often viewed by clinicians as a lesser problem, but patients misdiagnosed with multiple sclerosis or Alzheimer's disease may disagree. There is no room for complacency in either direction

Common reasons for making a wrong diagnosis of FND include placing emphasis on psychological comorbidity; making judgments that symptoms, especially gait and "episodes" are "bizarre" without considering whether they are typical of FND; relying on single signs rather than combinations of features; and placing reliance on normal laboratory or radiological investigations for recognised pathophysiological disease.

Conversely, common reasons for missing the diagnosis of FND include assuming that it cannot be the diagnosis in a patient with no psychological comorbidity or no prior functional disorders, or in a patient who goes against false stereotypes about functional disorders—for example, a patient who is male, older, and working.

Which functional disorder and psychological comorbidities may be present?

Other functional symptoms and disorders, especially those involving chronic pain, fatigue, and memory symptoms are common in patients with FND of all types, and in many patients these symptoms determine quality of life more than motor or sensory symptoms.[26]

Psychological comorbidities—especially anxiety, panic, and depression—are common, affecting over 50% of patients,[27] and are often worsened by the disability of the condition. Some patients will have had adverse experiences, but, importantly, these are neither necessary nor sufficient for the diagnosis.

Falsification of symptoms, as seen in factitious disorder or malingering, may lead to similar clinical features to FND but is acknowledged to be rare. Specifically excluding it is no longer part of the diagnosis of FND in DSM-5.[28] Consider wilful exaggeration if there is repeated evidence of lying or a major discrepancy between reported and observed function, but not if there is self reported variability in function as this is typical of FND,

How can the diagnosis of functional neurological disorder be explained?

A successful conversation about the diagnosis of the FND leaves the patient with a reasonable degree of confidence and understanding and is an essential platform for further treatment.

As with the delivery of the diagnosis of any disorder, include sufficient time, take the problem seriously, give the name of the condition, provide further reading information (such as www.neurosymptoms.org, www.nonepilepticattacks.info), and offer sources of support such as patient support groups (such as https://fnd-hope.org/, www.fndaction.org.uk, http://fnddimensions.org/, https://fndfriends.com/).[29]

Demonstrating positive clinical signs of FND can be especially helpful provided it is done as a way of helping the patient gain insight into the mechanism of their symptoms, as opposed to an approach that suggest a diagnosis of exclusion or that there is "no problem." It may also lead naturally to therapies. For example, if someone can be helped to see that their weak leg does return transiently normal during testing for Hoover's sign, or that their tremor transiently stops during an entrainment test, this offers a window on what may be possible with physiotherapy to "retrain the brain." The use of analogy, for example, that this a "software rather than hardware problem" or, for FND seizures, that there is a "red alert state which the brain has learnt to switch off automatically by going into a trance like state" can help translate neuroscience to the bedside.

Where explanation fails, it is common to find that the normal "rules" and expectations of a consultation are broken[29]: for instance, by focusing on what the person doesn't have, not giving a diagnosis, or jumping prematurely to conclusions about aetiology, especially psychological factors.

FND is not an easy diagnosis for a patient or their family and friends to understand, and some patients may not agree that its correct. Explanation may need to be repeated by the neurologist, members of a multidisciplinary team, and in primary care, ensuring that everyone understands the correct rationale for it.

Management of functional neurological disorder

Evidence from randomised clinical trials supports the role of specific physiotherapy for functional motor symptoms,[33 34] and specialised

cognitive behavioural therapy[19] across the range of FND, as well as multidisciplinary rehabilitation for refractory cases.[4]

The management of FND takes place in both primary and secondary care and is often multidisciplinary. We have looked at the care of individual patients in this article, but considerations need to be made at the level of healthcare systems too. Few healthcare systems plan well for this group of patients, which leads to missed opportunity, iatrogenesis, frustration for patients and clinicians, and poor use of resources.[35]

Diagnosing and explaining functional neurological disorder

A 28 year old man develops left leg paralysis and numbness gradually after a minor but painful ankle injury. He has felt dismissed and unbelieved by doctors, who have implied it was all in his head. He had a difficult upbringing and was frustrated but not depressed.

- *Make a diagnosis*—There was clear positive evidence of a diagnosis of FND with a pattern of weakness and physical signs including Hoover's sign that is only found in this condition.
- *What is it? Explain there is a name and it is a "rule-in" diagnosis*—"You have typical symptoms and signs of functional neurological disorder. Did you notice that the strength in the leg came back to normal briefly when you lifted up the other leg? Shall I show you that again?"
- *How? Talk about mechanism first*—"The physical signs of FND show that there is a potentially reversible problem with the software of the nervous system, the brain has got stuck with a faulty movement programme, but the hardware of the brain is OK."
- *Why? It's complicated*—There is no need to rush to try to understand everyone's vulnerability. Some patients have little to find, others a lot. Explore that at the patient's pace, not yours. Think of how you would explain the cause of stroke in a former smoker or non-smoker. Don't turn a risk factor into the "cause" of the problem.
- *What about a scan?*—It is important to consider other investigations, as people with FND often have other medical conditions that can trigger or increase their vulnerability to the disorder.
- *Treatment*—Physiotherapy can help "retrain the brain" so that movements become gradually more automatic and normal again. Psychological therapy may help address FND symptoms directly (as well as understanding what's happened) and address anxiety or mood to make it less likely to recur.

Education into practice

- What is your attitude to patients with functional neurological disorder?
- How much importance do you put on psychological features when considering a diagnosis?
- How do you explain that tests you are ordering are likely to be normal?
- Think about a recent patient you saw with FND: how did you explain their symptoms or diagnosis to them? What might you do differently next time?

How patients were involved in the creation of this article

The article was reviewed and improved by representatives from five patient organisations: FND Hope, FND Hope UK, FND Action, FND Dimensions, and FND Friends. They made many incorporated suggestions, especially focusing on language that promotes an aetiologically neutral approach which is not blaming or presupposing psychological causation and emphasising need to evaluate new symptoms without prejudice.

Contributors: JS drafted the manuscript, CB and AC revised the script. The manuscript was reviewed by Dawn Golder (FND Hope UK), Bridget Mildon (FND Hope), Emma Clark (FND Friends), Kim Hearne (FND Action), and Steven Webster (FND Dimensions).

Funding: JS is supported by an NHS Scotland Career Fellowship.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JS and AC are employed by NHS Lothian. JS and AC carry out independent expert testimony work for personal injury and medical negligence claims. JS receives royalties from UpToDate for articles on functional neurological disorder. JS runs a free non-profit self-help website, www.neurosymptoms.org, which is mentioned in the article. AC receives fees as an associate editor of *Journal of Neurology, Neurosurgery and Psychiatry*. CB is employed by the University of Sheffield and carries out sessional clinical work as a general practitioner. CB receives royalties from Wiley for one book.

We thank Catherine MacEwan for assistance with figures.

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Pediatric Neurology 69 (2017) 11–23

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Pathways for Neuroimaging of Childhood Stroke

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ABSTRACT

BACKGROUND: The purpose of this article is to aid practitioners in choosing appropriate neuroimaging for children who present with symptoms that could be caused by stroke. **METHODS:** The Writing Group members participated in one or more pediatric stroke neuroimaging symposiums hosted by the Stroke Imaging Laboratory for Children housed at the Hospital for Sick Children in Toronto, Ontario, Canada. Through collaboration, literature review, and discussion among child neurologists with expertise diagnosing and treating childhood stroke and pediatric neuroradiologists and neuroradiologists with expertise in pediatric neurovascular disease, suggested imaging protocols are presented for children with suspected stroke syndromes including arterial ischemic stroke, cerebral sinovenous thrombosis, and hemorrhagic stroke. **RESULTS:** This article presents information about the epidemiology and classification of childhood stroke with definitions based on the National Institutes of Health Common Data Elements. The role of imaging for the diagnosis of childhood stroke is examined in depth, with separate sections for arterial ischemic stroke, cerebral sinovenous thrombosis, and hemorrhagic stroke. Abbreviated neuroimaging protocols for rapid diagnosis are discussed. The Writing Group provides suggestions for optimal neuroimaging investigation of various stroke types in the acute setting and suggestions for follow-up neuroimaging. Advanced sequences such as diffusion tensor imaging, perfusion imaging, and vessel wall imaging are also discussed. **CONCLUSIONS:** This article provides protocols for the imaging of children who present with suspected stroke.

Keywords: childhood stroke, stroke mimics, magnetic resonance imaging, computed tomography

Pediatr Neurol 2017; 69: 11-23

Article History:
Received October 5, 2016; Accepted in final form December 8, 2016

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http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.004

Introduction and epidemiology

Stroke is a major cause of morbidity and mortality in children worldwide. The reported annual incidence of childhood stroke ranges from 2.3 to 13 per 100,000 children per year in developed countries.[1-3] Despite increasing awareness, this condition is often overlooked by medical providers and families. In adults, presentation with sudden onset hemiparesis with or without facial weakness and language problems constitutes hallmark presenting features of stroke which raise concern for the diagnosis without unnecessary delay. In children, stroke diagnosis is not as straightforward. Despite a growth in awareness about childhood stroke, when children present with acute neurological deficits, stroke is often not the first diagnosis considered by the medical providers. Delay in diagnosis derives, in part, from clinicians' difficulty recognizing that presenting signs and symptoms such as seizure, altered mental status, headache, and lethargy can be associated with acute stroke in children. Neuroimaging is essential for diagnosis and differentiation of stroke from stroke mimics that can present similarly such as hypoglycemia, demyelinating disorders, tumors, posterior reversible leukoencephalopathy syndrome, and complex migraine. Importantly neuroimaging is essential for identification of children who may be candidates for hyperacute therapy.

This report will briefly describe childhood stroke classification and then will discuss the imaging of each major stroke subtype individually. The objective is to provide practitioners with a guide for neuroimaging children with various stroke subtypes.

Pediatric stroke classification

Childhood stroke is defined as occurring in children aged 29 days after birth to 18 years. Perinatal stroke, defined as stroke occurring from birth to 28 days of life (and in some cases *in utero* beginning at 20 weeks' gestation), will be discussed in a separate article. Stroke is traditionally subdivided into two types: ischemic and hemorrhagic. As opposed to adults who have ischemic stroke 85% of the time, stroke in children is almost evenly divided between ischemic and hemorrhagic events.[3] Ischemic stroke is further subclassified into arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT). Childhood AIS is defined as presentation with a focal deficit or seizure that localizes to an ischemic area of brain injury in a known arterial territory. Most children present with hemiplegia, with or without aphasia. CSVT can occur alone or in association with venous infarction or hemorrhage. Isolated cortical vein thrombosis (ICVT) is rare, accounting for less than 1% of all cerebral infarctions.[4] Hemorrhagic stroke in children includes spontaneous intracerebral hemorrhage with or without intraventricular extension, intraventricular hemorrhage (IVH), and nontraumatic subarachnoid hemorrhage.

Childhood AIS

After childhood AIS, more than 75% of children will suffer long-term neurological deficits and 10% of children will die.[5-9] Recurrence risk after childhood AIS has been estimated at 12% at one year[10] and 19% at five years.[9]

Approximately 30% of children with AIS encountered in academic centers have an associated cardiac disorder that presumably leads to cardioembolism (Fig 1), whereas cerebral arteriopathy is found in up to half of all children with childhood AIS.[11,12] The presence of cerebral arteriopathy on neuroimaging also predicts recurrent stroke and stroke after transient ischemic attack (TIA).[9,13]

Cervicocephalic arterial dissection, one type of arteriopathy, accounts for 7.5% to 20% of childhood AIS.[14-16] Involvement of

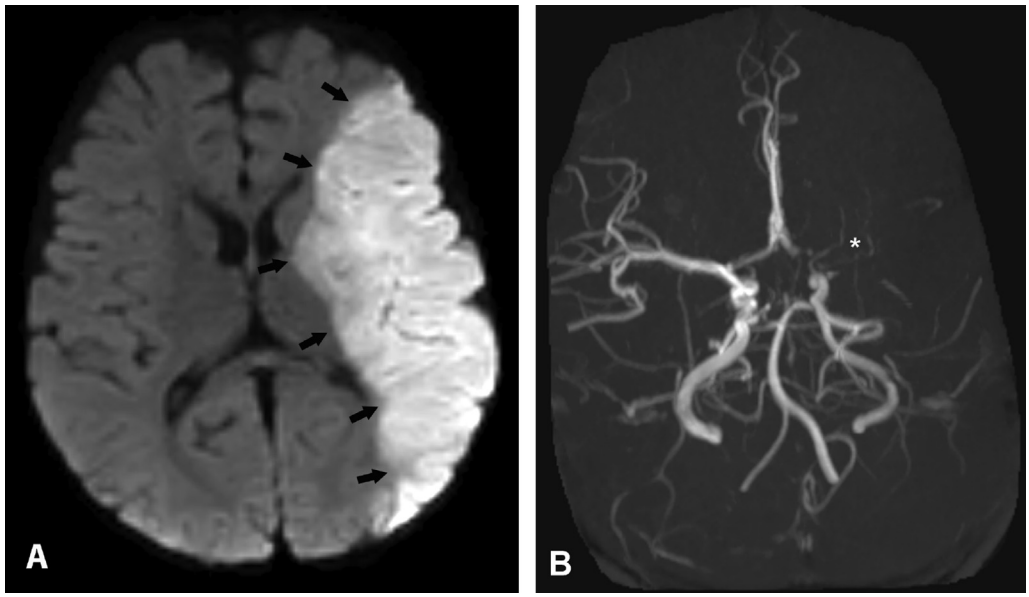

FIGURE 1.
Cardioembolic stroke. (A) Axial diffusion-weighted image (DWI) demonstrates a large left middle cerebral artery (MCA) territory infarct (black arrows) in a one-year-old boy found to have a thrombus within his left ventricle. (B) Three-dimensional time-of-flight magnetic resonance angiography maximum intensity projection image reveals lack of normal flow-related signal involving the left MCA and branch vessels (white asterisk).

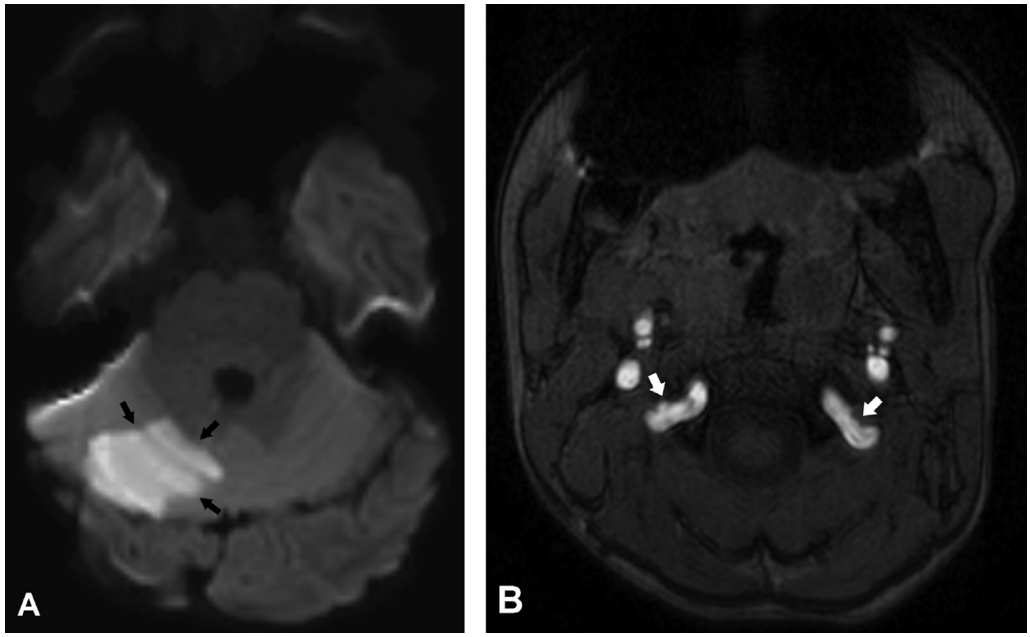

FIGURE 2.
Arterial dissection. (A) Axial diffusion-weighted image shows an infarct of the right cerebellum (black arrows). (B) Three-dimensional time-of-flight magnetic resonance angiography image illustrates focal irregularity of the V3 segment of the right vertebral artery and, to a lesser degree, the contralateral vessel (white arrows). The appearance and location of the vessels involved favor the diagnosis arterial dissection. Other less common entities such as fibromuscular dysplasia can have a similar appearance.

the anterior circulation is reported more often than the posterior circulation.[15,17] However, vertebral artery dissection was recently identified in 50% of children with posterior circulation stroke[18] (Fig 2).

Focal cerebral arteriopathy of childhood describes a localized intracranial arterial stenosis and accounts for approximately 25% of arteriopathies in childhood AIS.[16] It may comprise a monophasic process, also known as "transient cerebral arteriopathy of childhood," most commonly involving the proximal middle cerebral artery (MCA), that may resolve. Focal cerebral arteriopathy can also be a fixed vasculopathy with no improvement over time (Fig 3).[19] In contrast, moyamoya arteriopathy represents a progressive steno-occlusive arteriopathy that typically involves the distal internal carotid artery and proximal MCAs or anterior cerebral arteries bilaterally and, much less commonly, the posterior circulation. Ultimately there is development of "moyamoya" collaterals, which create the typical appearance of "puff of smoke" on angiography that inspired the name of this condition (Fig 4).

Sickle cell anemia is a risk factor for stroke. In studies that predate the STOP trial (Stroke Prevention Trial in sickle cell anemia), 11% of children with sickle cell anemia experienced a stroke before age 20 years.[20,21] Not all children with sickle cell disease or sickle cell disease and stroke have vasculopathy (including moyamoya), although many develop steno-occlusive vasculopathy and moyamoya. In a recent study, 43% of children with recurrent strokes on chronic transfusion therapy had moyamoya.[22] Given the robust association between progressive vasculopathy on

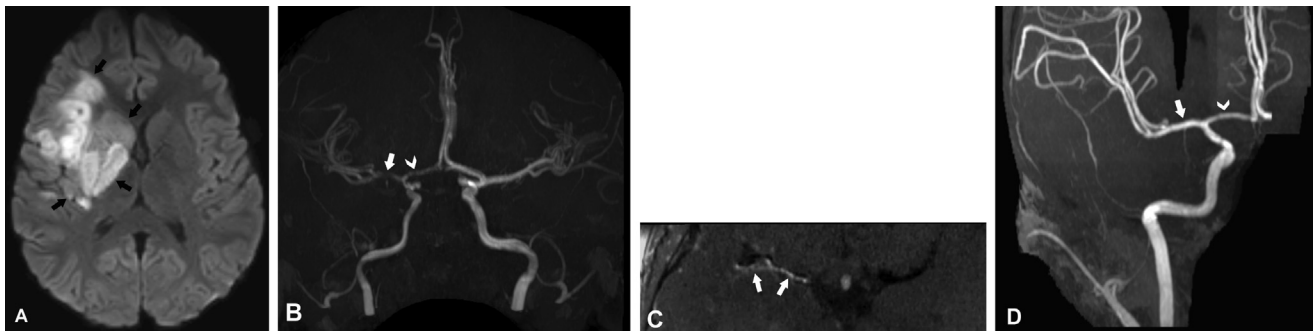

FIGURE 3.
Focal cerebral arteriopathy-transient cerebral arteriopathy. (A) Axial diffusion-weighted image demonstrates patchy areas of ischemia involving the right middle cerebral artery (MCA) territory (black arrows). (B) Three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) maximum intensity projection (MIP) image reveals focal severe narrowing of the right M1 segment (white arrow) and mild irregularity of the right A1 segment (white arrowhead). (C) Contrast-enhanced black blood vessel wall image illustrates wall enhancement of the right MCA (white arrows). (D) Four month follow-up 3D TOF MRA MIP image shows near-complete resolution of vascular irregularity (white arrow and arrowhead).

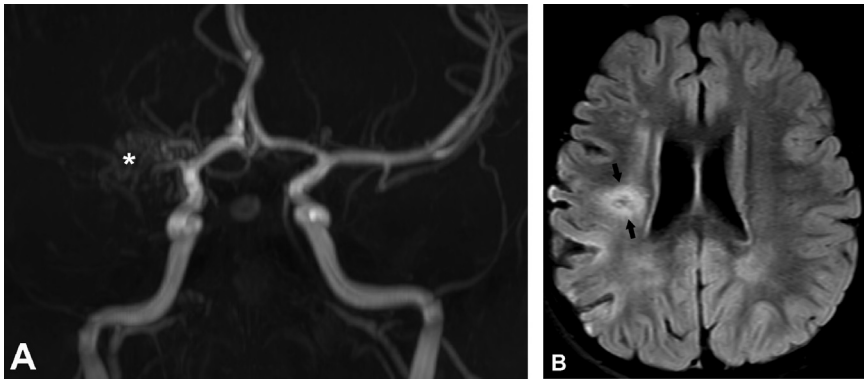

FIGURE 4.
Moyamoya. (A) Three-dimensional time-of-flight magnetic resonance angiography maximum intensity projection image demonstrates lack of flow-related signal involving the right middle cerebral artery with the presence of moyamoya collaterals (white asterisk). (B) Axial fluid attenuated inversion recovery (FLAIR) image illustrates a region of a chronic ischemia within the right periventricular white matter (black arrows).

magnetic resonance angiography (MRA) and new infarcts on magnetic resonance imaging (MRI) in children with sickle cell disease,[23] additional therapies like revascularization surgery should be considered in those with progression of arteriopathy or in whom recurrent stroke occurs despite chronic transfusion therapy.[24,25] Unfortunately, there are no evidence-based guidelines about the appropriate timing of revascularization surgery, the degree of arteriopathy progression that should prompt consideration for surgery, or the long-term efficacy of various revascularization procedures in this population. As in other patients with moyamoya, catheter angiogram is typically necessary for the evaluation for revascularization surgery. However, the value of perfusion imaging, particularly if there is bilateral arterial disease or recurrent stroke, is unknown. In the setting of progressive arteriopathy or recurrent strokes and sickle cell anemia, some hematologists will also consider hematopoietic stem cell transplant.[26]

Central nervous system vasculitis represents a less frequently encountered cause of childhood AIS. Vasculitis can be primary or secondary to a systemic cause such as collagen vascular disease or septic meningitis.[27,28] It is characterized by irregular vascular stenoses that result in both deep and superficial sites of ischemia. Fibromuscular dysplasia, a noninflammatory arteriopathy, rarely presents in childhood and is associated with both ischemic and hemorrhagic strokes in childhood.[29] The cervical vasculature is most frequently involved, classically described as having alternating areas of vascular constriction and dilatation.

Role of imaging in childhood AIS

Timely diagnosis of acute stroke remains challenging because of the following factors: (1) the wider differential diagnosis in children relative to adults, (2) the relative rarity of stroke in children compared with adults (including a lack of knowledge that children have strokes and that treatment is time-dependent in some circumstances), and (3) challenges to acquisition of urgent diagnostic neuroimaging in children.[30] Twenty percent to more than half of children presenting urgently with stroke-like symptoms will have stroke mimics;[31-33] therefore, more than in adults, the first question in children is whether the cause of the child's symptoms is a stroke or stroke mimic. In the setting of a stroke, the vascular distribution(s), presence of arterial clot, presence of associated hemorrhage, and presence of acute or chronic arteriopathy direct management. Given that some arteriopathies in childhood affect the cervical vessels and some the intracranial vasculature, vascular imaging of the head and neck is required in most cases.

Standardization of a stroke imaging protocol in children is challenging because various pediatric issues must be addressed. These include understanding the changing appearance of the developing brain because of ongoing myelination and cortical organization, concern for ionizing radiation from computed tomography (CT) and conventional angiography, the potential need for general anesthesia and/or sedation, presence of metallic orthodonture that can obscure MRI, and varying availability of MRI in the acute setting. Recent advances in adult stroke imaging and treatment protocols have provided an impetus to establish uniform protocols in children, particularly in the hyperacute/acute phase with the potential for thrombolytic therapy with or without endovascular intervention.

Noncontrast head CT is often the initial study in a child presenting with possible stroke and can rule out intracranial hemorrhage. However, CT has limited sensitivity for the detection of acute childhood AIS and stroke mimics. CT imaging fails to identify the diagnosis in more than 40% of children.[30] Considering this limited sensitivity, the concerns for radiation, and the likelihood of needing MRI to confirm diagnosis, many centers have developed "rapid brain" or hyperacute MRI protocols for stroke that take 15 to 20 minutes. These rapid brain protocols incorporate diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps to confirm the diagnosis of stroke as well as susceptibility-weighted imaging (SWI) or gradient echo (GRE) sequences to assess for hemorrhage. If a stroke is present on a rapid brain MRI study, a full protocol with vascular imaging is often required at some point during the initial hospitalization.

In general, the presence of diffusion restriction (reduced diffusivity) in the distribution of an arterial territory can confirm stroke, although other entities such as brain tumors, abscesses, white matter diseases, and seizures can

exhibit reduced diffusivity or demonstrate hyperintense signal abnormality as well. At the time of initial MR scan, an MRA of the head and neck is most often warranted to evaluate for cervical and/or intracranial arteriopathy or arterial obstruction because of thrombus. In a child who is medically unstable, in whom a contraindication to MRI is present, who presents to a center without MRI capabilities, or in whom sedation will delay MRI, CT with CT angiogram (CTA) of the head and neck may be preferable. Alternatively, some centers administer anesthesia by rapid induction for scanning. In patients with a strong suspicion of arteriopathy in whom MRA or CTA is nondiagnostic, conventional catheter angiogram might help elucidate the stroke etiology. In addition, in children with moyamoya disease or syndrome in whom revascularization is being considered, four vessel angiogram including the extracranial circulation may be required.

With the advent of newer therapeutic techniques and recent guidelines in adult stroke management, there is an increased need to balance comprehensive, but time intensive stroke imaging studies (for example inclusion of MRA neck) with a rapid protocol that allows for quick diagnosis and potentially acute treatment (e.g., thrombolysis). The development of acute therapies that are time-dependent underscores the need for more uniform, consensus-based practical neuroimaging algorithms focused on rapid and accurate diagnosis. These challenges have been addressed to an extent with shorter abbreviated protocols for acute stroke discussed subsequently.

A suggested imaging protocol for evaluating children with suspected stroke was devised by the International Paediatric Stroke Study (IPSS) Neuroimaging Subgroup (Fig 5). They are based on analysis of current literature, expert opinion, and formal consensus.

Imaging and therapy timing for AIS

Hyperacute therapy for AIS—intravenous or intra-arterial tissue plasminogen activator (tPA) and mechanical thrombectomy—has not been prospectively studied in children but is used on a case-by-case basis. Consideration of tPA for treatment of acute childhood AIS requires imaging confirmation of the diagnosis of AIS with occlusion or partial occlusion of an artery in the distribution of the stroke or thrombus in a vessel that corresponds to the territory of the clinical deficit.[32] In addition, assessment of stroke size on DWI or early change on CT and confirmation that intracranial hemorrhage is not present are required. Assessing AIS onset time is critical for the determination of whether a patient can be treated with tPA or thrombectomy; mismatch between DWI and fluid attenuated inversion recovery (FLAIR) changes may prove useful in determination of the time window for potential intervention.[34,35] In adults, DWI appears to reliably predict the core infarct[36] and the DWI–perfusion-weighted imaging (PWI) mismatch may then be used to assess tissue at risk (penumbra).[34] A number of dynamic susceptibility contrast (DSC) perfusion parameters including mean transit time, time to peak, and

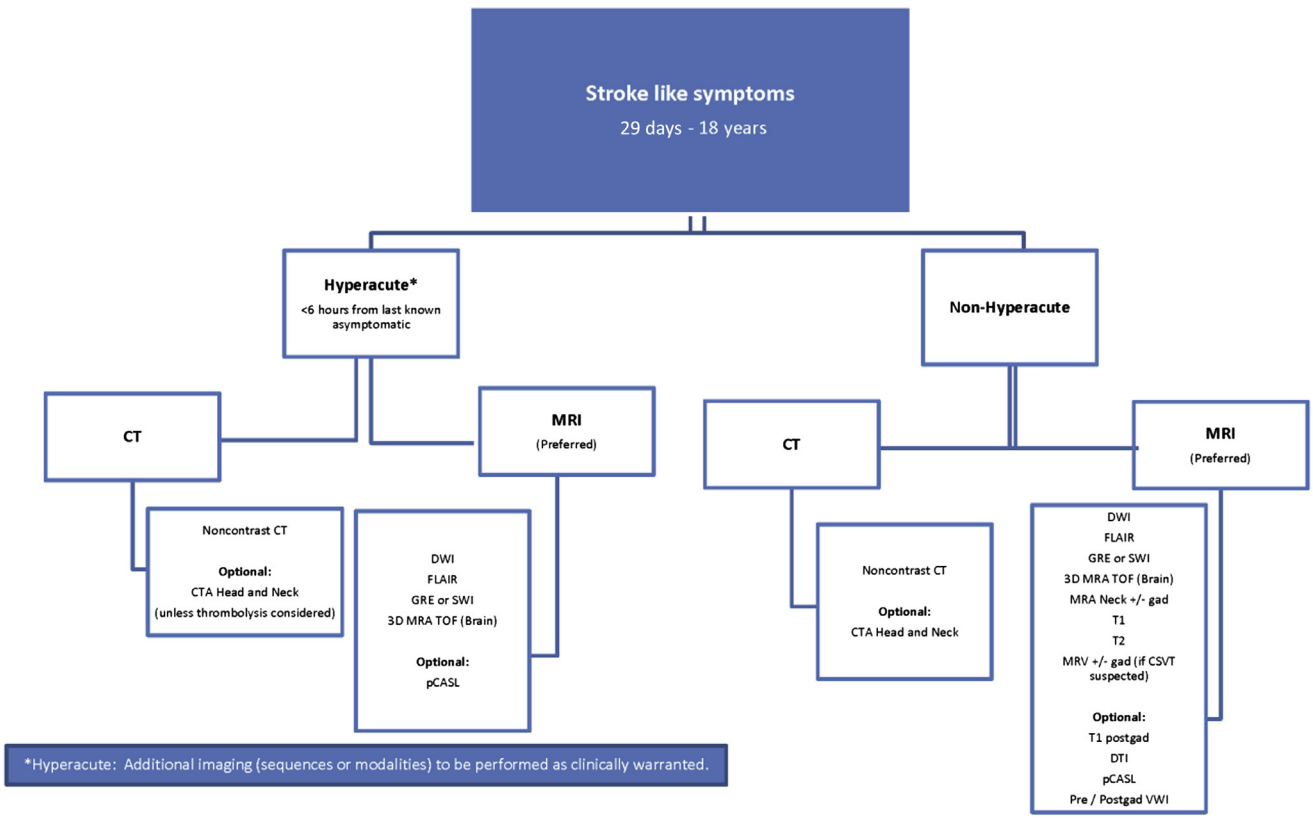

FIGURE 5.
Please refer to the Online Appendix for detailed parameters on suggested imaging. Sequences may be modified as clinically warranted. (The color version of this figure is available in the online edition.)

time to maximum (Tmax) using various thresholds have been used for determination of the ischemic penumbra in adults. Although these measures can be used in children, further validation is needed. Although arterial spin labeling (ASL) is correlated with DSC perfusion parameters in assessment of mismatch in AIS, the correlation is imperfect and improved methods are needed before routine clinical use in acute stroke.[37] In our experience, prominence of veins on SWI is not yet a suitable method for assessing mismatch as it may be seen in the infarct core, and delineation of the region of venous prominence is difficult. Intravenous tPA administration is predicated on rapid diagnosis of stroke by neuroimaging within 4.5 hours of its documented onset in children, just as in adults. As in adults, it may be reasonable to perform noncontrast CT and CTA if MRI with MRA cannot be obtained in a timely fashion and would create delays that would make the child ineligible for therapy.

In addition to stroke confirmation, neuroimaging can detect stroke risk factors that require prompt treatment such as cervical artery dissection, other large and medium vessel cerebral arteriopathies with risk of vessel-to-vessel emboli, and aneurysm. Surgical revascularization may decrease risk of further stroke in children with moyamoya syndrome or disease but can be associated with increased risk of stroke during the perioperative period. Children with malignant MCA infarction or cerebellar herniation after stroke may be candidates for decompressive craniectomy.[38]

Emerging MRI sequences in childhood AIS

PWI has been used in adult stroke evaluation to determine tissue at risk (penumbra).[39] Bolus CT perfusion and MRI perfusion techniques are available, but application has been limited in the setting of childhood AIS. PWI with MR can be performed with contrast, most commonly exploiting DSC technique. ASL, a family of perfusion imaging techniques not requiring the administration of an exogenous contrast but using the patient's blood as an endogenous contrast, are becoming more available and are likely to be applied to pediatrics to a greater degree in the future. However, such studies must be interpreted with caution and by experienced practitioners. ASL, for example, will be altered by a longer blood transit course from the neck arteries to the brain parenchyma; hence, ASL may appear abnormal in a child with moyamoya and collateral circulation even if perfusion is adequate. The utility of ASL in determining the penumbra remains unknown, as it may overestimate the penumbra because of arterial transit time artifacts.

Vessel wall imaging is a developing technique that may prove useful in the differentiation and monitoring of vasculopathies, particularly the different causes of focal cerebral arteriopathy (Fig 3).

Black-blood T1-weighted imaging after gadolinium contrast can show abnormal vessel wall enhancement in the setting of an active and potentially inflammatory process, differentiating it from a now quiescent or non-inflammatory process. Imaging before gadolinium contrast can be used to identify an arterial wall hematoma, which may indicate an intracranial dissection.

Follow-up imaging—subacute and chronic childhood AIS

Subacute imaging may be performed to assess hemorrhagic transformation, infarct extension, edema formation, mass effect, herniation, and stroke recurrence. MRI is optimal, but CT may be indicated for unstable patients. If a child undergoes thrombolysis, a CT or MRI scan 24 hours later is required for surveillance of intracranial hemorrhage.

Follow-up imaging is often performed at six weeks to three months after the incident AIS. Follow-up imaging is used to screen for silent infarction, evaluate for progression or improvement of existing arteriopathies, and diagnose arteriopathies that were not obvious at the time of initial stroke diagnosis. MRI with MRA is often the modality of choice in the chronic follow-up setting. Long-term complications after dissection can include pseudoaneurysm development; this can be monitored by MRI/MRA, CT/CTA, and if indicated, cervicocranial catheter angiogram.

Transient ischemic attack

TIAs occur in children, although the true incidence remains unclear as TIAs often cannot be distinguished from stroke mimics. The significance of TIA in children has not been as thoroughly evaluated as it has in adults. In adults, stroke occurs within 3 months of a TIA in 10% to 15% of patients with TIAs.[40,41] In a recent retrospective cohort of pediatric patients with childhood AIS, 13% had a stroke after TIA with a mean follow-up period of 4.5 years. Female sex, autoimmune disorders, and presence of arteriopathy were significantly associated with stroke following TIA presentation.[13] In particular, children with moyamoya often present with TIAs. Adults who experience a TIA have diffusion abnormalities on MRI at the time of their symptoms in 27% to 40% of cases.[42-45] Those adults who have diffusion abnormalities at the time of TIA have an increased risk of stroke in the following 7 days.[42,43,45] Similar observations in pediatric patients have yet to be reported. Imaging evaluation for children with suspected TIA is the same as for children with AIS.

CSVT and cortical vein thrombosis

Childhood CSVT is uncommon, with an incidence of 0.4 to 0.7 per 100,000 children per year.[46] However, CSVT is increasingly diagnosed with heightened awareness and increased use of modern neuroimaging. As in adults, etiology of CSVT in children is often multifactorial[47]; associated risk factors include acute conditions such as infection and trauma, and chronic conditions such as anemia, polycythemia, and prothrombotic disorders. Increased intracranial pressure from obstructed venous outflow can lead to nonspecific symptoms such as headache, encephalopathy, papilledema, or abducens palsies, whereas accompanying hemorrhage or venous infarction can cause seizures or hemiparesis.

Initial imaging often consists of CT or MRI. Focal brain lesions are found in approximately 40% of children with CSVT[48] and include hemorrhage from diapedesis of blood through a congested venous system and ischemia from local compression of arteries and/or reduction of cerebral blood

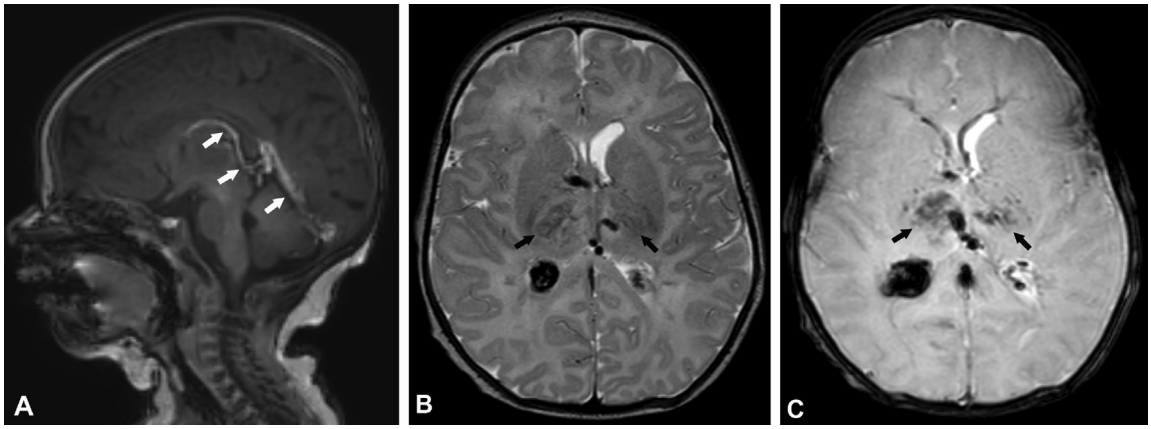

FIGURE 6.
Deep venous thrombosis. (A) Non-contrast sagittal T1-weighted image illustrates abnormal hyperintense signal (thrombus) of the straight sinus, vein of Galen, and internal cerebral veins (white arrows). (B) Axial T2-weighted and (C) axial gradient echo images demonstrate hemorrhagic edema of the thalami bilaterally (black arrows) as well as focal hemorrhage and/or thrombus of the right choroid plexus.

flow from retrograde venous pressure. Vasogenic (increased ADC values) and cytotoxic edema (decreased ADC values) may coexist; thalamic edema is classic for thrombosis of the deep venous system[49] (Fig 6). An atypical or non-arterial pattern of ischemia should prompt further investigation as should ischemia or hemorrhage in the biparietal lobes or bilateral thalami.

CT may demonstrate the venous thrombus itself as a hyperdensity within the intracranial dural sinus ("dense clot sign"), and contrast-enhanced CT may reveal a triangular intraluminal filling defect ("empty delta sign"), particularly in the torcular (Fig 7). Multiplanar reformatting can also be helpful.

Case series of ICVT report a "cord sign" or "dot sign" on CT in 13% to 51%[4] (Fig 8). On CT, high hemoglobin concentration in the setting of dehydration or polycythemia can also be confused with clot, but in these individuals the entire vascular system is dense.

T1- and T2-weighted image findings are variable, depending on the age of the clot. MR SWI is particularly adept at visualizing venous blood and is more sensitive than GRE or T1 spin echo (T1SE) for detecting thrombosis. In one case series, SWI was 90% sensitive for detecting CSVT and 97% sensitive for ICVT within the first week of clinical onset compared with T1SE (71 and 78% sensitive, respectively).[4] Three-dimensional volumetric GRE T1-weighted sequences do not suffer from the artifacts that may plague T1SE and are quite adept at demonstrating clot, particularly after the administration of contrast (Fig 8). DWI hyperintensity within the thrombosed sinus has also been described but has poor sensitivity.[50] Newer techniques such as black-blood imaging (MRI technique suppressing

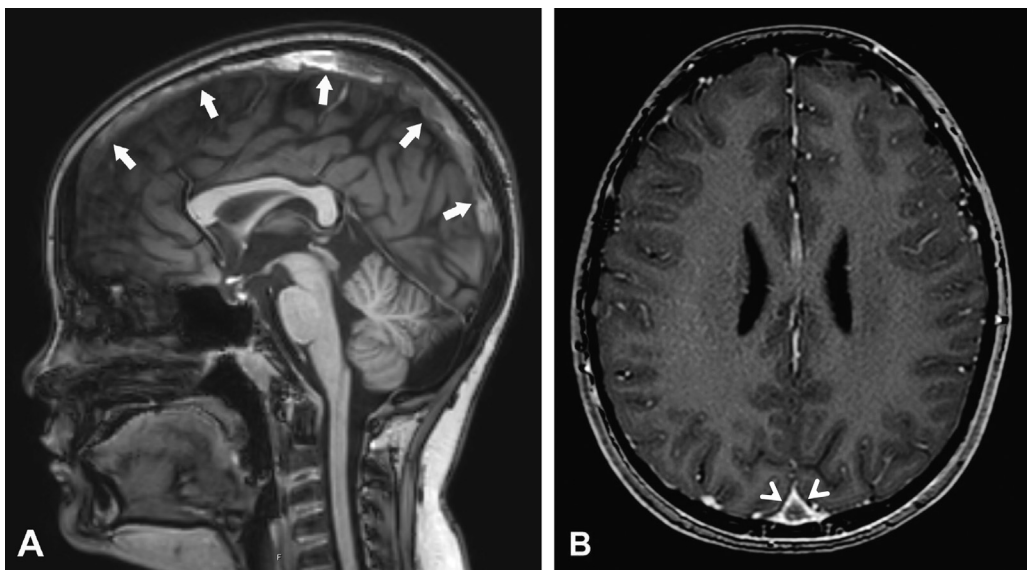

FIGURE 7.
Cerebral sinovenous thrombosis. (A) Noncontrast sagittal T1-weighted image reveals abnormal hyperintense signal in the superior sagittal sinus (white arrows). (B) Contrast-enhanced axial T1-weighted image demonstrates the empty delta sign of the superior sagittal sinus with contrast outlining a triangular thrombus (white arrowheads).

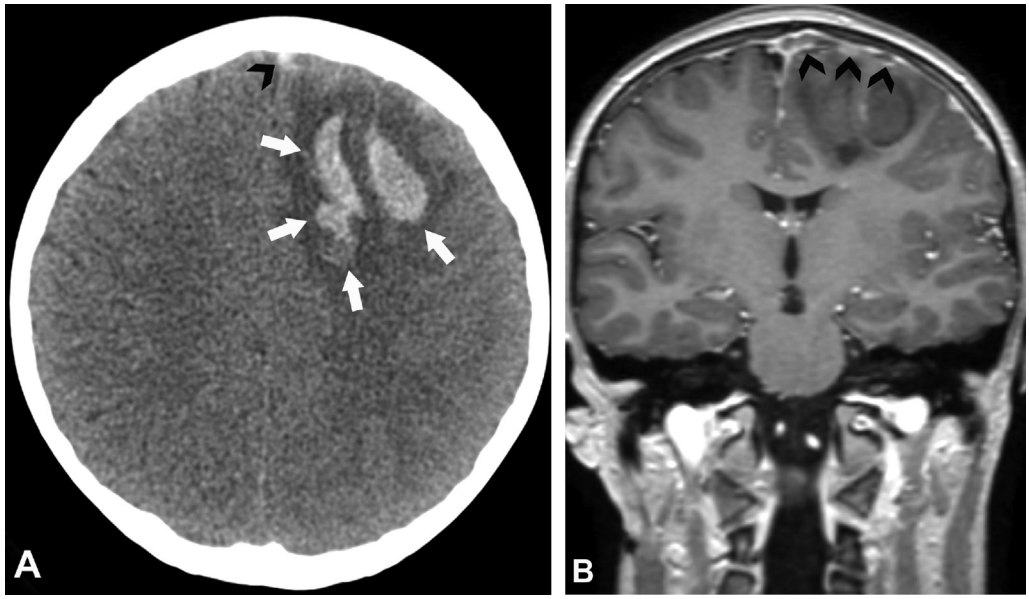

FIGURE 8.
Cortical vein thrombosis. (A) Axial noncontrast computed tomography image reveals a hematoma with surrounding edema within the left frontal lobe (white arrows) and focal hyperdensity of the superior sagittal sinus (black arrowhead). (B) Contrast-enhanced coronal T1-weighted image confirms the presence of thrombus within the superior sagittal sinus extending into a draining cortical vein (black arrowheads).

the signal from normal flowing blood) have demonstrated high sensitivity for venous thrombosis.[51]

Two-dimensional time-of-flight (TOF) MR venography is a sensitive modality for visualizing venous slow flow, particularly flow perpendicular to the plane of acquisition—thus axial, coronal (or any other two planes), and source images should be evaluated to reduce diagnostic error. Three-dimensional phase-contrast magnetic resonance venography (MRV) improves visualization of small veins and of the dural sinuses but has a longer acquisition time, thus rendering it more susceptible to motion artifact. However, newer versions using incomplete k-space acquisition and parallel imaging have made the acquisition times almost comparable with 2D TOF MRV. Follow-up imaging may demonstrate irregular filling of the sinus, indicating incomplete recanalization, or formation of dural collaterals from cortical veins proximal to the site of occlusion. Because MRV indirectly demonstrates clot *via* impaired flow dynamics, motion artifact is not uncommon (reported in up to 31% of TOF MRV).[51] Contrast-enhanced MRV can be useful because it can decrease various flow-related artifacts. Vessel hypoplasia, atresia, and arachnoid granulations protruding into the sinus lumen may all be mistaken for thrombosis.

Although MR may be preferred for its lack of radiation, CT venogram is at least equivalent in sensitivity for CSVT diagnosis[52] and is perhaps more reliable for small vessels and the deep venous system.[53] Directed and timely neuroimaging is essential because failure to recognize CSVT can lead to delayed treatment and poor outcomes.

Hemorrhagic stroke

Hemorrhagic stroke refers to nontraumatic intracerebral hemorrhage (with or without intraventricular extension), IVH, and subarachnoid hemorrhage (https://commondataelements.ninds.nih.gov/stroke.aspx#tab=Data_Standards). Childhood hemorrhagic stroke is typically defined as occurring after 28 days of life to age 18 years, and perinatal hemorrhagic stroke (discussed in a separate article) is defined as those occurring in neonates greater than 36 weeks' gestation at birth to 28 days of life to differentiate these from IVH of prematurity. A study from a California-wide discharge database estimated the incidence of hemorrhagic stroke among patients aged one month to 19 years as 1.1 per 100,000 per year.[3] The most frequent presenting symptom in children is headache, present in 60% to 80%.[54-57] Other frequently occurring symptoms include altered mental status, nausea and emesis, neck pain, seizures, and focal neurological deficits such as hemiparesis, aphasia, and ataxia. Hydrocephalus can develop rapidly or slowly because of IVH or direct compression by the hemorrhage on the ventricular system. In one study, more than half of children presented acutely but nearly half presented more insidiously,[55] which can lead to delays in diagnosis and treatment.

Vascular malformations, most frequently arteriovenous malformations (AVMs), cavernous malformations, and aneurysms, are the most common causes of pediatric hemorrhagic stroke reported in tertiary care settings[54,55] (Figs 9-11); however, other causes of hemorrhage include brain tumors and coagulopathy (acquired or congenital).

Just as in ischemic stroke, in a child with a presentation concerning for hemorrhagic stroke, rapid neuroimaging is critical for identifying hemorrhage and for differentiating hemorrhage from other stroke subtypes and from stroke mimics. CT is often the first neuroimaging modality performed because of its sensitivity for detecting hemorrhage, its short scan time (almost never needing moderate sedation or anesthesia), and its availability in the emergency setting. Rapid acquisition of neuroimaging is especially

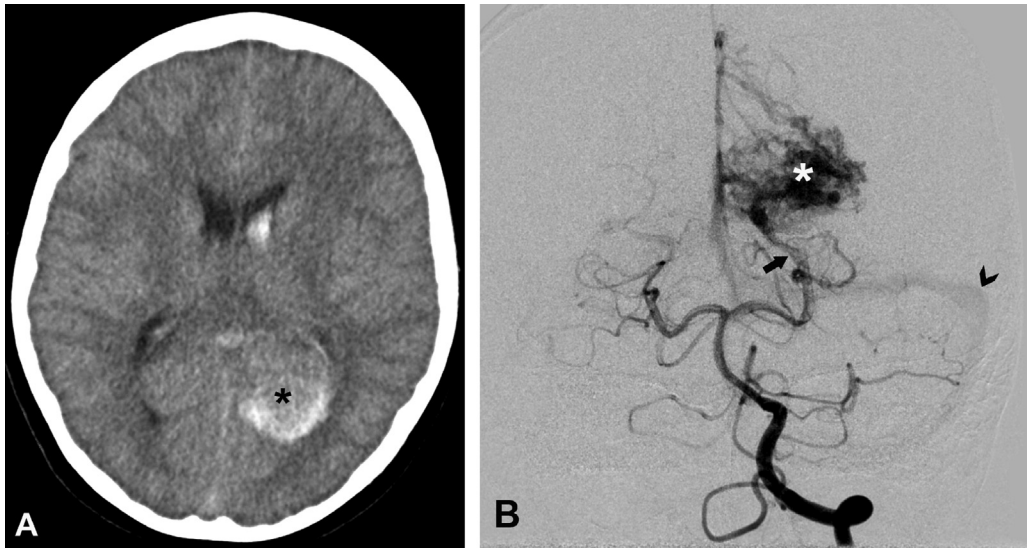

FIGURE 9.
Arteriovenous malformation. (A) Axial noncontrast computed tomography image shows a hematoma within the posterior left periventricular white matter (black asterisk) with extension of blood products into the left lateral ventricle. (B) Anteroposterior digital subtraction angiography of a left vertebral artery injection illustrates a vascular nidus (white asterisk) primarily supplied by the left posterior cerebral artery (black arrow) with early venous drainage (black arrowhead).

important for children with altered mental status or coma or in whom the airway is not stable. However, in a stable and cooperative child, MRI brain with DWI, SWI or GRE, FLAIR, MRA, and MRV can diagnose hemorrhage, differentiate hemorrhagic transformation of arterial or venous infarction from primary hemorrhage, and evaluate the brain parenchyma. Cavernous malformations can sometimes be identified on CT as hyperdense round lesions or are conspicuous on T2*-weighted MRI sequences as a round hypointense area with blooming.[58,59] ASL has been useful preoperatively and postoperatively in the setting of pediatric AVMs for detecting focal increased cerebral blood flow through the AVM nidus and within the draining veins.[60]

With suspected or diagnosed hemorrhagic stroke, it is critical to evaluate the integrity of the cerebral vasculature. CTA or MRA can be performed at the time of initial head CT or brain MRI. In many cases, these modalities can diagnose underlying AVMs or aneurysms; however, if no vascular malformation is detected and no hematologic cause or brain tumor is identified, a conventional catheter angiogram should be considered in most cases because CTA and MRA

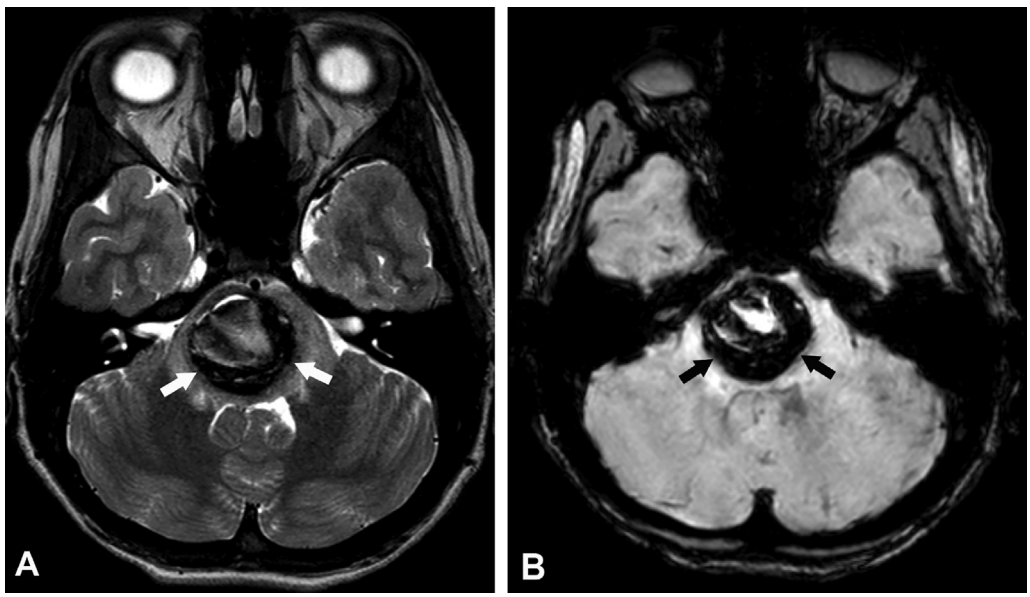

FIGURE 10.
Cavernous malformation. (A) Axial T2-weighted image reveals a mixed signal intensity, popcorn-like cavernous malformation of the pons (white arrows) with surrounding edema because of recent intralesional bleeding. (B) Axial susceptibility-weighted image illustrates "blooming" of the hemosiderin rim surrounding the lesion (black arrows).

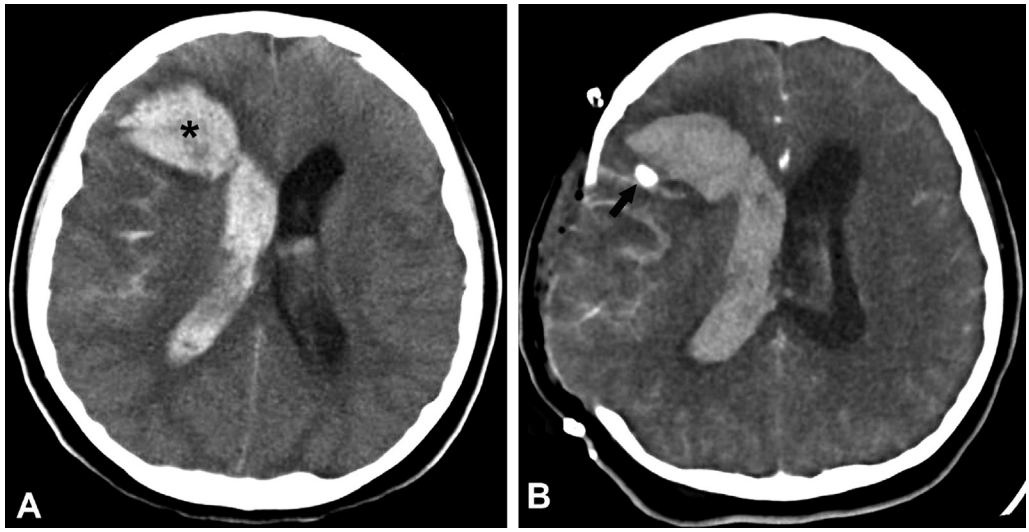

FIGURE 11.
Ruptured aneurysm. (A) Axial noncontrast computed tomography (CT) image demonstrates a right frontal intraparenchymal hematoma (black asterisk) with extension of blood products into the right lateral ventricle and the presence of subarachnoid hemorrhage. (B) Axial contrast-enhanced CT image reveals an aneurysm (black arrow) just posterior to the right frontal hematoma. Note the performance of a right decompressive craniotomy in the interval between the two scans.

can miss small AVMs and aneurysms, particularly those less than 2 mm in size. During AVM resection, intraoperative catheter angiography can help to identify residual AVM, allowing the surgeon to complete the resection at the time of the initial procedure.[61]

If no vascular malformation is noted on catheter angiography, repeat neuroimaging should be obtained after the hematoma has resolved because small vascular lesions can be compressed and concealed by the hematoma. In one report of 28 childhood AVMs that were surgically resected, some AVMs were identified up to two years after the incident hemorrhage, and recurrent AVMs were identified in some children even after complete surgical resections.[61] Therefore follow-up vascular imaging is recommended in most children in whom no cause for hemorrhage was identified or in whom a vascular lesion like an AVM was treated.

The timing, modality, and frequency of follow-up imaging are often center-dependent. Some centers obtain noninvasive imaging like MRI with MRA at three months and one year after the incident hemorrhage. Some pediatric centers, like many adult centers, advocate a conventional angiogram in the follow-up period. If this imaging does not show an underlying or recurrent vascular malformation, performance of additional imaging at age five years or 18 years is sometimes performed. More frequent neuroimaging follow-up may be indicated in some children, for example, those with cerebral cavernous malformation gene mutations or multiple cavernous malformations.

Stroke mimics

In adults, presentation with sudden onset hemiparesis with or without facial weakness and speech problems are hallmark presenting features, which clinch the diagnosis of stroke without unnecessary delay in most cases. In children, the stroke diagnosis is not as straightforward. Despite a

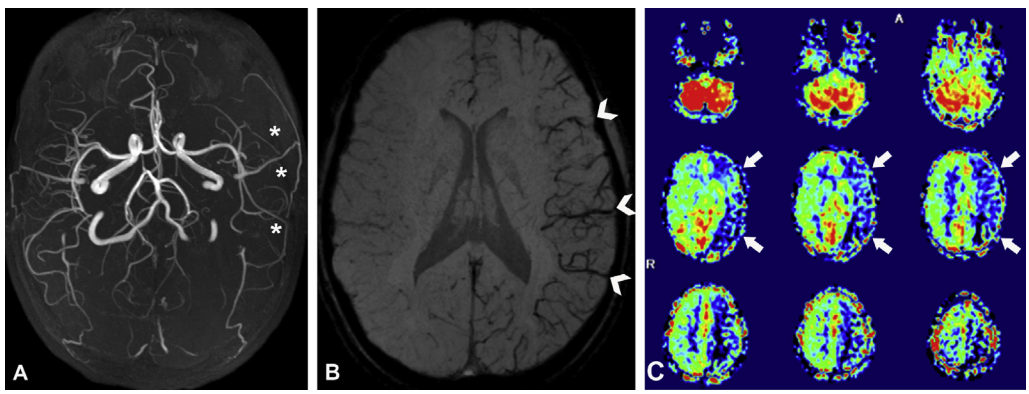

FIGURE 12.
Hemiplegic migraine. (A) Three-dimensional time-of-flight magnetic resonance angiography maximum intensity projection image illustrates diffuse attenuation of the left middle cerebral artery and branch vessels (white asterisks). (B) Axial susceptibility-weighted image shows increased conspicuity of the left cerebral sulcal veins (white arrowheads) because of increased deoxyhemoglobin concentration in a hypoperfused vascular territory. (C) Multiple axial arterial spin labeled images reveal decreased perfusion to the left cerebral hemisphere (white arrows). (The color version of this figure is available in the online edition.)

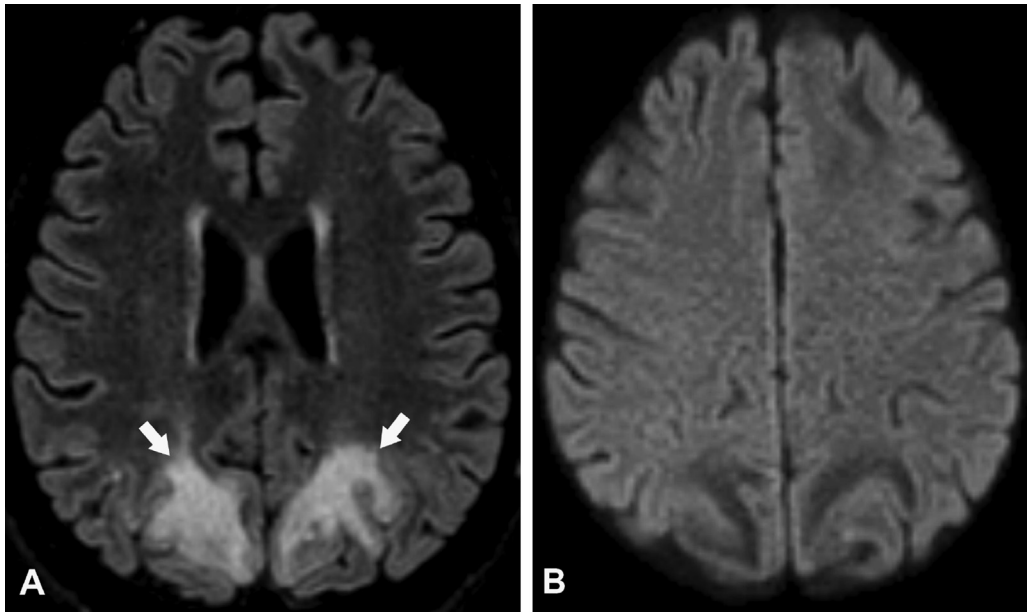

FIGURE 13.
Posterior reversible encephalopathy syndrome (PRES). (A) Axial FLAIR image demonstrates patchy parieto-occipital cortical and subcortical edema (white arrows). (B) Axial diffusion-weighted image shows no restricted diffusion.

growth in awareness about childhood stroke, when children present with acute neurological deficits, stroke is often not the first diagnosis considered by health personnel. The diagnosis is even more challenging in children who present with nonlocalizing and nonspecific signs, such as headache and vomiting. Also, localizing signs of stroke such as lateralized weakness after seizure or ataxia are often overlooked. In children with AIS, studies report total delay from symptom onset to AIS diagnosis of 16 to 24.8 hours, in-hospital delay of 9.6 to 12.7 hours, and neuroimaging delay of over eight hours.[30,62-64] In a study of 209 children with acute AIS, 70% of children reached a hospital within six hours of stroke symptom onset, but only 20% were diagnosed with stroke within six hours. Stroke was not suspected in more than 62% of children at initial presentation.[30] Failure to consider stroke in the differential diagnosis of children who present with signs suggesting it continues to delay its diagnosis until well beyond the time that acute interventional therapy can be effectively administered. The relative frequency of other diagnoses that can present similarly to stroke contribute to stroke diagnosis delay in children (Fig 12).

Shellhaas et al.[31] reported that among 30 children with stroke mimics, presentations included focal weakness in 14

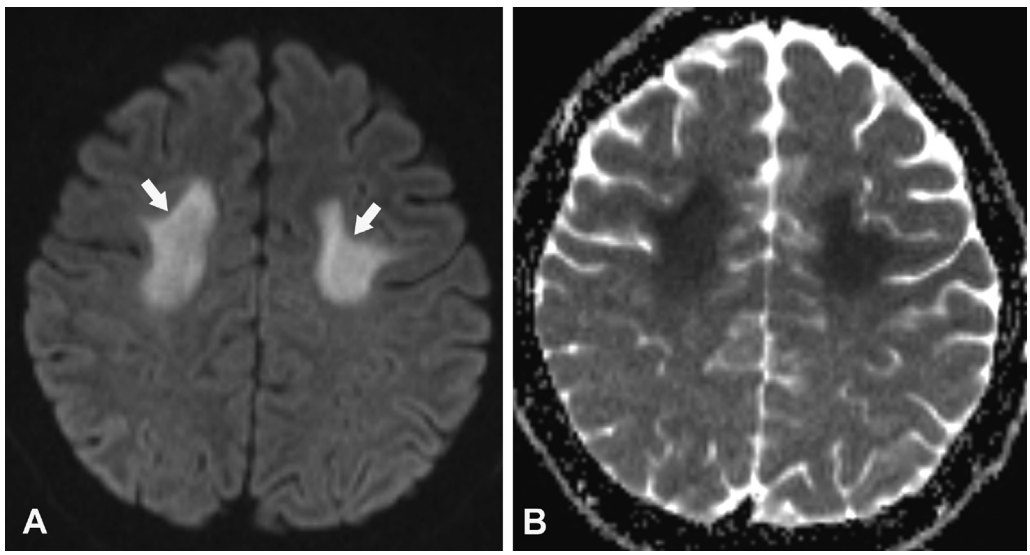

FIGURE 14.
Methotrexate toxicity. (A) Axial diffusion-weighted image and (B) Apparent diffusion coefficient map demonstrate patchy areas of restricted diffusion within the centrum semiovale (white arrows on diffusion-weighted image).

(47%), seizure in 11 (36%), headache in nine (30%), focal sensory abnormality in seven (23%), and mental status change in six (20%). Most children (63%) had other serious neurological diagnoses (posterior reversible leukoencephalopathy (Fig 13), epilepsy, intracranial infection, inflammation, focal lesions, drug toxicity) (Fig 14); few had benign diagnoses (migraine, psychogenic, and musculoskeletal disorders). In another recent prospective observational study of 124 children who presented to a tertiary pediatric emergency department and in whom a stroke alert was activated, 40% had a stroke or other neurological emergency. Thirty children (24%) had confirmed ischemic strokes, two (1.6%) had a TIA, 20 (17%) had complicated migraine syndromes, 19 (15%) had seizures, five (4%) had meningitis or encephalitis, and four (3%) had intracranial neoplasms.[33]

Future areas of investigation

Pediatric stroke is a growing field with many avenues to explore. An initial focus should be directed toward aid to centers for streamlining childhood stroke imaging protocols that minimize delays and diagnose stroke syndromes rapidly while at the same time evaluating the vasculature for stroke risk factors. In addition, given that there are many other neurological diseases that can present similarly to stroke, sequences that diagnose stroke mimics should also be included when possible.

Future areas of investigation in the setting of pediatric stroke include the role of PWI to aid in defining stroke onset and ischemic penumbra in order to help identify children who might be candidates for thrombolysis. Vessel wall imaging may improve diagnosis and characterization of arteriopathies. Understanding the pathophysiology of the various arteriopathies may lead to the rational design of specific treatment plans.

Ultimately, imaging protocols must be designed and standardized across pediatric centers and must address the challenges of imaging the pediatric brain and of differentiation of stroke syndromes from other entities to inform treatment, clinical trials, and evidence-based guidelines. A benefit to consensus-based neuroimaging is that it will facilitate multicenter treatment trials and allow for research collaborations that address clinical outcomes.

We would like to thank Gabrielle's Ride for funding this one-day workshop (http://www.gabriellesride.com/).

We wish to acknowledge the following International Paediatric Stroke Study Members who contributed to the manuscript: Drs. Andrew Demchuk, Christopher Filippi, Heather Fullerton, Manu Goyal, Kristin Guilliams, Manoelle Kossorotoff, Guillaume Sebire, Mukta Sharma, Nicholas Stence, and Arastoo Vossough.

The Recommended Imaging Protocols for evaluating neonates and children with suspected stroke were devised by the International Paediatric Stroke Study (IPSS) Neuroimaging subgroup and Pediatric Stroke Neuroimaging Consortium, led by Drs. Max Wintermark, Stanford and Michael Rivkin, Boston Children's Hospital.

Significant contributors to this effort included Aashim Bhatia, Monroe Carell Jr. Children's Hospital at Vanderbilt; Adam Kirton, Alberta Children's Hospital; Allen Newton, Monroe Carell Jr. Children's Hospital at Vanderbilt; Arastoo Vossough, Children's Hospital of Philadelphia; Bruce Bjornson, British Columbia Children's Hospital; Chris Hess, University of California San Francisco; Christine Fox, University of California San Francisco; David Mirsky, Children's Hospital Colorado; Elka Miller, Children's Hospital of Eastern Ontario; Gabrielle deVeber, The Hospital for Sick Children; Helen Carlson, Alberta Children's Hospital; Jerome Rusin, Nationwide Children's Hospital; Jessica Carpenter, Children's National Medical Center; Jonathan Murnick, Children's National Medical Center; Kate Lefond, Seattle Children's Hospital; Khaled Mohamed, Alberta Children's Hospital; Kristin Guilliams, St. Louis Children's Hospital; Lauren Beslow, Yale University School of Medicine; Manoelle Kossorotoff, Hôpital Necker-Enfants Malades; Manu Goyal, St. Louis Children's Hospital; Manu Shroff, The Hospital for Sick Children; Mark Halverson, Nationwide Children's Hospital; Max Wintermark, The Stanford University Medical Center; Michael Rivkin, Boston Children's Hospital; Mubeen Rafay, Winnipeg Children's Hospital; Mukta Sharma, Children's Mercy Hospitals and Clinics; Nany Rollins, University of Texas Southwestern Medical Center; Nicholas Stence, Children's Hospital Colorado; Noma Dlamini, The Hospital for Sick Children; Paola Pergami, Children's National Medical Center; Pradeep Krishnan, The Hospital for Sick Children; Risto Filippi, Northwell Health; Ryan Felling, Johns Hopkins Hospital; Sahar Hassanein, Ains Shams University; Sarah Lee, The Stanford University Medical Center; Suzanne Laughlin, The Hospital for Sick Children; Trish Domi, The Hospital for Sick Children; Warren Lo, Nationwide Children's Hospital; and Wayne Lee, The Hospital for Sick Children.

Other contributors included Chris Watson, Boston Children's Hospital; Andrew Demchuk, Foothills Medical Center; Sumit Pruthi. Monroe Carell Jr. Children's Hospital at Vanderbilt; Gamil Fteeh, Loma Linda University School of Medicine; Dennis Shaw, Seattle Children's Hospital; and Tim Zinkus, Children's Mercy Hospitals and Clinics.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.004.

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Ramgopal et al. BMC Pediatrics (2020) 20:14
https://doi.org/10.1186/s12887-020-1919-3

BMC Pediatrics

RESEARCH ARTICLE Open Access

Rapid brain MRI protocols reduce head computerized tomography use in the pediatric emergency department

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Abstract

Background: Rapid magnetic resonance imaging (MRI) protocols may be effective in the emergency department (ED) to evaluate nontraumatic neurologic complaints. We evaluate neuroimaging (rapid MRI [rMRI]), head computerized tomography [HCT], and full MRI) use following widespread implementation of rMRI protocols in a pediatric emergency department (ED).

Methods: We conducted a retrospective study in a tertiary care pediatric ED of encounters with neuroimaging during two 9-month periods: one prior to (control period) and one after generalized availability of 4 rMRI protocols (rMRI period). The primary outcome was differences in neuroimaging rates between the two periods. Secondary outcomes included ED process measures, unsuccessful imaging, and undetected pathology, with full MRI within 14 days as the reference standard.

Results: There were 1052 encounters with neuroimaging during the control and 1308 during the rMRI periods. Differences in neuroimaging between periods were 27.7% for rMRI (95% CI, 24.4, 31.0), − 21.5% for HCT (95% CI, − 25.5, − 17.5), and − 6.2% for full MRI (95% CI, − 9.3, − 3.1%.) Time to imaging (182 [IQR 138–255] versus 86 [IQR 52–137] minutes) as well as ED length of stay (396 [IQR 304–484] versus 257 [IQR 196–334] minutes) was longer for rMRI versus HCT ($p < 0.01$). Between the control and rMRI periods, there were differences in types of neuroimaging performed for patients with altered mental status, headache, seizure, shunt dysfunction, stroke, syncope, trauma, vomiting, infection, and other neurologic complaints ($p < 0.05$). rMRI studies were unsuccessful in 3.6% of studies versus 0.0% of HCTs ($p < 0.01$). The 22 unsuccessful rMRI studies were unsuccessful due to artifacts from dental hardware ($n = 2$) and patient motion ($n = 20$). None of the rMRI studies with full MRI follow-up imaging had undetected pathology; the false negative rate for the HCT exams was as high as 25%.

Conclusions: After routine ED use of 4 rMRI protocols, there was a more than 20% decrease in HCT use without missed diagnoses. Time to neuroimaging and length of stay were longer for rMRI than HCT, with higher rates of unsuccessful imaging. Despite these limitations, rMRI may be an alternative to HCT for nontraumatic complaints in the ED.

Keywords: Fast MRI, Quickbrain MRI, Rapid MRI, Emergency medicine, Neuroimaging

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Background

Brain magnetic resonance imaging (MRI) is an accurate, safe, non-radiating cross-sectional imaging modality. Historically, MRI use in children, particularly patients evaluated in the emergency department (ED), has been limited by the exam duration and need for sedation in many cases. Consequently, head computed tomography (HCT) is often the default imaging modality. HCT carries the benefits of being a rapid, readily available, and generally more inexpensive neuroimaging modality. For example, multicenter data from pediatric hospitals between the years 2009–2013 suggest that 56 patients per 1000 encounters (ED or inpatient) get a CT, with the majority (60%) being HCTs [1]. Additionally, HCT is preferred in cases of trauma within the context of Advanced Trauma Life Support guidelines [2]. Despite these advantages, HCT carries the carcinogenic risks associated with radiation, which are particularly concerning in pediatric patients [3, 4]. Additionally, HCT is limited in its evaluation of posterior fossa lesions as well as findings related to ischemic stroke [5].

Rapid-sequence magnetic resonance imaging of the brain (rMRI) has gained acceptance as an alternative to HCT in children because of the speed of image acquisition. Previous studies highlight experiences with rMRI protocols for a single indication, including ventricular shunt malfunction [6–10], stroke [11], and abusive head trauma [12, 13]. These studies demonstrate a role for rMRI as a radiation-sparing alternative to HCT. In patients evaluated for ventricular shunt malfunction, for example, retrospective studies have suggested that rapid MRI is not inferior to HCT, with comparable measures of diagnostic accuracy [9, 14]. Additionally, HCT imaging is frequently used to also evaluate other common pediatric neurologic complaints in the ED, including headache, syncope, and seizure, for example [15]. rMRI imaging may be an alternative to HCT for these patients as well. At present, there are very limited single center data which suggest that availability of 24/7 MRI facilities may be associated with increased rates of MRI [16]. No investigation to date, however, has identified if availability of rapid MRI protocols may allow for decreased HCT utilization.

The primary objective of this study was to evaluate the rates of neuroimaging (rMRI, HCT, and full MRI) before and after widespread implementation of four rMRI protocols in the ED. Secondary objectives were to evaluate ED process measures within these time periods, specifically, time to neuroimaging, total ED length of stay (LOS), and rates of unsuccessful initial imaging, follow-up imaging, and undetected pathology.

Methods

Study setting

We performed a single center retrospective study in a tertiary care freestanding children's hospital ED with an annual volume of over 80,000 patients. Ours is the only children's hospital in the region and is part of a large, integrated healthcare delivery system that includes 42 hospitals with a shared electronic medical record, including the radiology Picture Archiving and Communication System. Since November 2017, our ED implemented widespread ED availability of 4 distinct rMRI neuroimaging protocols (Table 1): ventricular shunt evaluation, abusive head trauma screen, stroke, and nonspecific neurologic complaints (e.g. headache, seizure, altered mental status, vomiting). Prior to this time, although some protocols were available, they were not yet utilized as part of routine ED practice. rMRI are performed using five MRI scanners: 1) three GE Signa 1.5 T, 2) one GE Signa 3 T (GE Healthcare, Chicago, IL), and 3) one Siemens Skyra 3 T (Siemens Medical Solutions, Malvern, PA). The protocols performed are the same for all patients irrespective of age.

Neuroimaging studies performed as part of an ED encounter at our institution are not done with sedation; and, if sedation is needed, imaging is performed once the patient is admitted (or scheduled as an outpatient.) It is possible, however, for patients to receive oral,

Table 1 rMRI protocols

Protocol	Sequences	Duration
Shunt	Coronal T2 SSFSE	7 min
	Sagittal T2 SSFSE	
	Axial T2 SSFSE	
	Axial 3D SWAN	
Abusive head trauma screen	Axial DWI	16 min
	Axial GRE	
	Axial T2 Propeller	
	Coronal T1 FLAIR	
	Axial 3d SWAN	
	Axial fast FLAIR	
	Axial T2 SSFSE	
Stroke	Axial DWI	22 min
	3D ASL	
	Axial T2 FLAIR	
	Axial 3D SWAN	
	3D Time-of-flight 3-slab MRA	
Neurologic	DWI	7 min
	Axial GRE	
	Axial T2 SSFSE	
	Axial T2 FLAIR	
	Sagittal T1 FSPGR	

SSFSE single-shot fast spin-echo sequence, *SWAN* Susceptibility-weighted angiography, *DWI* Diffusion-weighted magnetic resonance imaging, *GRE* gradient echo, *FLAIR* Fluid-attenuated inversion recovery, *ASL* arterial spin labeling, *MRA* magnetic resonance angiography, *FSPGR* fast spoiled gradient echo. Protocol durations include the localizer time

intranasal, or intravenous anxiolysis (e.g. midazolam, dexmedetomidine) to facilitate neuroimaging. We did not specifically identify use of sedative agents utilized for the purposes of neuroimaging in the context of this study.

Study cohort

We included neuroimaging studies (rMRI brain, HCT, and full MRI) performed as part of an ED encounter during two periods: November 1, 2016 to July 31, 2017 (control period) and November 1, 2017 to July 31, 2018 (rMRI period). We excluded studies performed for patients > 18 years-old. HCT remains the modality of choice for acute head trauma [2], therefore, we excluded imaging studies in patients > 12 months of age if the imaging was for trauma as documented as part of the "indication" section of the radiology report. We included studies in patients with possible trauma ≤12 months of age because of a dedicated rMRI protocol to evaluate for abusive head trauma in this age group, which may or may not be associated with a corroborating history or physical examination for an acute traumatic injury.

Neuroimaging studies

For each encounter, we defined the "index" neuroimaging study as the first study (non-contrast rMRI, non-contrast HCT, or full MRI with and/or without contrast) performed in the ED. We included only one ED encounter per patient per study period, and, a priori, determined that if a patient had multiple encounters during one of the two study periods, only the last encounter for that period would be included.

We assessed for follow-up imaging after the index study, defined as any neuroimaging (including outpatient, inpatient, and ED) performed within 14 days of the index study. For cases when more than one study was performed within this period, the earliest was considered the follow-up study. We further evaluated within this 14-day period if a full MRI was performed, even if it was not the first follow-up imaging study performed.

For index and follow-up neuroimaging studies, two pediatric emergency medicine physicians (S.R. and J.R.M), blinded to the clinical history and examination and to the type of imaging performed, reviewed all attending radiology interpretations and classified them into one of four categories: a) *positive*, in which the findings from neuroimaging would require further testing, admission, or subspecialist consultation; b) *negative*, defined as no acute pathology identified or would typically not require further investigation or follow up, c) *unknown*, in which the results could not be classified as positive or negative, and d) *unsuccessful*, defined as a study which was sufficiently limited to preclude radiology interpretation. For this process, the investigators both reviewed approximately 50% of all of the included imaging studies in order to determine if there was sufficient agreement, defined, a priori, as Kappa ≥0.70 [17], before reviewing the remainder independently. For discordances between the two raters as well as interpretations deemed *unknown,* an attending radiologist (also blinded as described above) reviewed the interpretation and classified the study as *positive* or *negative*.

For patients with a follow-up full MRI within 14 days of the index study and for whom the index scan was either a HCT or rMRI during the rMRI study period, two attending radiologists, blinded to the index study modality, independently reviewed the full MRI interpretations and compared them to HCT or rMRI index exam interpretations to evaluate for undetected pathology in these studies. Specifically, they categorized index studies as: true positive (including possible progression of disease), true negative, false positive, and false negative.

Data acquisition

We used Centricity RIS-IC (version 6.0; GE Healthcare, Chicago, IL) to determine which patients had neuroimaging during the two study periods. These data were then linked to radiology results obtained using mPower Clinical Analytics (version 3.2.1; Burlington, Massachusetts) using unique accession numbers. Patient-related data were obtained from data harbored by the electronic health record using the business intelligence platform SAP BusinessObjects (SAP, Waldorf, Germany). We extracted the following for each encounter: patient age, sex, race, ED chief complaint, reason for neuroimaging, emergency severity index (ESI) score, time of arrival, time of final disposition, ED disposition (admitted, discharged, transferred to another institution, or deceased), time and duration of index neuroimaging, and follow-up neuroimaging. The ESI is assigned by a triage nurse and is an ED triage algorithm that stratifies patients into 5 groups on the basis of acuity and resource needs, with 1 representing the most acute [18]. ED chief complaint is also assigned by a triage nurse at the time of arrival and is based on a standardized list of 109 complaints.

Outcomes

The primary outcome was rates of neuroimaging (rMRI, HCT, and full MRI) between both periods. Secondary outcomes were time to index neuroimaging study, ED LOS, rates of unsuccessful index imaging, follow-up imaging, and undetected pathology on initial imaging for patients with rMRI or HCT as the index study and for whom a subsequent MRI was performed within 14 days of initial evaluation.

We also assessed imaging patterns across the entire ED population (not exclusively those with neuroimaging) and evaluated use of any neuroimaging as well as

modality-specific rates for each time period. We applied the same exclusion criteria as in our primary cohort and identified those with trauma using the International Classification of Diseases, revision-10 codes, S00-T88.

Data analysis

We summarized demographics between the two time periods using proportions. We calculated interrater reliability using Cohen's Kappa statistic [17]. All continuous data were nonparametric. For our primary outcome, we compared the difference in proportions for each type of neuroimaging (HCT, rMRI, and full MRI) between the two periods and analyzed changes in neuroimaging by chief complaint and assessed for differences using chi-squared tests. For secondary outcomes we compared results using chi-squared and Wilcoxon rank-sum tests. For the evaluation of undetected pathology on index imaging during the rMRI period, we calculated the false negative rate of rMRI or HCT using full MRI performed within 14 days as the reference standard. We further assessed the accuracy of these index studies by calculating the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio with 95% confidence intervals. Analyses were performed using the epiR (version 0.9.99) package for R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). This study was approved with a waiver of informed consent by the University of Pittsburgh Human Research Protection Office.

Exploratory analysis

In order to assess the effect of our assumptions regarding non-accidental trauma (i.e. including patients < 12 months with any trauma) on the primary outcome, we performed an additional analysis excluding all patients with trauma regardless of age. Additionally, we reported the number of rMRI performed and the percent of neuroimaging performed as rMRI during each week of the rMRI period.

Results

Demographics

A total of 4306 neuroimaging studies were performed during the two periods. After applying exclusions, there were 2360 index studies (1052 in the control period; 1308 in the rMRI period) among 2295 patients (Fig. 1). There was a higher proportion of high-acuity patients (ESI 1 and 2) as well as of patients admitted to the intensive care unit in the control period compared to the rMRI period (Table 2).

Primary outcome

Use of rMRI as the index ED imaging modality was 10.8% during the control period and 38.5% in the rMRI period (percent difference 27.7%; 95% CI 24.4, 31.0%); HCT use in the control and rMRI periods were 70.0 and 48.5%, respectively (percent difference, − 21.5%; 95% CI, − 25.5, − 17.5%) (Table 3). These differences all reached statistical significance ($p < 0.01$).

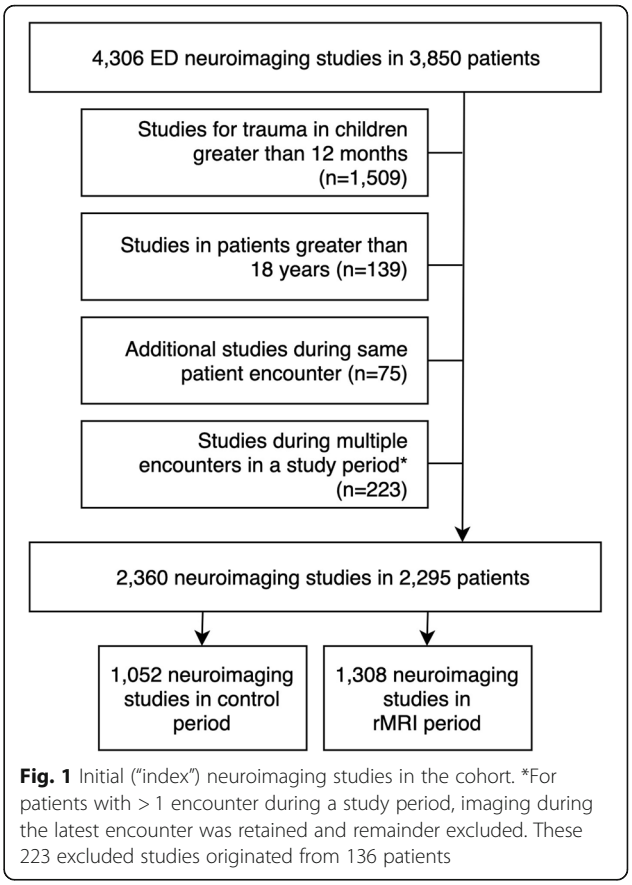

Fig. 1 Initial ("index") neuroimaging studies in the cohort. *For patients with > 1 encounter during a study period, imaging during the latest encounter was retained and remainder excluded. These 223 excluded studies originated from 136 patients

Neuroimaging by chief complaint

Neuroimaging studies were performed in patients with 15 different complaints across the two time periods. Compared to the control period, during the rMRI period, there were statistically significant differences in neuroimaging patterns for altered mental status, headache, seizure, shunt dysfunction, stroke, syncope, trauma, vomiting, infection, other neurologic complaints, and other complaints (Table 4). Relative rates of neuroimaging were not statistically significantly different in patients with abdominal complaints, eye complaints, fussiness, nonaccidental trauma, and vomiting with diarrhea, respiratory complaints, and brief resolved unexplained events. During the control period, there were 114 (10.8%) rMRI studies, including 85 (74.6%) abusive head trauma screen protocols, 14 (12.3%) shunt protocols, 7 (6.1%) stroke protocols, and 8 (7.0%) neurologic protocols. During the rMRI period, 504/1308 (38.5%) of studies were rMRI protocols including 330 (65.5%)

Table 2 Demographics of patients who received ED neuroimaging

Variable	All encounters with neuroimaging (*N* = 2360) n (%)	Control period (*N* = 1052) n (%)	rMRI period (*N* = 1308) n (%)
Age			
< 1 year	734 (31.1)	327 (31.1)	407 (31.1)
1 to < 4 years	283 (12.0)	134 (12.7)	149 (11.4)
4 to < 12 years	621 (26.3)	278 (26.4)	343 (26.2)
12 to < 19 years	722 (30.6)	313 (29.8)	409 (31.3)
Number male	1257 (53.3)	660 (50.5)	597 (56.7)
Race			
White	1769 (75.0)	778 (74.0)	991 (75.8)
Black	458 (19.4)	198 (18.8)	260 (19.9)
Other	61 (2.6)	30 (2.9)	31 (2.4)
Unknown	72 (3.1)	46 (4.4)	26 (2.0)
Weekend presentation	566 (24.0)	247 (23.5)	319 (24.4)
Day time (06:00–17:59) presentation	1344 (56.9)	619 (58.8)	725 (55.4)
ESI Codes			
4 or 5	204 (8.6)	62 (5.9)	142 (10.9)
3	1.769 (75.0)	755 (71.8)	1014 (77.5)
2	340 (14.4)	208 (19.8)	132 (10.1)
1	35 (1.5)	19 (1.8)	16 (1.2)
Not listed	12 (0.5)	8 (0.8)	4 (0.3)
ED Disposition			
Discharged	1219 (54.6)	538 (51.1)	751 (57.4)
PICU	367 (15.6)	194 (18.4)	173 (13.2)
Admitted	693 (29.4)	316 (30.0)	377 (28.8)
Transferred	10 (0.4)	4 (0.4)	6 (0.5)
Expired	1 (0.0)	0 (0.0)	1 (0.1)

rMRI rapid magnetic resonance imaging, *ESI* Emergency Severity Index, *ED* emergency department, *PICU* pediatric intensive care unit

neurologic protocols, 82 (16.3%) abusive head trauma screen protocols, 46 (9.1%) stroke protocols, and 46 (9.1%) shunt protocols.

Time to neuroimaging and unsuccessful neuroimaging

The median time to neuroimaging in the control cohort was significantly shorter than in the rMRI cohort. Total ED LOS in the two periods were similar, as were rates of follow up imaging. There were differences in time to neuroimaging and total ED LOS when comparing imaging modalities during the rMRI time period, with HCT having the shortest times (Table 5). Across both periods, 22/618 (3.6%) rMRI, 0/1370 (0.0%) HCT, and 11/372 (3.0%) full MRI studies were unsuccessful ($p < 0.01$). Reasons for the 22 unsuccessful rMRI studies were artifacts caused by dental hardware ($n = 2$) and patient motion ($n = 20$). Seven abusive head trauma screen rMRI, 12 neurologic, and 3 stroke protocols were unsuccessful. The median age of patients with unsuccessful rMRI was 1.69 years (IQR 0.36–3.70), compared to 5.19 years (IQR 0.38–12.8) for those with successful rMRI ($p = 0.12$).

Follow-up neuroimaging

Index studies were deemed positive for 16.3 and 11.4% of all neuroimaging studies during the control and rMRI periods, respectively (Additional file 2: Table S1). For the classification of imaging results, the two pediatric emergency medicine physicians demonstrated substantial agreement (κ-statistic of 0.71 [95% CI 0.67–0.72]). There were 118 patients who received a full MRI within 14 days of the index study during the rMRI period with 82 (69.5%) having had an index HCT and 36 (30.5%) having had an rMRI. Both radiologists determined the rate of undetected pathology (false negative rate) was 0% for

Table 3 Neuroimaging by modality between time periods and secondary outcomes comparing time periods

Variable	Control period (*N* = 1052) n (%)	rMRI period (*N* = 1308) n (%)	Difference in percent (95% CI)	*P*
rMRI	114 (10.8)	504 (38.5)	27.7 (24.4, 31.0)	< 0.01
Head CT	736 (70.0)	634 (48.5)	−21.5 (−25.5, −17.5)	< 0.01
Full MRI	202 (19.2)	170 (13.0)	−6.2 (−9.3, −3.1)	< 0.01
Time to neuroimaging in minutes; median (IQR)	119 (64–193)	139 (84–208)	–	< 0.01
Total ED LOS in minutes; median (IQR)	304 (231–387)	304 (232–397)	–	0.82
Any follow-up neuroimaging within 14 days, n (%)	130 (12.4)	169 (12.9)	0.6 (−2.2, 3.3)	0.72
Full MRI within 14 days, n (%)	91 (8.7)	130 (10.0)	1.3 (−1.1, 3.7)	0.36
Time to follow up neuroimaging, n (%)				0.96
1–2 days	100 (76.9)	128 (75.7)	−1.2 (−11.6, 9.2)	
3–7 days	16 (12.3)	21 (12.4)	0.1 (−7.5, 7.8)	
8–14 days	14 (10.8)	20 (11.8)	1.1 (−6.8, 9.0)	

rMRI rapid MRI, *CT* computerized tomography, *MRI* magnetic resonance imaging, *IQR* interquartile range, *ED* emergency department, *LOS* length of stay

Table 4 Neuroimaging performed in the control and rMRI periods for those complaints with significant differences between the time periods. For each chart, the y axis represents the percent of studies in each time period

Category	Control Period Number of rMRI/total number in category (%)	rMRI period Number of rMRI/total number in category (%)	*P*
Headache	13/217 (6.0)	135/284 (47.5)	< 0.01
Trauma in infant	17/196 (8.7)	44/253 (17.4)	0.02
Seizure	13/135 (9.6)	73/200 (36.5)	< 0.01
Shunt evaluation	2/90 (2.2)	30/70 (42.9)	< 0.01
Neurologic complaints	4/65 (6.2)	29/71 (40.8)	< 0.01
Altered mental status	5/57 (8.8)	17/54 (31.5)	< 0.01
Vomiting	7/44 (15.9)	31/66 (47.0)	< 0.01
Non-accidental trauma	20/46 (43.5)	22/46 (47.8)	0.29
Infection	5/33 (15.2)	20/40 (50.0)	< 0.01
Syncope	2/30 (6.7)	13/33 (39.4)	< 0.01
Eye complaint	2/25 (8.0)	11/34 (32.4)	0.07
Fussiness	10/17 (58.8)	14/26 (53.8)	0.70
Stroke	1/16 (6.3)	7/14 (50.0)	0.02
Respiratory	0/9 (0.0)	6/15 (40.0)	0.09
Vomiting with diarrhea	2/8 (25.0)	8/15 (53.3)	0.42
BRUE	4/12 (33.3)	7/10 (70.0)	0.07
Abdominal complaint	2/8 (25.0)	8/13 (61.5)	0.16
Other*	5/44 (11.4)	29/64 (45.3)	< 0.01

**Other* sickle cell disease with pain (*n* 6), dehydration, neck pain (*n* 5 each), ingestion/overdose (*n* 4), abnormal labs, cardiac arrest, hematemesis/bloody stool (*n* 3 each), congestion, ear pain, eye injury (*n* 2 each) allergic reaction, back pain, constipation, cough, croup, diabetes, genitourinary complaint, hemophilia, poor feeding, rash, sore throat, wound evaluation (*n* 1 each), and otherwise unclassified general medical complaint (*n* 67). BRUE, brief resolved unexplained event

rMRI; for HCT, one radiologist found a false negative rate of 18% and the other of 25%. rMRI was found to be both highly sensitive and specific. HCT demonstrated a specificity of 94–95% and a sensitivity of 75–82% (Additional file 3: Table S2).

Overall neuroimaging rates

In the analysis comparing rates of neuroimaging among all ED encounters for nontraumatic complaints, there were 33,117 encounters in the control period and 35,582 in the rMRI period. There was an increase in the percent of patients who had any neuroimaging between these periods, with the increase driven by rMRI use (Additional file 4: Table S3).

Exploratory analyses

When we excluded all patients < 12 months with trauma ($n = 811$), changes in the rates of neuroimaging were similar to those demonstrated in the primary analysis (Additional file 5: Table S4). In light of the increased proportion of high acuity patients in the control group, we evaluated the association between ESI and HCT using multivariable logistic regression and found that in addition to ESI, time period remained independently associated with HCT utilization after consideration of potential confounders (Additional file 6: Table S5). We noted an increasing number and percent of rMRI performed during each week of the rMRI period (Additional file 1: Figure S1).

Discussion

Following implementation of 4 standardized rMRI protocols in a pediatric ED, we identified an increase in rMRI imaging that was associated with a significant reduction in HCT use. There were no differences in rates of follow-up imaging and in the group of patients for whom a full MRI was performed within 2 weeks of the index study, there were no false negative rMRI studies. In addition to the limitation in radiation exposure from HCT use, these data support potentially limiting subsequent full MRI imaging, particularly given the need for sedation in some cases, and the cost associated with such imaging.

The benefit of rMRI for shunt dysfunction has been previously investigated [7–10], as has the use of rMRI as a screening tool for nonaccidental trauma [12, 13]. Few

Table 5 Secondary outcomes for patients in the rMRI period, by index study modality

Variable	rMRI ($N = 504$)	Head CT ($N = 634$)	Full MRI ($N = 170$)	*P* value
Time to neuroimaging in minutes; median (IQR)	182 (138–255)	86 (52–137)	200 (146–262)	< 0.01
Total ED LOS in minutes; median (IQR)	396 (304–484)	257 (196–334)	338 (269–420)	< 0.01
Any follow-up neuroimaging within 14 days, n (%)	49 (9.7)	95 (15.0)	25 (14.7)	0.02
Full MRI within 14 days, n (%)	36 (7.1)	82 (12.9)	N/A	< 0.01
Time to follow up neuroimaging, n (%)				0.77
1–2 days	35 (71.4)	75 (78.9)	18 (72.0)	
3–7 days	8 (16.3)	9 (9.5)	4 (16.0)	
8–14 days	6 (12.2)	11 (11.6)	3 (12.0)	

studies have reported on the generalized use of rMRI for other indications, and none specifically in the ED setting. Missios, et al., reported on an institution-wide registry of 1146 patients who received rMRI. Two patients were found to have previously undetected pathology on subsequent neuroimaging [19]. Another evaluation of 101 rMRI studies reviewed by a radiologist and neurosurgeon suggested that these studies served as adequate screening evaluations and that such imaging had a low requirement (5%) for follow up full MRI [20]. The findings from our study build upon these prior studies, specifically reporting on ED patients, and demonstrating a concomitant decline in HCT use.

Widespread rMRI implementation includes several barriers. We observed a longer time to neuroimaging and LOS for patients undergoing rMRI compared to HCT. Other studies have reported similar findings [9, 14, 21]. Our ED has a dedicated HCT scanner, compared with the MRI machines which are located on a different floor. Equipment location as well as the preparation time that is needed for screening prior to MRI imaging are likely contributors to the longer times associated with rMRI. It is likely that in the future these times will be reduced as the technology becomes less expensive and more easily accessible. Nonetheless, for the majority of patients, who are clinically stable and for whom the longer time to neuroimaging is unlikely to affect clinical outcomes, this additional time is likely outweighed by the patient benefits. A higher proportion of rMRI studies were unsuccessful compared with HCT in our study. While these studies are "rapid," they remain longer in duration than a non-contrast HCT. The cost of an MRI Is often cited as a barrier to its use over CT [22]. However, according to hospital charge data at our institution, that for a non-contrast brain MRI is comparable to that for a head CT. Although this may not be consistent across all institutions, and more importantly, the insurance reimbursement rate may not be the same, it is likely that the current cost differences are not as discrepant as once thought. The charge for a rMRI if coded appropriately is significantly less than that for the full MRI. Other concerns highlighted in surveys include lack of rMRI access during evenings or weekends [22]. Finally, it is critical to implement appropriate MRI sequences specific to the diagnosis of interest. While we found no missed diagnoses on rMRI, a previous study reporting on a FIESTA-based protocol found a significant false negative rate, including a missed venous sinus thrombosis and subdural hemorrhage [23]. We did observe that a higher proportion of patients received any neuroimaging in the rMRI period compared with the control. This may reflect a lower threshold to obtain imaging given the availability of rMRI during this period. To what extent this increase represents overuse warrants further exploration.

The findings from this study are subject to limitations. As a single center retrospective study, our results do not generalize to all EDs, particularly those outside of children's hospitals. We attempted to blind the physicians who reviewed study interpretations, but subtle clues may have biased them in their assessment of positivity. By not excluding infants < 12 months with trauma to ensure inclusion of possible abusive head trauma, we invariably included some patients with acute trauma, for whom HCT is the more appropriate study. However, this would have biased the results towards an underestimation of the rMRI rate and overestimation of the HCT rate; and, a sensitivity analysis excluding these patients produced similar results. While the lower acuity in the rMRI period may have contributed to the lower HCT rate during this period, the time period variable was also independently associated with HCT, indicating that the decrease in HCT use would not completely be explained by the differences in ESI across the two periods. Although it is possible that patients received follow-up neuroimaging outside of our health system resulting in an underestimated rate of follow-up imaging, we would expect this number to be small and also similar between the two time periods. For those patients with multiple encounters during a study period, we retained the last visit. It is possible that imaging decisions at this visit were influenced by imaging performed during prior visit(s). However, these excluded studies represent a small fraction (223 patients from 136 patients, or approximately 5%) of our original study population, and the impact of this exclusion is likely to be minimal. We did not utilize a washout period after the implementation of rMRI protocols in our institution. However, given the weekly trends observed in rMRI patterns, this would only lead to an underestimation of rMRI use (and an underestimation of CT reduction) since we included data from implementation without accounting for any washout period. We were unable to assess the test characteristics, including the rates of undetected pathology for the entire cohort, as not all patients received the reference standard (full MRI). Additionally, given the small number of patients available for this analysis, the confidence intervals surrounding these point estimates are wide and warrant further confirmation with larger sample sizes. Finally, we were unable to provide data with respect to use of anxiolytic medications, which were not available in our dataset.

Conclusion

Widespread implementation of distinct rMRI protocols in our ED was associated with a 20% reduction in HCT, without missed diagnoses or increase in follow-up

imaging. Important considerations with rMRI use compared to HCT in the ED setting include longer time to neuroimaging and LOS, and a higher rates of unsuccessful imaging. Despite these limitations, rMRI has the potential to supplant HCT for nontraumatic indications in the pediatric ED.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12887-020-1919-3.

Additional file 1: Figure S1. a) number and b) percent of neuroimaging studies ordered as rMRI for each week of the rMRI study period.

Additional file 2: Table S1. Index neuroimaging findings by time period and imaging modality.

Additional file 3: Table S2. Diagnostic accuracy of index HCT and rMRI in 122 patients with follow-up full MRI within 14 days during the rMRI period.

Additional file 4: Table S3. Rates of neuroimaging across both time periods among all emergency department encounters for nontraumatic complaints.

Additional file 5: Table S4. Rates of neuroimaging across both time periods when performed as a sensitivity analysis (further exclusion of patients < 12 months with trauma).

Additional file 6: Table S5. Results of exploratory multivariable logistic regression identifying predictors associated with dichotomous outcome (CT versus no CT).

Abbreviations

ED: Emergency department; HCT: Head computerized tomography; IQR: Interquartile range; LOS: Length of stay; MRI: Magnetic resonance imaging; rMRI: Rapid magnetic resonance imaging

Acknowledgements

We thank Gabriella Butler RN MSN, Srinivasan Suresh MD, MBA, and Thomas Sutcavage MSIS, R.T.(R.), CIIP, for their assistance with data acquisition.

Authors' contributions

SR and JRM conceptualized and designed the study, drafted the initial manuscript, collected data, and carried out the initial analyses. SK acquired data and critically revised the manuscript for intellectually important content. AF and SS carried out data analysis and critically revised the manuscript for intellectually important content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

None.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy limitations but are available from the corresponding author on reasonable request and with the presence of a data use agreement.

Ethics approval and consent to participate

This study was approved by the University of Pittsburgh Human Research Protection Office (protocol number PRO18070213).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 27 October 2019 Accepted: 8 January 2020
Published online: 13 January 2020

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Publisher's Note

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

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Optimizing Advanced Imaging of the Pediatric Patient in the Emergency Department: Policy Statement

AMERICAN ACADEMY OF PEDIATRICS Committee on Pediatric Emergency Medicine, Section on Radiology; AMERICAN COLLEGE OF EMERGENCY PHYSICIANS Pediatric Emergency Medicine Committee; AMERICAN COLLEGE OF RADIOLOGY; Jennifer R. Marin, MD, MSc, FAAP, FACEP,[a] Todd W. Lyons, MD, MPH, FAAP,[b] Ilene Claudius, MD, FACEP,[c] Mary E. Fallat, MD, FAAP, FACS,[d] Michael Aquino, MD,[e] Timothy Ruttan, MD, FACEP, FAAP,[f] Reza J. Daugherty, MD, FAAP[g]

Advanced imaging, including ultrasonography, computed tomography, and magnetic resonance imaging, is an integral component to the evaluation and management of ill and injured children in the emergency department. As with any test or intervention, the benefits and potential impacts on management must be weighed against the risks to ensure that high-value care is being delivered. There are important considerations specific to the pediatric patient related to the ordering and interpretation of advanced imaging. This policy statement provides guidelines for institutions and those who care for children to optimize the use of advanced imaging in the emergency department setting and was coauthored by experts in pediatric and general emergency medicine, pediatric radiology, and pediatric surgery. The intent is to guide decision-making where children may access care.

INTRODUCTION

As diagnostic imaging has advanced over the last several decades, imaging modalities have become more accurate, faster, and more widely available. Advanced imaging (ie, ultrasonography, computed tomography [CT], and magnetic resonance imaging [MRI]) is commonly used in the emergency department (ED) to assist and facilitate diagnosis and management, and such use has increased dramatically over time.[1,2] However, imaging carries risks including those from radiation exposure,[3–5] false-positive and incidental findings and the downstream testing that may result,[6–10] increases in ED length of stay,[11,12] sedation,[13] transport away from the ED, and overall health care costs.[14] In addition, there is the risk that a study will need to be repeated if not optimally performed, thus compounding the aforementioned risks. It is important that physicians, physician assistants, and nurse practitioners

abstract

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To cite: Marin JR, Lyons TW, Claudius I, et. al; American Academy of Pediatrics Committee on Pediatric Emergency Medicine, Section on Radiology; American College of Emergency Physicians Pediatric Emergency Medicine Committee; American College of Radiology. Optimizing Advanced Imaging of the Pediatric Patient in the Emergency Department: Policy Statement. *Pediatrics*. 2024;154(1): e2024066854

weigh the risks and benefits when ordering advanced imaging studies to ensure there is a net benefit delivered to patients.

Pediatric patients represent a distinct population that requires unique considerations with respect to advanced imaging in the ED. Pediatric patients typically have a small body habitus and less subcutaneous fat, which makes ultrasonography an ideal imaging tool for several indications.[15] Children are particularly sensitive to ionizing radiation, such as from CT, because of the larger organ-specific dosing conferred, the increased susceptibility of these organs to developing malignancy secondary to radiation, and the increased life span over which those cancers may develop.[16] MRI is becoming increasingly available as an option in the emergent evaluation of pediatric patients because of abbreviated protocols, which have decreased the duration of studies and increased the feasibility.[17] This policy statement provides recommendations for optimizing advanced imaging of ill and injured children in the ED, and the accompanying technical report may be used as a more detailed resource. Point-of-care ultrasonography use by emergency physicians is not addressed in this document, as it is outside the scope.[18–20]

INSTITUTIONAL CONSIDERATIONS

To provide timely and appropriate imaging to pediatric patients presenting to the ED, there are important institutional considerations. More than 80% of pediatric patients in the United States receive emergency care from general EDs.[18,19] However, over 80% of EDs treat fewer than 10 children per day.[21] It is important that general EDs are prepared and have access to adequate resources to care for pediatric patients. Such "pediatric readiness" includes the provision of advanced imaging studies.[20] In keeping with the "as low as reasonably achievable" (ALARA) principle,[22] weight- and size-based CT parameters should be adjusted for pediatric patients, and there is guidance available for institutions about how to implement this.[23] However, nearly 25% of EDs do not have reduced-dose radiation protocols for CT and radiograph imaging.[21] The use of ultrasonography as a nonradiating imaging modality has increased in pediatric patients over time[2] and may supplant the use of CT for many patients.[24] However, ultrasonography is operator-dependent, and many facilities do not have sonographers with sufficient training or experience in pediatrics. Facilities that have access to MRI should ensure that pediatric-specific protocols and size adjustments are available.

Imaging services extend beyond the actual imaging study, and patients will sometimes benefit from remote imaging consultation from a pediatric radiologist or other pediatric subspecialist. Such consultation should be considered depending on the nature of the suspected pathology, severity of illness, or comfort level of the treating clinician. Discussion may include the best imaging strategy prior to imaging being completed, if any, as well as interpretation of imaging results. These policies may reduce the need for transfer to a pediatric institution. When transfers are deemed necessary, it is imperative that any imaging and interpretation report performed during the referring ED encounter be transferred with the patient or remotely accessible to the receiving facility. In many circumstances, patients are destined for transfer to a pediatric facility regardless of imaging results at the referring ED. In cases when the results of imaging will not alter the decision to transfer or impact management prior to and/or during transport, it is in the best interest of the patient that imaging be deferred to the receiving hospital. Imaging prior to transfer delays definitive treatment, may increase the number of imaging studies performed for a patient, and can result in higher radiation exposure and increased health care costs.[25–28] Advanced imaging is best performed when it will allow the patient to be discharged from the ED or remain at the originating hospital.

PHYSICIANS, PHYSICIAN ASSISTANTS, AND NURSE PRACTITIONERS CONSIDERATIONS

Although this statement is primarily directed toward those who work in the acute care setting, the care of the ill or injured child may begin with the primary care provider (PCP) who serves an important role, whether evaluating patients by phone, remotely, or in-person. It is important that PCPs are familiar with optimal imaging strategies (Table 1) for common pediatric conditions to adequately prepare patients who are referred to the ED and may require advanced imaging. It is equally as important for PCPs to be familiar with imaging resources at local EDs to best inform families and also decide to which ED a referral may be made when multiple options are available.

In the ED, physicians, physician assistants, and nurse practitioners are tasked with determining first whether advanced imaging is indicated and second which test is optimal to order. Such decisions are based on patient factors (eg, clinical presentation, age, need for sedation, comorbidities, availability of PCP follow-up) and ED resources available, including imaging availability and resources to manage abnormalities diagnosed. Guidelines such as published clinical decision rules that assist with risk stratification[29–31] hospital clinical guidelines (see technical report supplemental file), Choosing Wisely recommendations,[32] and the American College of Radiology Appropriateness Criteria[33] can assist with these decisions, as can consultation with a pediatric medical subspecialist (eg, pediatric emergency physician, pediatric radiologist) or pediatric surgical specialist, when available. Evidence-based guidelines may additionally reduce racial and ethnic disparities in

TABLE 1 Recommendations for Emergency Department Advanced Imaging Strategies for Common Pediatric Conditions

Clinical Problem	Risk-Stratification Tools	Recommendations	First-Line Imaging (if Available)[c]	Alternative/Additional Imaging
Seizures				
Simple febrile		Neuroimaging is not necessary for children with a simple febrile seizure[b]		
Complex febrile		Emergency neuroimaging is usually not indicated if the patient is back to baseline and without significant clinical findings.	MRI	CT
Afebrile		Do not order emergent imaging for children ≥6 mo with an unprovoked, generalized seizure who have returned to baseline mental status and have a normal neurologic examination.[b] Routine neuroimaging is not necessary after a breakthrough seizure in a patient with established epilepsy.[b]	MRI	CT
Headache (atraumatic)		Emergent neuroimaging is not necessary in patients with uncomplicated headache or those with stable headaches that meet criteria for migraine.[b]	MRI	CT
Ventricular shunt evaluation			MRI	CT
Stroke			MRI	CT
Trauma[a]		Routine whole-body CT should not be performed in pediatric trauma patients.[b] Whole-body CT is not used to screen asymptomatic children with a high-energy mechanism. When such imaging is used in children, venous-phase imaging of the chest and abdomen is often sufficient for screening.[44]		
Head	Kuppermann et al, 2009[29] Osmond et al, 2010[49] Dunning et al, 2006[50]	CT scans should not be routinely obtained for mild head injuries.[b]	CT	
Cervical spine	Leonard et al, 2019[51] Herman et al, 2019[52]	Routine advanced imaging is not warranted.[b]	XR	CT, MRI
Chest	American College of Surgery, Trauma Quality Improvement Program, 2018[44]	Chest CT is indicated if concern for blunt mediastinal vascular injury, wide mediastinum on chest XR, or for patients with penetrating thoracic trauma	CT with IV contrast	
Abdomen/pelvis	American College of Surgery, Trauma Quality Improvement Program, 2018[44]		CT (with IV contrast)	

TABLE 1 Continued

Clinical Problem	Risk-Stratification Tools	Recommendations	First-Line Imaging (if Available)[c]	Alternative/Additional Imaging
	Arbra et al, 2018[53] Holmes et al, 2013[30]			
Child abuse				
Abusive head trauma	Berger et al 2016[45]		MRI CT if acute trauma or concern for skull fracture	CT
Cervical spine injury		Immobilize cervical spine in cases of suspected abusive head trauma	MRI	
Abdominal trauma		Imaging is warranted if signs of abdominal injury or unexplained elevated transaminases (>80 u/L)[46]	CT (with IV contrast)	
Appendicitis	Pediatric Appendicitis Score[54] Alvarado score[55] Pediatric Appendicitis Risk Calculator[31]		US[b]	MRI without contrast, CT with IV contrast, repeat US,[d] observation
Neck infections			US, CT with IV contrast, MRI	
Nephrolithiasis			US	Low-dose CT (stone protocol)

IV, intravenous; US, ultrasonography; XR, radiography. All imaging is without contrast unless otherwise specified.
[a] Excludes patients with concern for child abuse.
[b] Indicates Choosing Wisely recommendation.
[c] When MRI is recommended, it should be performed only in a stable patient given the duration of obtaining and completing the examination.
[d] Patients with equivocal initial ultrasonography (eg, nonvisualized appendix) may undergo follow-up ultrasonography after a period of observation (eg, 6–12 hours).

ED imaging,[34–37] as these tools reduce variability in practice and provide a standardized approach to the evaluation for certain conditions.[38–40] Imaging typically falls into 3 categories: Imaging that determines the need for emergent intervention provided by the originating ED, imaging that may determine whether transfer is needed, and imaging in a patient who will be transferred regardless of the imaging findings (Table 2). Framing imaging decisions in this manner may help to curb unnecessary imaging.

In many cases, there may be more than one reasonable choice regarding advanced imaging, and shared decision-making is appropriate to ensure that the patient and family's needs and values are considered and incorporated into decision-making.[41] For example, a child with abdominal pain may be at moderate risk of appendicitis and need advanced imaging to evaluate the appendix; however, neither ultrasonography nor MRI are available at the referring ED. This situation presents an opportunity to weigh the options for imaging with the family including a CT at the referring ED or transfer to a pediatric facility for ultrasonography or MRI. For patients who are at low risk, an additional option to discuss with family members and document in the electronic health record is discharging home with monitoring for worsening symptoms and follow-up with the PCP.

RECOMMENDATIONS

1. EDs (including hospital and freestanding) that care for pediatric patients should ensure appropriate imaging resources are available to meet the needs of children

TABLE 2 Imaging Decision-Making Recommendations

Question to Be Answered	Recommendation	Example
Will imaging assist with determining whether emergent intervention is needed?	Perform imaging	Patient with altered mental status and possible cerebral edema
Will imaging assist with determining whether transfer is needed?	Perform imaging	Patient with head trauma who is awake and alert but with signs/symptoms concerning for clinically important traumatic brain injury and could be discharged if imaging is negative
Will patient be transferred regardless of imaging findings?	Defer imaging to the receiving institution	Patient with significant abdominal pain and/or concern for acute abdomen, presenting to an ED without pediatric surgical capabilities

or that they have transfer protocols and guidelines in place with a pediatric center. It is important that all EDs:

a. Evaluate their pediatric readiness, including pediatric imaging services, and have a plan to address any deficiencies. This plan is ideally facilitated by appointing a pediatric emergency care coordinator.[18]
b. Have a mechanism to securely transmit or share images with receiving hospitals electronically, and have mechanisms for sharing images on physical media when online image transfer is not available.[42] This capability may reduce the need for repeat imaging at the receiving ED.
c. Have processes in place to ensure timely and efficient transfer of pediatric patients who require specialized care, which minimizes potentially avoidable imaging and facilitates definitive imaging at the receiving hospital. Sample protocols are available from the Emergency Medical Services for Children Innovation and Improvement Center.[43]
d. Have policies in place for imaging consultation with a pediatric radiologist or general radiologist with expertise in pediatric imaging to discuss best imaging practices and minimize transfers that may only require imaging review. Ideally, such policies should outline processes and billing by pediatric radiologists for secondary readings of images completed prior to transfer.
e. Strive to provide high-quality ultrasonography services as first-line imaging for pediatric patients when indicated for common pediatric complaints (eg, abdominal pain with concern for appendicitis or nephrolithiasis). It is important for EDs that lack comprehensive imaging services for children to have guidelines and agreements in place. Guidelines should include alternatives when ultrasonography is the preferred imaging modality but not readily available and protocols for timely remote consultation with a pediatric medical subspecialist or transfer to a pediatric center.
f. Partner with imaging services to ensure that CT protocols and parameters are pediatric-specific and adhere to the ALARA principle. Specific guidelines are available.[23]

2. Primary care and emergency physicians, physician assistants, and nurse practitioners who care for ill and injured children and/or who refer patients for ED evaluation and management can optimize advanced imaging by:
   a. Familiarizing themselves with pediatric imaging resources available at local EDs and using this information to decide where best to refer patients. Pediatric specialists, including pediatric radiologists and/or hospitalists, can help support decision-making for ED clinicians.
   b. Discussing and deferring advanced imaging in children for whom the decision to transfer and management prior to and during transfer will not be altered by the results of imaging.
   c. Using shared decision-making with the patient/family, when appropriate, prior to ordering imaging in EDs without access to ultrasonography or MRI when these modalities are considered first-line for the evaluation of the patient. Specifically, the risks and benefits of each of the following options should be considered: Deferring immediate imaging and obtaining as an outpatient, transferring the patient to a referral center for imaging and interpretation, and performing the imaging that is available locally.
   d. Using publicly available evidence-based guidelines and protocols, such as the ACR Appropriateness Criteria[33] and/or clinical decision rules (with or without clinical decision support) that objectively risk-stratify patients, to minimize potentially unnecessary imaging and possibly reduce racial and ethnic disparities in imaging delivery.
3. Condition-specific imaging recommendations:
   a. Seizures
      i. Emergent neuroimaging is not recommended for simple febrile seizures.
      ii. Emergent neuroimaging is not recommended for complex febrile seizures if the patient is without neurologic deficits and returns to baseline, as the incidence of emergent and/or significant intracranial findings is very low.
      iii. Advanced imaging of children (≥6 months) with afebrile generalized seizures may often be deferred to outpatient or nonurgent settings in the absence of high-risk historical (eg, comorbidities, developmental regression) or clinical examination findings. Imaging is typically not indicated after a seizure in patients with a preexisting diagnosis of epilepsy if the seizure is typical of the patient's seizure semiology. It is prudent to have a low threshold for neuroimaging in patients who present with status epilepticus or who do not return to their neurologic baseline.
      iv. In children with a seizure for whom neuroimaging is indicated, noncontrast MRI is generally the preferred imaging modality for stable patients. Noncontrast CT is acceptable if MRI is not readily available.
   b. Headache
      i. The incidence of pathology in children presenting with a headache and without other neurological signs or symptoms is low, and emergent neuroimaging may be reserved for those with neurologic signs and/or symptoms.
      ii. When neuroimaging is indicated, MRI is generally preferred over CT in stable patients. CT is acceptable if MRI is not readily available.

c. Ventricular shunt evaluation
    i. Interpreting neuroimaging in patients with concern for shunt malfunction is best performed when compared with the patient's prior imaging, in order to detect subtle changes in ventricular size. If there is strong clinical suspicion of a shunt malfunction without baseline imaging available, imaging may be deferred and performed where definitive treatment can be delivered.
    ii. Children with ventricular shunts typically undergo frequent neuroimaging evaluations. Therefore, rapid MRI, when available, should be considered for the evaluation of shunt malfunction to reduce lifetime radiation exposure when resources are available to reprogram a programmable shunt if needed. Ultra-low–dose CT protocols specific to ventricular shunt evaluation that reduce radiation exposure without compromising image quality are another option if MRI or the ability to reprogram the shunt is not available.
d. Pediatric stroke
    i. Consultation with clinicians with expertise in pediatric stroke can aid in determining the optimal imaging strategies for children with stroke symptoms. Although there is no clear recommendation for thrombolytics in children, emergent advanced neuroimaging performed within 1 hour of arrival for children with stroke symptoms can aid in identifying children who may benefit from timely, specific stroke therapies.
    ii. MRI has a high sensitivity for ischemic stroke in children and can also aid in identifying stroke mimics. Rapid MRI stroke protocols may overcome challenges associated with traditional protocols in pediatric patients.
    iii. In children with stroke-like symptoms and negative noncontrast CT, anti- thrombotic therapies are typically not warranted given the high rate of stroke mimics in this age group.
e. Trauma
    i. Advanced imaging should be obtained for an injured patient if it will allow the patient to be discharged from the ED or remain at the initial ED. It is optimal for injured patients who have indications for transfer to a pediatric trauma center to not undergo advanced imaging at the referring center unless performed in consultation with a receiving pediatric trauma center.
    ii. Cervical spine CT and chest CT imaging are seldom indicated as screening studies in pediatric patients. Evidence-based clinical guidelines and pathways, including those for minor head injury, cervical spine injury, and abdominal trauma should be used when possible to avoid CT use in patients at very low risk for clinically important injuries. Alternatively, the child may be transferred to a pediatric trauma center where advanced imaging can be obtained if needed.
    iii. Imaging decisions should be made with the intention of identifying clinically- important, rather than just radiographically apparent, injuries (with the exception of injuries from child abuse, as all injuries are important for forensic documentation; see specific imaging recommendations below for evaluating suspected abuse).
    iv. Routine whole-body CT (ie, "pan scan") should not be performed in pediatric trauma patients. When it is necessary, it should be performed with single-phase contrast to avoid scanning body regions multiple times. Selective region-specific scanning based on clinical prediction models is preferred unless the patient has an unreliable physical examination because of severe neurotrauma with or without intubation and a high-energy mechanism of injury.[43] If there is concern for vascular or renal collecting system injury, consultation with a radiologist is recommended to ensure appropriate timing of contrast for each body region.
f. Child abuse
    i. When possible, imaging studies for the evaluation of child abuse are best interpreted by a pediatric radiologist to minimize the risk of missed findings or misinterpretation of normal developmental anatomy as abnormal. If clinical suspicion for abuse is high, consultation or transfer to a center with a child abuse specialist is important.
    ii. Skeletal surveys should be performed to evaluate for occult or healing fractures when there is concern for abuse and should be performed in those less than 2 years of age. There is limited utility in older children unless recommended by a child abuse specialist.
    iii. Either noncontrast CT or MRI of the brain is recommended in any child in whom there is suspicion of abusive head trauma. Given the high incidence of occult brain injury in children <6 months, physicians, physician assistants, and nurse practitioners should have a low threshold to perform neuroimaging. The imaging modality used depends on several factors, with CT preferred for unstable patients and those with acute trauma and concern for skull fracture. It is important to note that the Pediatric Emergency Care Applied Research Network head injury clinical decision rule[29] excluded children with concern for abuse, and therefore should not be applied to these patients. The Pittsburgh Infant Brain Injury Score[45]

may be used as a clinical decision aid to risk-stratify children with subtle nonspecific signs and symptoms suggestive of abusive head trauma.

iv. In patients with suspected or confirmed abusive head trauma, the cervical spine should be immobilized until definitive MRI imaging can be performed to evaluate for associated ligamentous injury and/or spinal cord injury without radiographic or CT abnormality.

v. Abdominal imaging via IV-contrast CT scan should be considered in children with suspected abuse who have signs or history of abdominal injury or otherwise unexplained elevated liver enzymes (aspartate transaminase or alanine transaminase >80 u/L).[46]

vi. The high risk of reinjury and death in victims of child abuse must be factored into the risk–benefit ratio when considering imaging of these children.

vii. Unless discharge from the ED is anticipated, the imaging evaluation for child abuse is best performed and interpreted at a hospital with a child protection team.

g. Appendicitis

i. Risk-stratification tools can be used to assist with determining which patients are unlikely to have appendicitis and do not need imaging.

ii. When imaging is indicated, ultrasonography is the preferred first-line imaging modality. If unavailable, physicians and physician assistants and nurse practitioners may incorporate shared decision-making to determine whether immediate CT imaging, transfer for ultrasonography or MRI, or watchful waiting with admission or observation at home with next-day follow-up is the best plan.

h. Pulmonary embolism

i. Lower extremity Doppler ultrasound can be considered as a first-line test in patients with concern for a deep vein thrombosis or a pulmonary embolism (PE). A positive ultrasound may allow for presumptive diagnosis of PE in the appropriate clinical scenario. However, a negative ultrasound study is insufficient to exclude the diagnosis, and depending on the pretest probability, CT would be appropriate.

ii. CT pulmonary angiogram is the diagnostic test of choice when there is high clinical suspicion for PE, and low-radiation dosing protocols are important to minimize radiation exposure. Clinicians should consider risk factors and clinical presentation to risk-stratify patients, as decision tools, including the Wells Criteria[47] and Pulmonary Embolism Rule-out Criteria,[48] have not been validated in children.

i. Neck infections

i. Ultrasonography, contrast-enhanced CT, and MRI are all considered appropriate for the diagnosis of neck lesions. Availability of resources, suspected location of pathology (eg, superficial versus deep neck), preference of surgical staff, test characteristics of each of the imaging modalities, risks of ionizing radiation, and need for sedation are important to consider when determining the optimal imaging approach. Lateral neck radiographs may be used as the initial test to evaluate for a retropharyngeal infection given the high sensitivity and specificity. However, given their limited ability to evaluate for other deep neck space infections, advanced imaging is typically indicated if there is continued clinical concern.

j. Musculoskeletal infections

i. Although radiographs are insensitive for the detection of acute bone infections, they may be considered as an initial examination to evaluate for other pathologies such as trauma or malignancy.

ii. If there is high clinical suspicion for osteomyelitis, MRI should be considered as the diagnostic test of choice, given its accuracy for diagnosis and ability to detect concomitant adjacent infections. It is best that such imaging is performed at the institution where definitive care will be delivered.

iii. Ultrasonography is an appropriate diagnostic modality to identify joint effusions; however, it cannot distinguish between sterile joint fluid and septic arthritis. Therefore, a definitive diagnosis requires synovial fluid analysis. MRI may be helpful in patients in whom there is clinical suspicion for concomitant osteomyelitis.

k. Nephrolithiasis

i. The American Urological Association and the European Society for Pediatric Radiology recommend ultrasonography as first-line imaging for children with suspected nephrolithiasis.

ii. CT should typically be reserved for indeterminate cases or if further clarification is needed, such as for surgical planning.

iii. If CT is performed, a noncontrast, low-dose, or ultra-low–dose protocol will minimize radiation exposure.

SUMMARY

Important advances in imaging technology have resulted in increased use of advanced imaging to diagnose and manage pediatric patients in the ED. To optimize imaging, there are important considerations for the institution and for physicians, physician assistants, and nurse practitioners who care for patients. These include adherence to the ALARA principle, using ultrasonography when appropriate and feasible as an alternative to CT, ensuring there are policies to facilitate consultation with pediatric subspecialists, including pediatric radiologists, and ensuring appropriate transfer to a pediatric center when necessary. For patients

who will be transferred and for whom the imaging will not alter management prior to or during transport, it is optimal for imaging to be deferred to the receiving institution. Physicians, physician assistants, and nurse practitioners should always weigh the benefits and risks of imaging and incorporate the recommendations, resources, and strategies in this policy statement and data in the accompanying technical report to optimize imaging in children.

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ABBREVIATIONS

ALARA: as low as reasonably achievable
CT: computed tomography
ED: emergency department
PCP: primary care provider
PE: pulmonary embolism

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DOI: https://doi.org/10.1542/peds.2024-066854

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FUNDING: No external funding.

FINANCIAL/CONFLICT OF INTEREST DISCLOSURE: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2024-066855.

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Stroke in Childhood

Clinical guideline for diagnosis, management and rehabilitation

Stroke association

RCPCH Royal College of Paediatrics and Child Health
Leading the way in Children's Health

Identify children with suspected stroke

1 Identify potential stroke

- Acute focal neurological deficit
- Speech disturbance
- Unexplained, persistent change in conscious level (GCS ≤ 12 **OR** AVPU < V)

Also consider stroke in children with:

- New onset focal seizures
- New onset severe headache
- Ataxia
- Dizziness
- Resolved acute focal neurological deficit
- Sickle Cell Disease

Neurological assessment

PedNIHSS definitions	Scale definition
1a. Level of Consciousness:	**0** = Alert; keenly responsive **1** = Not alert, but arousable by minor stimulation **2** = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make non-stereotyped movements **3** = Responds only with reflex motor or autonomic effects or totally unresponsive
1b. LOC Questions: *Tested by asking age and 'where is XX', XX referring to the name of the parent or other familiar family member present (> 2 years)*	**0** = Answers both questions correctly **1** = Answers one question correctly **2** = Answers neither question correctly
1c. LOC Commands: *Tested by asking to open / close the eyes and to 'show me your nose' or 'touch your nose' (> 2 years)*	**0** = Performs both tasks correctly **1** = Performs one task correctly **2** = Performs neither task correctly
2. Best Gaze: *Horizontal eye movements tested*	**0** = Normal **1** = Partial gaze palsy **2** = Forced deviation / complete gaze palsy
3. Visual: *Tested by visual threat (2–6 years); confrontation, finger counting (> 6 years)*	**0** = No visual loss **1** = Partial hemianopia **2** = Complete hemianopia **3** = Bilateral hemianopia (including cortical blindness)
4. Facial Palsy: *Tested by patient showing teeth or raising eyebrows / close eyes*	**0** = Normal symmetrical movement **1** = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) **2** = Partial paralysis (total or near total paralysis of lower face) **3** = Complete paralysis of one or both sides
5 & 6. Motor Arm and Leg: *Tested by patient extending arms 90 degrees (if sitting) or 45 degrees (if supine), and the leg 30 degrees*	**5a. Left Arm, 5b. Right Arm** **0** = No drift for full 10 seconds **1** = Drift ≤ 10 seconds **2** = Some effort against gravity **3** = No effort against gravity **4** = No movement **5** = Amputation **6a. Left Leg, 6b. Right Leg** **0** = No drift for full 5 seconds **1** = Drift 5 seconds **2** = Some effort against gravity **3** = No effort against gravity **4** = No movement **5** = Amputation
7. Limb Ataxia: *Tested for by reaching for a toy / kicking a toy (< 5 years); finger-nose-finger / heel-shin tests (> 5 years)*	**0** = Absent **1** = Present in one limb **2** = Present in two limbs
8. Sensory: *Observe behavioural response to pin prick*	**0** = Normal; no sensory loss **1** = Mild to moderate sensory loss **2** = Severe to total sensory loss
9. Best Language: *Tested by observing speech and comprehension (2–6 years); describe picture (> 6 years)*	**0** = Normal **1** = Mild to moderate aphasia **2** = Severe aphasia **3** = Mute, global aphasia

2 Pre-hospital care: Ring 999 / 111

- Manage Airway
- Administer high flow O_2 if clinically indicated
- Perform a capillary glucose test within 15 minutes of presentation
- Treat HYPOGLYCAEMIA (If capillary blood glucose 3 mmol/L give 2 ml/kg of 10% dextrose)
- Assess using **FAST**
- Transport to nearest ED with acute paediatric services
- Priority call / pre-alert ED of impending arrival of child with suspected stroke
- Activate (locally defined) acute paediatric stroke pathway
- If Sickle Cell Disease is suspected, discuss with paediatric haematologist who should be present in pre-hospital care / ED

3 ED: Activate acute stroke pathway

This algorithm is not wholly applicable to children with Sickle Cell Disease. If Sickle Cell Disease is suspected:

- Discuss with paediatric haematologist
- Exchange transfusion even if initial imaging is normal

- Intubate if GCS < 8, AVPU = U, if there is a loss of airway reflexes or there is suspected / proven raised intracranial pressure
- Administer high flow O_2 and target SpO_2 ≥ 92%
- If the circulation is compromised give a 10 ml/kg isotonic fluid bolus
- Perform a capillary glucose test within 15 minutes of presentation. If capillary blood glucose 3 mmol/L give 2 ml/kg of 10% dextrose and consider a hypoglycaemia screen

4 Investigations

- Venous or capillary blood gas
- FBC, PT, APTT
- Fibrinogen
- Urea and electrolytes
- Blood glucose
- Group and save
- C-reactive protein
- Liver function tests
- Blood cultures as appropriate

Monitoring

- BP
- Temperature
- SpO_2
- HR
- RR
- GCS
- Assess PedNIHSS score

See 'Neurological assessment'

5 Urgent brain imaging

Perform CT / CTA < 1 Hour of ED admission

Record time of symptom onset
Window for tPA = 4.5 hours

Record time of admission
Window for imaging = 1 hour

6

Stroke mimic

MRI with stroke-specific sequences should be performed in patients with suspected stroke when there is diagnostic uncertainty.

Haemorrhagic stroke

Urgent discussion with neurosurgical team regarding need for transfer.

Arterial ischaemic stroke

Consider suitability for other emergency interventions, such as; Thrombectomy or Decrompressive craniectomy.

7 Treatment for Arterial ischaemic stroke (AIS)

Aspirin

- 5mg/kg ≤ 1 hour (Unless CI, e.g. parenchymal haemorrhage)
- Delay for 24 hours in context of thrombolysis

In children presenting with AIS Thrombolysis, the use of tPA...
may be considered if 2–8 years and ***could*** be considered if ≥ 8 years

IF ALL OF THE FOLLOWING ARE TRUE:

- PedNIHSS ≥ 4 and ≤ 24
- tPA can be administered ≤ 4.5 hours of symptom onset
- CT has excluded intracranial haemorrhage
- CTA demonstrates normal brain parenchyma or minimal early ischaemic change
- CTA demonstrates partial / complete occlusion of the intracranial artery corresponding to clinical / radiological deficit

OR

- MRI and MRA showing evidence of acute ischaemia on diffusion weighted imaging + partial / complete occlusion of the intracranial artery corresponding to clinical / radiological deficit

PROVIDING THAT THERE ARE NO CONTRAINDICATIONS

aPTT=Activated partial thromboplastin time; **AVPA**=Alert, Voice, Pain, Unresponsive; **CI**=Contra-indication; **CT**=Computerised tomography; **CTA**=Computerised tomography angiography; **ED**=Emergency Department; **FAST**=Face, Arms, Speech Time; **FBC**=Full blood count; **GCS**=Glasgow Coma Scale; **HR**=Heart rate; **LOC**=Level of consciousness; **MRA**=Magnetic resonance angiogram; **MRI**=Magnetic resonance imaging; **AIS**=Arterial ischaemic stroke; **O_2**=Oxygen; **PedNIHSS**=Paediatric National Institute of Health Stroke Scale; **PT**=Prothrombin time; **RR**=Respiratory rate; **SpO_2**=Oxygen saturation; **tPA**=Tissue plasminogen activator.

Produced in line with the full RCPCH clinical guideline.
For further details on all recommendations, visit: www.rcpch.ac.uk/stroke-guideline

A practical approach to acute hemiparesis in children

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PUBLICATION DATA
Accepted for publication 3rd February 2015.
Published online 1st April 2015.

ABBREVIATIONS

AIS	Arterial ischaemic stroke
MCA	Middle cerebral artery

Acute hemiparesis in children is a common clinical syndrome presenting to a variety of care settings. The recognition and the differential diagnosis is challenging, particularly in young children. Arterial ischaemic stroke (AIS) is the primary diagnosis to be considered as this requires emergency investigations and management; however, there are several conditions collectively described as 'stroke mimics' that need consideration. Accurate diagnosis is essential for appropriate management. Clinical data combined with neuroimaging are important for accurate diagnosis and management. This review and the accompanying illustrative case vignettes suggest a practical approach to differential diagnosis and management of children presenting with acute hemiparesis.

Acute hemiparesis is a common clinical syndrome in children that may present to primary, secondary, or tertiary health care professionals. Challenges in clinical practice include difficulty in recognizing acute hemi-syndromes in young children or in children with subtle presentations. For example, whereas older children with vascular stroke syndromes would usually meet the 'FAST' (face, arm, speech, and time) criteria used by paramedics to recognize stroke in adults in the community (where patients with face, arm, and speech problems are triaged as likely cases of stroke), younger children may present with a more subtle motor deficits, and diffuse neurological signs such as encephalopathy. Subtle clinical presentations 'soft signs' are also a feature of acute vascular events in children with sickle-cell disease, and it is important to consider a central cause in these children rather than attributing limping or writing difficulty to pain. Transient ischaemic attack as a clinical syndrome is not very useful in younger children because of subtle presentations.[1]

This review considers the clinical approach to a child with lateralized weakness in a practical way, considering a staged approach towards clinical assessment and investigation to reach a diagnosis. It does not consider management of specific individual disorders as this is comprehensively covered elsewhere.

Is it central or peripheral?

This may seem an obvious point, but in our experience insufficient effort is sometimes made to distinguish between central and peripheral deficits, especially in the emergency room. The difficulty of ascertaining the cause of limb weakness in a child with sickle-cell disease, at risk of painful crises or osteomyelitis, has already been discussed. It is important not to be overly swayed by a history of trauma: we have seen several children who sustained falls, presumably as a result of acute weakness, whose orthopaedic or soft-tissue injuries were managed without appreciation of the central neurological signs. Naturally, a competent neurological examination is key here; facial weakness, encephalopathy, or seizures are also all signs that should point the clinician to the central nervous system (CNS). Specific points in neurological examination are helpful indicators of a central lesion. It is important to note that the typical signs of increased tone and exaggerated reflexes on the affected side are late signs in acute hemiparesis. The absence of these signs is not sufficient to exclude a central lesion. In a comatose patient, asymmetry of posture with external rotation of the leg at hip joint may be the only indication of a hemiplegia. Similarly, head version or gaze deviation to one side is a clue to a hemispheric lesion. In older, cooperative children, it may be possible to demonstrate the typical pyramidal distribution of weakness in the limbs, namely predominant weakness of shoulder abduction, elbow extension, and wrist extension in the upper limb, and hip flexion, knee flexion, and ankle dorsiflexion in the lower limb. Careful examination to establish the level of lesion in facial weakness is valuable. Idiopathic lower motoneuron facial palsy (Bell's palsy), particularly if partial and sparing upper face, can be mistaken for an ipsilateral upper motoneuron facial palsy as a component of hemiplegia due to stroke (and vice versa). Facial palsy contralateral to the hemiplegia localizes the lesion to pons and the posterior circulation in vascular events.

The signs in younger children are often more diffuse; however, asymmetry of movements, posture, or tone should be evident on close observation.

Is it a neurosurgical emergency?

Studies[1–5] in a variety of healthcare settings have shown that there is lack of appreciation of the potentially life-threatening causes of acute weakness in children, with major delays in imaging and diagnosis, even where health care is not limited by resources. The immediate priority in the acute setting is to identify or exclude a neurosurgical emergency: for example acute intracranial haemorrhage, massive arterial ischaemic stroke (AIS), brain tumour, or acute hydrocephalus. Brain computed tomography (CT) will enable these to be identified or excluded. Magnetic resonance imaging (MRI) has better temporal, spatial, and diagnostic resolution but is unlikely to be available as an emergency in most settings. The decision about what imaging modality to select, and with what degree of urgency, is really a matter of clinical judgement. However, in our view any child with encephalopathy or unstable vital signs needs stabilization and brain imaging as a matter of urgency. Inevitably a proportion of children will have both

What this paper adds

- Acute hemiparesis in children is a clinical syndrome with diverse causes.
- A systematic approach including clinical data and neuroimaging can help establish accurate diagnosis.

Table I: Differential diagnosis of acute hemiparesis in children

Condition	History	Examination	Investigations
Intracranial haemorrhage	Abrupt onset. Headache, vomiting	Reduced level of consciousness, rapid evolution of neurological findings. Note potential neurocutaneous signs, e.g. in hereditary haemorrhagic telangiectasia	Imaging may identify aetiology, e.g. arteriovenous malformation
Arterial ischaemic stroke	Abrupt or stuttering onset; latter associated with arteriopathy. Preceding chicken pox, febrile illness, cardiac condition, (minor) head injury, neck injury	Consciousness generally preserved unless large middle cerebral artery stroke/brainstem infarct. Note neurocutaneous features, e.g. neurofibromatosis type 1	Arteriopathy may be evident on imaging
Meningitis/ meningo-encephalitis	Fever, headache systemic symptoms	Fever, neck stiffness, reduced level of consciousness	Imaging shows multiple areas of involvement, not conforming to vascular territory, variable diffusion-weighted imaging characteristics, cerebrospinal fluid shows pleocytosis, increased protein, organism may be isolated
Acute disseminated encephalomyelitis	Fever, headache systemic symptoms; subacute onset	Fever, neck stiffness, reduced level of consciousness, focal neurological deficits	Mainly white matter involvement in a patchy distribution, variable diffusion characteristics, usually not restricted
Posterior reversible encephalopathy syndrome	Seizures, drugs (cyclosporine A, tacrolimus, cyclophosphamide)	Reduced level of consciousness, arterial hypertension	Patchy grey and white matter involvement, usually free diffusion
Bleeding or oedema associated with CNS tumour	Preceding chronic/subacute history of neurological symptoms followed by acute change		
Metabolic	History of developmental delay, hypotonia, fatigue, encephalopathy, vomiting	Movement disorder, seizures	Symmetric basal ganglia/ brainstem involvement, white mater changes, changes not confined to a vascular territory, abnormal biochemistry
Reversible cerebral vasoconstriction syndrome	History of thunderclap headache, history of vasoactive drugs	Focal neurological deficit	Vascular imaging shows diffuse segmental narrowing of intracranial arteries
Hemiplegic migraine	Headache, history of recurrent episodes with normal imaging, family history of hemiplegic migraine	Hemiparesis generally resolves in 72h (rarely longer)	Normal imaging; genetic testing may be considered
Postictal[a]	Preceding focal motor seizure, history of epilepsy		Normal imaging, electroencephalography may be helpful
Non-organic[a]	Fluctuating weakness, disproportionate effect on function	Examination findings not confirming to neuroanatomical localization	Normal investigations

[a]It is important to remember that both postictal Todd's paralysis and non-organic hemiparesis are diagnostic of exclusion, particularly in younger children, and full assessment including investigations is required to exclude other causes. CNS, central nervous system.

a CT and an MRI; however, unless emergency MRI is easily available, CT will provide sufficient information to manage a sick child safely.

What is the diagnosis?

Acute hemiparesis is the most common presentation of the vascular stroke syndromes, particularly AIS and intraparenchymal haemorrhage. However, around 20% to 30% of children with acute hemiparesis will have a non-vascular diagnosis; collectively these conditions are termed 'stroke mimics'.[6] This is in contrast to adults, where the frequency of stroke mimics is much lower, and it is fairly safe to consider acute hemiparesis as usually having a vascular aetiology. This difference between adults and children is often not readily appreciated by non-paediatricians. Table I lists some clinical features that may be helpful in differentiating between vascular stroke syndromes and stroke mimics; however, these are not reliable and imaging is essential to make a clear diagnosis. For any child with hemiplegia, imaging should be performed as soon as possible as this is critical for correct further management.

An abrupt onset is suggestive of a vascular stroke syndrome; in particular, headache and coma are highly suggestive of intracranial haemorrhage. Arteriopathic AIS may have a stuttering onset.[7] Encephalopathy is suggestive of CNS infection or acute disseminated encephalomyelitis. A reduced conscious level is a sinister sign in AIS, indicating significant raised intracranial pressure that can be secondary to 'malignant' middle cerebral artery (MCA) territory infarction or associated with brainstem or posterior fossa infarction. Headache can be a feature of AIS (especially with arterial dissection), sinovenous thrombosis, CNS infection, or hemiplegic migraine. It is important to recognize that hemiplegic migraine is a diagnosis of exclusion, especially in the index episode. 'Thunderclap' headache is classically a feature of subarachnoid haemorrhage; it is also a feature of reversible cerebral vasoconstriction syndrome, which is associated with stroke (ischaemic and haemorrhagic) in 10% of cases. Reversible cerebral vasoconstriction syndrome is commonly associated with ingestion of vasoactive drugs such as nasal decongestants. Seizures are a common feature of posterior reversible encephalopathy syndrome, also called reversible posterior leukoencephalopathy syndrome, CNS infection, and cerebral sinovenous thrombosis.

Important points in the clinical assessment include cutaneous examination (e.g. for features of neurofibromatosis type 1 or hereditary haemorrhagic telangiectasia), a comprehensive cardiovascular examination, including careful evaluation of peripheral pulses and blood pressure, and systemic features of sepsis, endocarditic, or an underlying genetic or syndromic disorder. A drug history is relevant to many of the differential diagnoses under consideration.

Children presenting with hemiparesis on the background of pre-existing conditions with high risk of AIS, for example sickle-cell disease, congenital heart disease (especially after surgery), or pre-existing arteriopathy, are likely to have AIS but not invariably so. For example, posterior reversible encephalopathy as well as intracranial haemorrhage can be seen in sickle-cell disease. Intracranial haemorrhage needs to be excluded in patients with cardiac disease who are on anticoagulation treatment. Children with moyamoya disease can have prolonged transient ischaemic attack without a completed stroke following triggers such as hyperventilation or dehydration. Hypoglycaemia in children with insulin-dependent diabetes mellitus can manifest with neurological symptoms including hemiplegia. Urgent neuroimaging is critical in these settings to establish the diagnosis and formulate management plans.

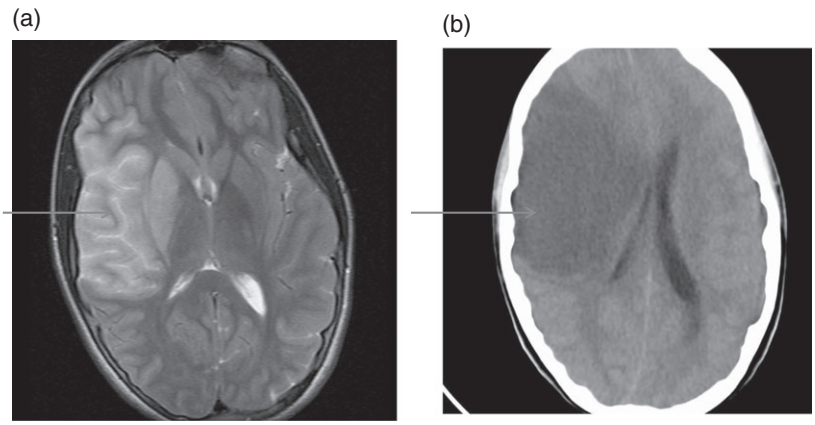

Figure 1: Malignant middle cerebral artery (MCA) territory stroke. Eleven-year-old female presented with acute dense left hemiplegia. Admission magnetic resonance image (a) showed right MCA territory infarction affecting large part of right MCA territory. Magnetic resonance angiogram showed evidence of left internal carotid artery dissection. She was stable apart from a dense hemiplegia on admission. She deteriorated acutely after 48 hours, rapidly progressing to coma. Axial computed tomogram (b) showed large area of hypo-density with slit-like ventricle and midline shift (malignant MCA stroke). The case emphasizes the need for careful monitoring for late deterioration in this group of patients.

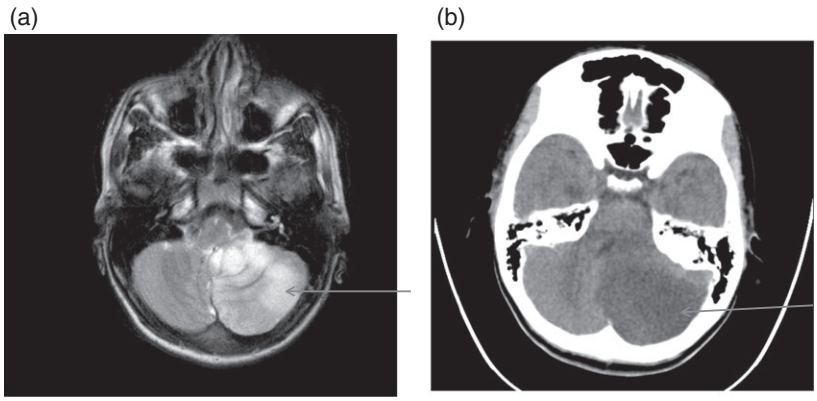

Figure 2: Massive cerebellar infarction. Ten-year-old male presented with acute onset of headache and dizziness. He was ataxic and had mild left sided weakness. Imaging on admission showed a large left cerebellar infarct. He became drowsy and developed bradycardia over the next 24 hours. Computed tomography scan 24 hours later showed swelling of left cerebellar hemisphere and brainstem distortion due to the large left cerebellar infarct. He went on have emergency posterior fossa decompression. This case highlights the need for identifying and treating raised intracranial pressure in patients with large cerebellar infarcts.

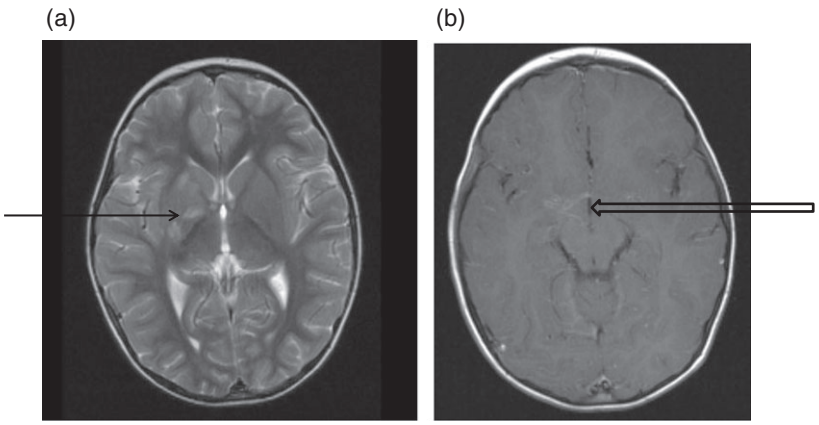

Figure 3: Stroke mimic/infection/tuberculous meningitis. Four-year-old male presented with acute left hemiplegia and was initially diagnosed to have stroke. He had history of fever and neck stiffness. Magnetic resonance imaging showed high-signal T2 changes in the right basal ganglia region (a) and basal meningeal enhancement after contrast (b). Cerebrospinal fluid showed evidence of inflammation, and the γ-interferon test for tuberculosis was positive. This case highlights the importance of identifying and treating infection in children with suspected stroke.

It is important to identify venous infarction as a cause of hemiplegia as this will have important management implications. Venous infarction is often haemorrhagic and may be mistaken for primary intraparenchymal haemorrhage. The distribution of injury on imaging may be suggestive. A plain CT scan that is almost universally performed as the first investigation requires careful examination as this will often provide diagnostic information.

Figures 1–7 provide case vignettes illustrating the range of conditions that may present with hemiplegia.

Management

The initial assessment should focus on resuscitation and establishment of homeostasis. Early recognition and management of coma can be lifesaving. It is important to be aware that patients with large MCA territory AIS are at risk of delayed coma in the 24 to 96 hours after onset of the ictus. A deteriorating level of consciousness is a medical emergency, and only close and careful observation will ensure this is recognized promptly. Important practical considerations are whether the child is likely to need transfer to an intensive care unit, as it is clearly optimal to undertake transfer early in a planned and safe way rather than as an emergency. A further practical consideration is whether the child is likely to need urgent neurosurgical intervention (e.g. haematoma evacuation, external ventricular drain, decompressive craniectomy).[8] It would be important to consider infection and cover with antimicrobials when

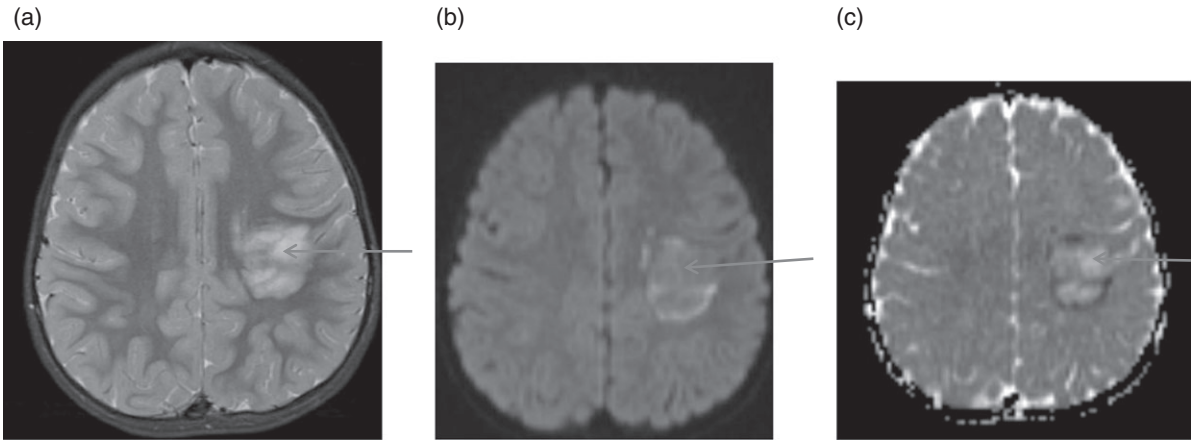

Figure 4: Stroke mimic/demyelination. Two-year-old female presented with acute onset of right-sided weakness. Magnetic resonance imaging (a) showed a high-signal T2 lesion in the left hemisphere not typically in vascular distribution. Diffusion-weighted imaging (b) showed a mixture of free and restricted diffusion. Apparent diffusion coefficient map (c) did not show typical restricted diffusion expected in ischaemic stroke. Follow-up imaging showed complete resolution of the lesion.

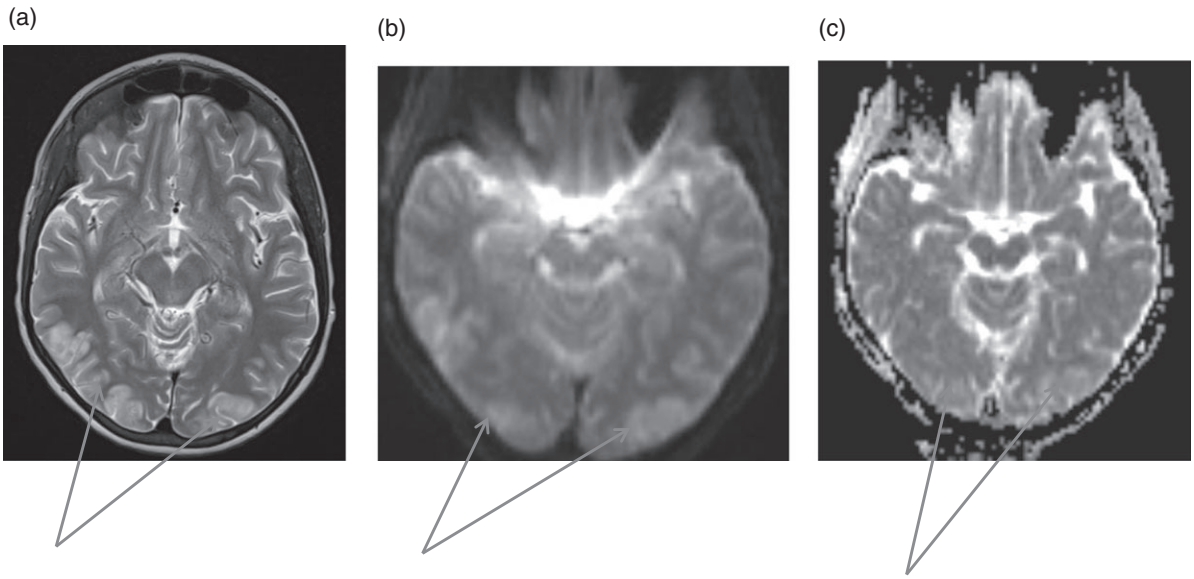

Figure 5: Stroke mimic/posterior reversible leucoencephalopathy syndrome. Fifteen-year-old male with sickle-cell disease and nephrotic syndrome on prednisolone and cyclosporine A presented acutely with left-sided eye deviation, left focal seizures, and left-sided weakness. His blood pressure was 180/110 and magnetic resonance imaging showed increased T2 signal bilaterally affecting parietal and occipital lobes asymmetrically. There was no evidence of restricted diffusion on diffusion-weighted imaging (b) and apparent diffusion coefficient maps (c). He made a full recovery. The imaging characteristics were critical for establishing the right diagnosis.

there is diagnostic uncertainty. There is no evidence that steroids have any benefit in the management of large MCA strokes, whereas high-dose steroids such as intravenous methylprednisolone clearly benefit in patients with inflammatory demyelination. Anticoagulation with unfractionated or low-molecular-mass heparin needs to be considered early in patients with cerebral sinovenous thrombosis, especially in those with reduced levels of consciousness.

Further investigations

Although the history and examination enables formulation of a differential diagnosis, a definitive diagnosis and the subsequent investigations will be based on imaging findings. It is important to appreciate that it may be difficult to differentiate definitively between conditions such as CNS infection and inflammatory demyelination on imaging, and it is often safest to cover the possibility of infection pending additional results, for example lumbar

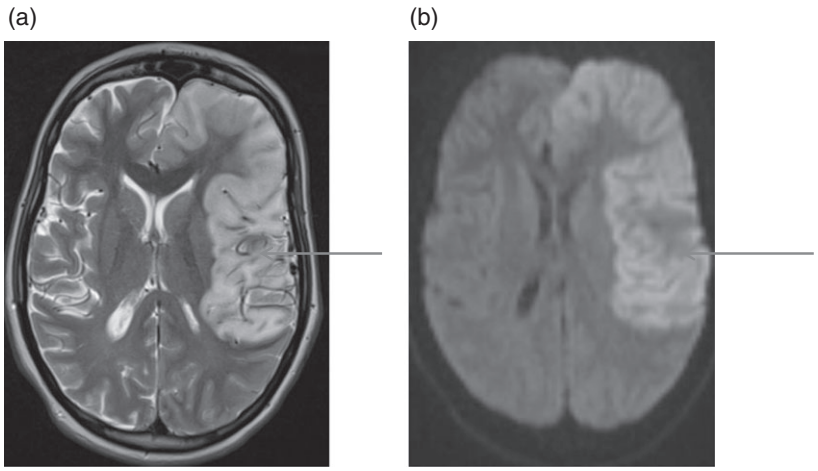

Figure 6: Stroke mimic/mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Fourteen-year-old female with documented myoclonic epilepsy with ragged red fibres (MERRF) mutation presented with focal seizures and weakness of the right side. Axial T2- (a) and diffusion-weighted imaging (b) showed high T2 signal lesions with restricted diffusion. Although the lesions are within left middle and anterior cerebral artery territory, there is selective cortical involvement with sparing of white matter and basal ganglia. A vascular occlusion involving such large segments of middle cerebral artery territory would be expected to involve these structures as well. This selective cortical involvement is highly suggestive of metabolic stroke.

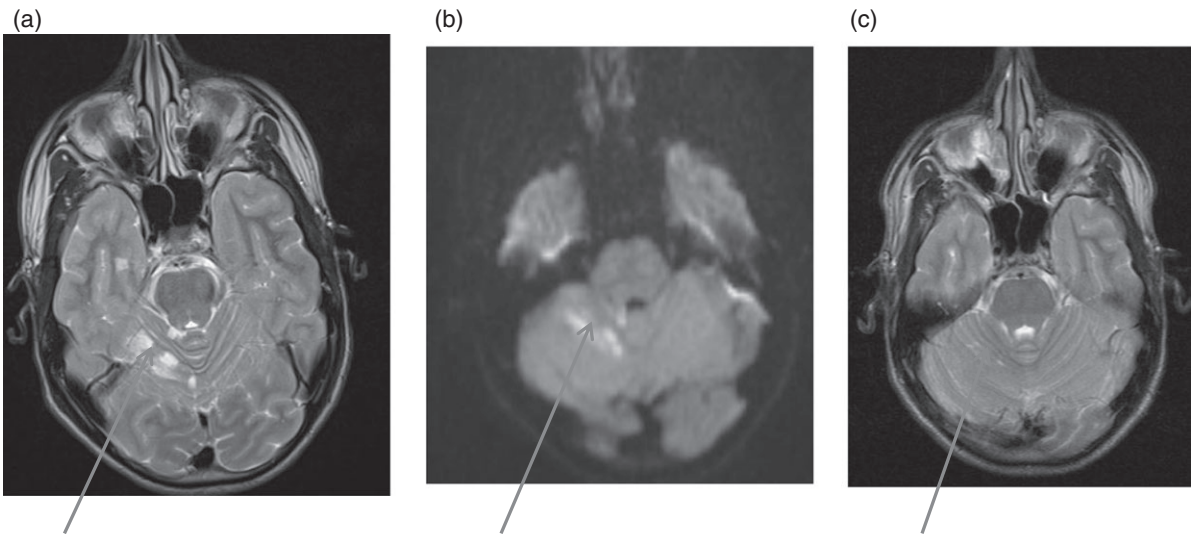

Figure 7: Stroke mimic/probable inflammation. Fifteen-year-old male presented with headache and dysarthria. A diagnosis of right cerebellar infarction was made based on the imaging findings of T2 hyperintense lesions (a) with restricted diffusion (b). No evidence of vasculopathy or a cardiac source for embolism was found despite extensive investigations including formal digital subtraction angiography and transoesophageal echocardiography. Follow-up imaging (c) showed almost complete resolution of initial changes with minimal residual volume loss. This sequence of events would be in keeping with inflammatory changes.

puncture. Sometimes the final diagnosis only becomes apparent with the evolution of the clinical or imaging picture over time. Figure 8 summarizes further investigations that may be considered according to the likely diagnosis. Testing for prothombotic risk factors is important, particularly where cerebral sinovenous thrombosis is suspected. Current guidelines suggest estimation of protein C, protein S, functional antithrombin, activated protein C resistance, lupus inhibitor, anticardiolipin antibodies, prothombotic mutations (factor V Leiden G1691A, MTHFR C677T, prothrombin G20210A), and measurement of plasma homocysteine.[9] Prothombotic risk factors (except homocystinuria) are rarely the primary cause but contribute to the overall risk in the pres-

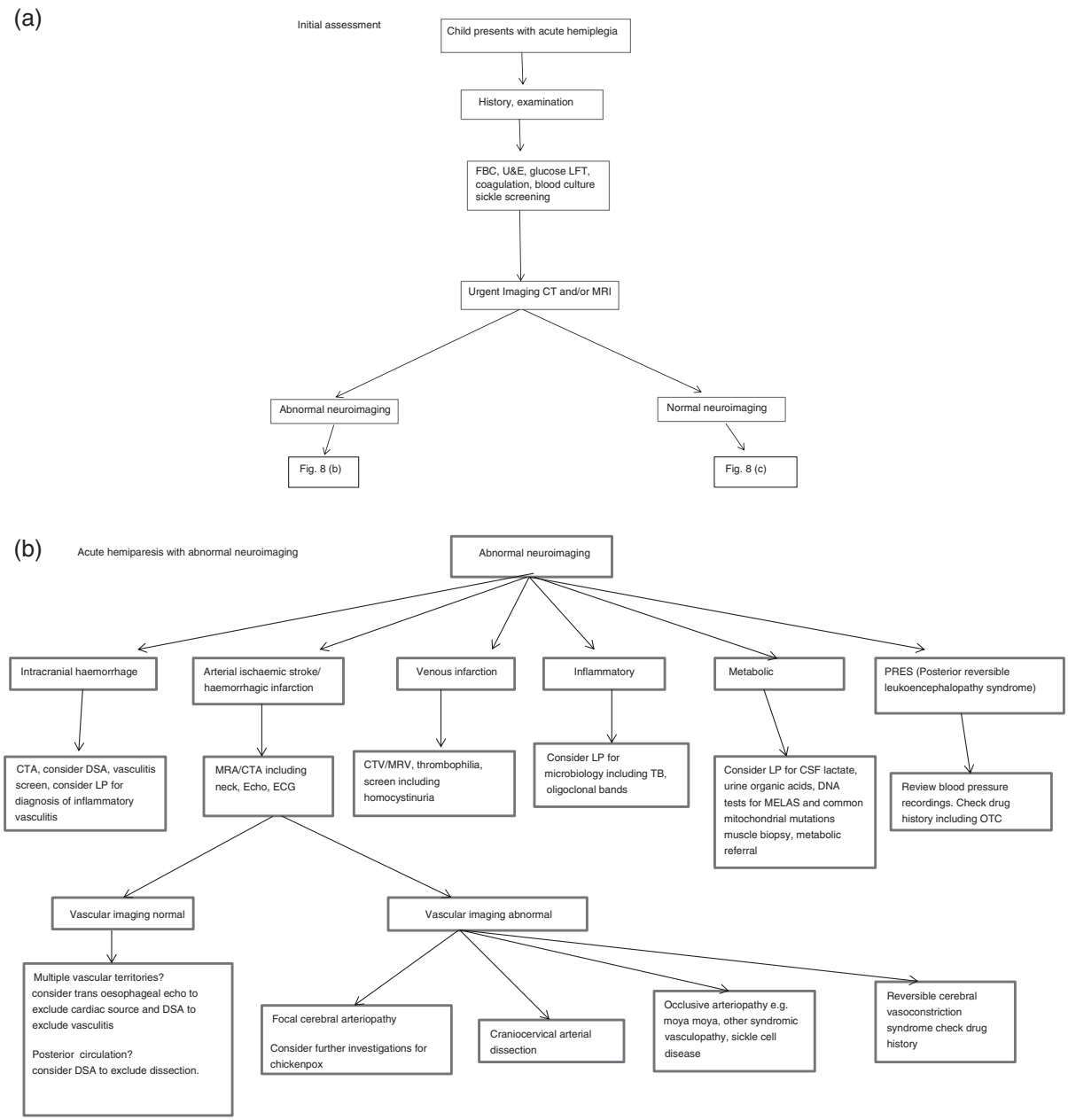

Figure 8: Flow charts showing initial investigations and management of a child presenting with acute hemiparesis with normal and abnormal imaging findings. (a) Initial assessment, (b) acute hemiparesis with abnormal neuroimaging, (c) acute hemiparesis with normal neuroimaging. CSF, cerebrospinal fluid; CT, computed tomography; CTA, Computerised tomographic angiography; CTV, Computerised tomographic venography; DSA, digital subtraction angiography; ECG, electrocardiogram; Echo, echocardiogram; FBC, Full blood count; LFT, liver function tests; LP, lumbar puncture; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MRA, Magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; OTC, Over the counter; TB, Tuberculosis; TIA, Transient ischaemic attack; U&E, urea, Creatinine and electrolytes, glucose.

ence of primary risk factors, for example vasculopathy and are more likely to cause venous than arterial thrombosis.

Metabolic stroke is usually the result of metabolic defects that cause energy failure, the most common being respiratory chain disorders. Serum and cerebrospinal fluid lactate is usually but not universally increased. Plasma amino acids and urine organic acids may show suggestive abnormalities such as high alanine, serine, and threonine. Genetic testing for common mitochondrial mutations such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) or myoclonic epilepsy with ragged red fibres (MERRF) is generally available; however, muscle biopsy with estimation of respiratory-chain enzyme activities is often required to establish the diagnosis of respiratory chain disorder.

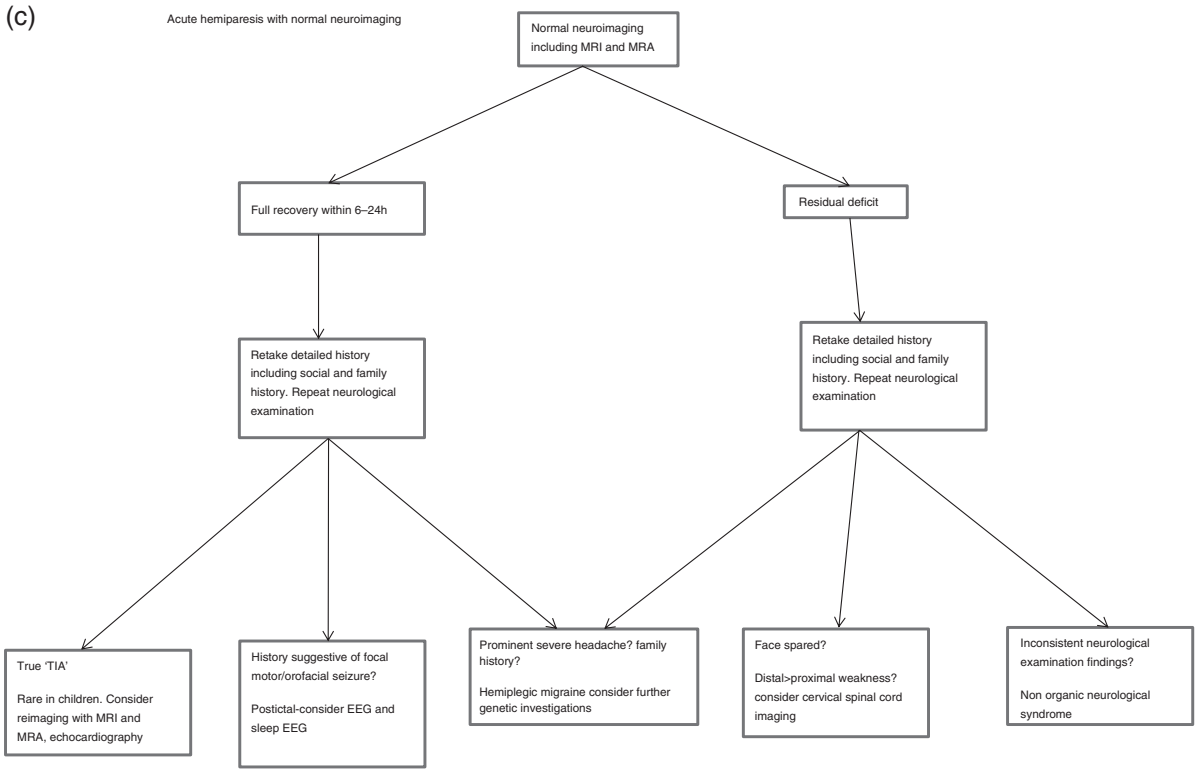

Figure 8: (Continued).

Secondary deterioration

Children presenting with hemiplegia should be observed on a high dependency unit with careful neurological observations. Secondary deterioration, which could be in the form of reduced level of consciousness, new neurological deficit, seizures, or recurrent 'transient ischaemic attacks', should prompt urgent clinical and radiological re-evaluation by MRI and MR angiography, or CT and CT angiography if MRI is not available. The aim is to identify development of cerebral oedema and herniation syndromes, extension of infarction, and secondary haemorrhagic transformation urgently. The same questions about neurosurgical intervention and intensive care transfer are applicable and more pressing after secondary deterioration. In the less acute situation of recurrent transient ischaemic attacks that resolve, vascular imaging is critical in identifying progressive vascular disease or recurrent embolic events to guide escalation of treatment, for example immunomodulation.

Hemiplegia with normal imaging

A similar approach starting with history, clinical examination, and relevant investigations is outlined for children presenting with hemiplegia who have normal findings on imaging, including dedicated vascular imaging. Seizures and migraine are the commonest reasons for children to present with a 'brain attack'.[1] Recurrent stereotyped attacks without imaging changes are likely to be epileptic or migrainous postictal Todd's paresis, particularly if the seizure has been unwitnessed; for example, a nocturnal seizure and can pose a diagnostic challenge. Interictal electroencephalography may be helpful but is rarely diagnostic. A period of observation may be required before the diagnosis can be confirmed.

Headache and hemisensory symptoms are characteristic of migraine with aura. Motor weakness is rare but can occur in the context of sporadic or familial hemiplegic migraine. Onset in hemiplegic migraine is slower than an ischaemic event, which is typically hyper-acute rather than developing over minutes. Headache as a presenting symptom is uncommon in AIS except in craniocervical arterial dissection and reversible cerebral vasoconstriction syndrome. Even in these conditions, the headache is a new-onset acute severe headache and may have a distinctive character and location. Mutations (in the genes *CACNA1A*, *ATP1A2*, and *SCNA1A*) have been characterized in patients with familial hemiplegic migraine and can be tested for if compatible family history is obtained.

Alternating hemiplegia of childhood is a disorder presenting with episodic hemiplegia affecting alternate sides of the body and variable dystonia, epilepsy, and developmental delay caused by mutation in *ATP1A3*. The clinical presentation is characteristic and the diagnosis can be confirmed by mutation analysis.

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OPEN

Differentiating Childhood Stroke From Mimics in the Emergency Department

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Background and Purpose—Clinical identification of stroke in the pediatric emergency department is critical for improving access to hyperacute therapies. We identified key clinical features associated with childhood stroke or transient ischemic attack compared with mimics.

Methods—Two hundred and eighty consecutive children presenting to the emergency department with mimics, prospectively recruited over 18 months from 2009 to 2010, were compared with 102 children with stroke or transient ischemic attack, prospectively/retrospectively recruited from 2003 to 2010.

Results—Cerebrovascular diagnoses included arterial ischemic stroke (55), hemorrhagic stroke (37), and transient ischemic attack (10). Mimic diagnoses included migraine (84), seizures (46), Bell's palsy (29), and conversion disorders (18). Being well in the week before presentation (odds ratio [OR] 5.76, 95% confidence interval [CI] 2.25–14.79), face weakness (OR 2.94, 95% CI 1.19–7.28), arm weakness (OR 8.66, 95% CI, 2.50–30.02), and inability to walk (OR 3.38, 95% CI 1.54–7.42) were independently associated with increased odds of stroke diagnosis. Other symptoms were independently associated with decreased odds of stroke diagnosis (OR 0.28, 95% CI 0.10–0.77). Associations were not observed between seizures or loss of consciousness. Factors associated with stroke differed by arterial and hemorrhagic subtypes.

Conclusions—Being well in the week before presentation, inability to walk, face and arm weakness are associated with increased odds of stroke. The lack of positive or negative association between stroke and seizures or loss of consciousness is an important difference to adults. Pediatric stroke pathways and bedside tools need to factor in differences between children and adults and between stroke subtypes. **(*Stroke*. 2016;47:2476-2481. DOI: 10.1161/STROKEAHA.116.014179.)**

Key Words: brain attack ■ intracranial hemorrhage ■ seizure ■ stroke ■ transient ischemic attack

Long delays in diagnosis of childhood stroke limit access to hyperacute interventions that improve outcome in adults.[1–3] However, a recent US study has demonstrated the benefits of developing a pediatric Code Stroke protocol for shortening time to diagnosis and increasing rates of thrombolysis and mechanical thrombectomy.[4] Clinical differentiation of stroke from mimics by pediatric triage nurses and emergency physicians influences the decision-making process, in particular the rapidity of medical assessment, the need for emergent neuroimaging to confirm diagnosis, the initiation of antithrombotic treatment in ischemic stroke, and neurosurgical intervention in hemorrhagic stroke (HS). Correct clinical identification of stroke avoids unnecessary diagnostic or therapeutic procedures and allows early implementation of measures to maintain physiological homeostasis.

Three studies on adults have described clinical features that differentiate stroke from mimics. Focal neurological symptoms and signs were associated with increased odds of stroke, whereas loss of consciousness, altered mental state, dizziness, confusion, and seizures were associated with increased odds of mimic.[5–7] It may not be appropriate to extrapolate data from adults because of different presenting features, such as frequent occurrence of seizures,[8] and the different spectrum of disorders that mimic childhood stroke.[9]

Several prospective case series have reported the presenting features of childhood stroke,[10–13] but most have focused on arterial ischemic stroke (AIS), and none have explored differences between stroke and other conditions that mimic stroke. Therefore, our primary aim was to identify key clinical features that were positively and negatively associated with

Received May 24, 2016; final revision received July 14, 2016; accepted July 19, 2016.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014179/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.116.014179**

pediatric stroke, compared with mimics, in children presenting with brain attack symptoms. We hypothesized that the clinical features associated with stroke are similar to those of adults, with the exception of seizures.

Materials and Methods

The study population comprised 2 groups of children presenting to the Royal Children's Hospital Melbourne Emergency Department (ED). The first consisted of a consecutive group of children with stroke mimics, presenting between July 2009 and December 2010. The second consisted of a mixed prospective and retrospective group of children with radiologically confirmed AIS, transient ischemic attack (TIA), and HS, presenting between January 2003 and December 2010 (Figure).

Inclusion criteria, exclusion criteria, study procedure, and diagnostic definitions for the prospective cohort of patients with brain attack symptoms[9] (defined as acute onset focal brain dysfunction) and retrospective stroke patients[14] have been previously described. Children with stroke mimics (including those presenting with a first seizure) had persistent neurological symptoms (headache, subjective visual or sensory disturbance) on presentation to the ED or abnormal neurological signs on examination. TIA required a known history of cerebrovascular disease, a clinical history typical of a vascular brain event with full resolution of symptoms within 24 hours, and absence of acute infarction on magnetic resonance imaging.[15] There was no time limit on duration of symptoms after arrival at ED in the mimic group. The following stroke subgroups were excluded: perinatal stroke, cerebral sinovenous thrombosis, admission directly to the ward, and incomplete medical records. Children with subdural or extradural hemorrhage were also excluded.

Variables collected included demographics and neurological symptoms and signs. Clinical variables were selected on the basis of being common presenting features of stroke or being discriminatory between stroke and mimics in the published studies on adults.[5–7] Key demographic factors and neurological symptoms variables were compared between the prospective and retrospective cerebrovascular patients to account for threats to study validity by ensuring both statistical and substantive similarity of the 2 cohorts.

Analyses were performed for the following outcomes: (1) combined stroke (AIS and HS) or TIA versus mimics, (2) AIS subtype versus mimics, and (3) HS subtype versus mimics. For simplicity, stroke and TIA are referred to as stroke in the combined analysis section of the results. Categorical variables are descriptively presented as counts and percentages. Continuous variables are presented as mean and standard deviation for normally distributed data or median and interquartile range for non-normally distributed data.

Logistic regression modeling was used to investigate associations between independent variables and stroke diagnosis. Selection of variables for regression analyses was determined by a combination of computational analyses and clinical importance. Variables were initially individually examined by univariate logistic regression for associations with the outcome of interest. Odds ratios (ORs) and corresponding 95% confidence intervals (95%CIs) were estimated. Variables with P values of <0.05 were considered for entry into the multivariable model to determine the adjusted association with the

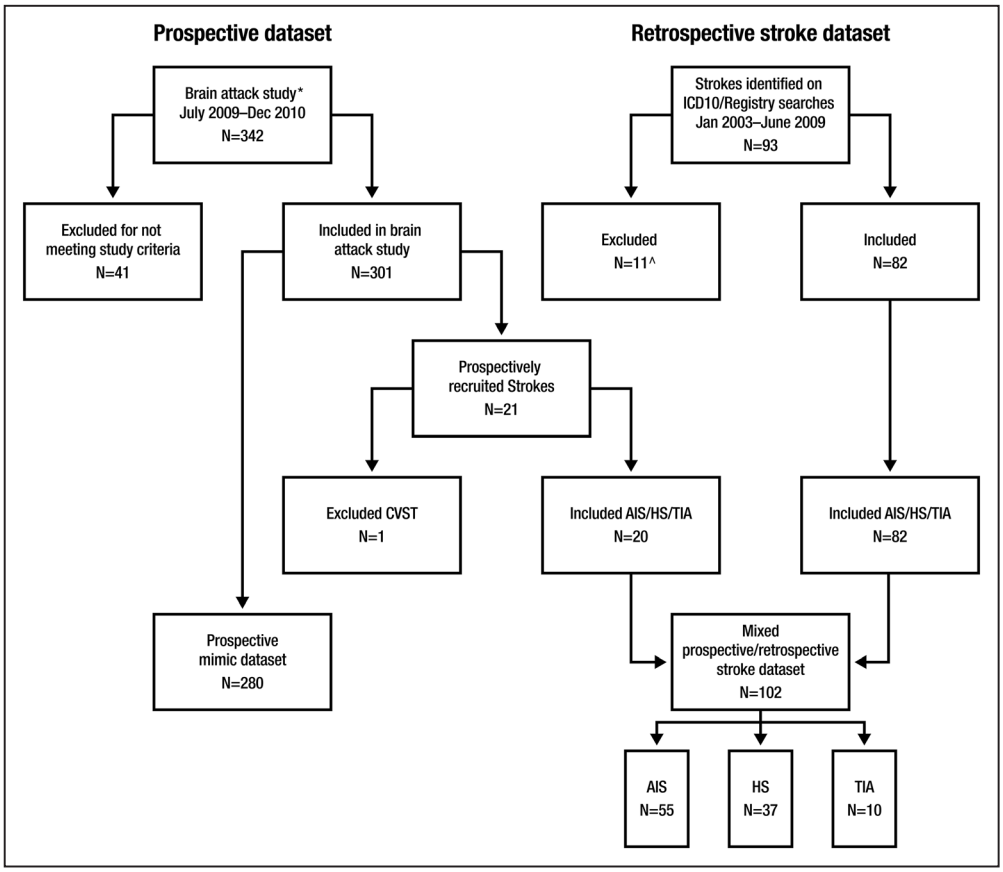

Figure. Case ascertainment for stroke and mimic data sets. Causes of ischemic strokes/TIAs: focal cerebral arteriopathy 19 (29%), bilateral cerebral arteriopathy 14 (22%), arterial dissection 5 (8%), cardioembolic 3 (5%), other determined etiology 5 (7%), multifactorial etiologies 2 (3%), and undetermined 17 (26%). Causes of hemorrhagic strokes: arteriovenous malformation 20 (54%), cavernous malformation 3 (8%), arterial dissection 3 (5%), subarachnoid, cause undetermined 2 (5%) and because of aneurysm 1 (3%), tumor-related bleed 1 (3%), focal cerebral arteriopathy with ruptured collaterals 1 (3%), and undetermined 7 (19%). AIS indicates arterial ischemic stroke; CVST, cerebral sinus venous thrombosis; HS, hemorrhagic stroke; N, number; and TIA, transient ischemic attack. *Brain attack study.[7] ^Reasons for exclusion: CVST (1), direct admission to inpatient unit (5), and incomplete medical records (5).

outcomes of interest for combined AIS and HS diagnoses versus mimics. Multivariable modeling was not performed for AIS or HS stroke subtypes versus mimics because of the relatively small sample sizes. Unadjusted (produced by univariate models) and adjusted (produced by multivariable models) ORs are presented with corresponding 95% CIs and *P* values. CIs not including 1 are indicative of statistical significance, with the *P* value set at 0.05. Standard analyses of model fit and excessive collinearity diagnostics were performed, including (1) computation of pairwise correlation coefficients to assess interdependence of causal variables and (2) measures of multicollinearity, including variance inflation factors and condition number, to determine whether there was a linear association between ≥2 predictor variables. Statistical analyses were performed using STATA 13 (StataCorp, TX). This study was reviewed and approved by the Royal Children's Hospital Human Research Ethics Committee (HREC30194A).

Results

The study population comprised 280 children with mimics, prospectively recruited from July 2009 until December 2010 and 102 children with stroke, prospectively and retrospectively identified from January 2003 until December 2010. No statistically significant difference between the 2 stroke cohorts was observed, with sex (*P*=0.09) being the only variable approaching significance (Table I in the online-only Data Supplement). AIS was the most common stroke subtype in 55 children, followed by HS subtype in 37 and TIAs in 10 children. Twelve children with stroke were excluded: 2 had cerebral sinovenous thrombosis, 5 were direct admissions to the inpatient unit, and 5 had incomplete medical records (Figure). In children with neurological symptoms or signs on arrival at the ED, the most common mimic diagnoses included migraine in 84 children, febrile or afebrile seizures in 46, Bell's palsy in 29, conversions disorders in 18, and syncope in 14 children. A full list of mimic diagnoses has been previously published.[9]

Fourteen factors associated with increased odds, and 2 factors with decreased odds of stroke diagnosis (Tables 1 and 2), were included in the multivariable logistic regression model. Four factors emerged as being significantly associated with stroke diagnosis in the adjusted analysis. Being well in the week before presentation (OR 5.76, 95% CI 2.25–14.79) was associated with increased odds of stroke. Arm weakness (OR 8.66, 95% CI 2.50–30.02) was the neurological sign most strongly associated with stroke, but the association was poorly estimated as indicated by the wide 95% confidence intervals. Face weakness (OR 2.94, 95% CI 1.19–7.28) and inability to walk (OR 3.38, 95% CI 1.54–7.42) were also associated with increased odds of stroke. In contrast, the presence of other symptoms (OR 0.28, 95% CI 0.10–0.77) was negatively associated with stroke diagnosis (Table 3).

Factors significantly associated with AIS diagnosis on univariate analyses included symptoms of focal weakness and

Table 1. Univariate Analyses of Demographic Factors, Time Course, and Symptoms Associated With Stroke and Mimic Diagnoses

	Total, n (%)	Stroke (n=102), n (%)	Mimic (n=280), n (%)	OR	95% LCI	95% UCI	*P* Value
Demographics							
Male sex	179/382 (47%)	48/102 (47%)	131/280 (47%)	1.01	0.64	1.59	0.96
Past medical history	149/382 (39%)	44/102 (43%)	105/280 (38%)	1.26	0.80	2.00	0.32
Sudden symptom onset	285/378 (75%)	87/102 (85%)	198/276 (71%)	2.28	1.24	4.19	0.008
Woke with symptoms	70/373 (19%)	20/100 (20%)	50/273 (18%)	1.11	0.63	1.99	0.71
Well in the week prior	292/381 (77%)	90/102 (88%)	202/279 (72%)	2.86	1.48	5.15	0.002
Mean age, y	9.2 (SD 5.1, 0.1–17.7)	8.3 (5.0, 0.1–17.7)	9.6 (5.1, 0.1–17.6)	0.95	0.91	0.99	0.01
Symptoms							
Headache	219/380 (58%)	58/100 (58%)	161/280 (58%)	0.93	0.64	1.62	0.93
Vomiting	135/380 (36%)	32/100 (32%)	103/280 (37%)	0.81	0.50	1.31	0.39
Focal weakness	151/378 (40%)	58/102 (57%)	93/276 (34%)	2.59	1.63	4.12	<0.0001
Focal numbness	85/376 (23%)	17/102 (17%)	68/274 (25%)	0.61	0.34	1.09	0.01
Visual disturbance	83/376 (22%)	17/100 (17%)	66/276 (24%)	0.65	0.36	1.17	0.16
Seizure	78/382 (20%)	21/102 (21%)	57/280 (20%)	1.01	0.58	1.77	0.97
Altered mental status	84/380 (22%)	31/102 (30%)	53/278 (19%)	1.85	1.10	3.11	0.02
Dizziness	73/375 (19%)	15/99 (15%)	58/276 (21%)	0.67	0.36	1.25	0.21
Speech disturbance	80/379 (21%)	37/102 (36%)	43/277 (16%)	3.10	1.84	5.20	<0.0001
Ataxia	59/377 (16%)	18/101 (18%)	41/276 (15%)	1.24	0.68	2.28	0.48
Loss of consciousness	45/380 (12%)	10/102 (10%)	35/278 (11%)	0.75	0.36	1.59	0.46
Vertigo	12/371 (3%)	2/97 (2%)	10/274 (4%)	0.55	0.12	2.58	0.45
Other symptoms	64/381 (17%)	5/102 (5%)	59/279 (21%)	0.19	0.07	0.49	0.001

Other symptoms, in order of frequency, included pain or stiffness, lethargy, gait disturbance, fever, involuntary movements, nausea, and irritability. Well in the week prior was defined as no fever or prodromal symptoms before the day of presentation. LCI indicates lower 95% confidence interval; n, number; OR, unadjusted odds ratios; and UCI, upper 95% confidence interval.

Table 2. Univariate Analyses of Signs Associated With Stroke and Mimic Diagnoses

Signs	Total, n (%)	Stroke (n=102), n (%)	Mimic (n=280), n (%)	OR	95% LCI	95% UCI	*P* Value
Face weakness	85/378 (22%)	44/99 (44%)	41/279 (15%)	4.64	2.77	7.79	<0.0001
Arm weakness	74/378 (20%)	47/99 (47%)	27/279 (10%)	8.44	4.82	14.76	<0.0001
Leg weakness	72/378 (19%)	37/99 (37%)	35/279 (13%)	4.16	2.43	7.14	<0.0001
Dysarthria	33/374 (9%)	22/96 (23%)	11/278 (4%)	7.22	3.34	15.56	<0.0001
Dysphasia	17/374 (5%)	10/96 (10%)	7/278 (3%)	4.50	1.66	12.18	0.003
Ataxia	37/378 (10%)	8/99 (8%)	29/279 (10%)	0.76	0.33	1.72	0.51
Inability to walk	59/373 (16%)	30/98 (31%)	29/275 (11%)	3.74	2.10	6.67	<0.001
Abnormal eye movement	30/376 (8%)	6/99 (6%)	24/277 (9%)	0.68	0.27	1.71	0.41
Visual defects	30/366 (8%)	9/89 (10%)	21/277 (8%)	1.37	0.60	3.11	0.45
Facial sensory disturbance	18/372 (5%)	6/99 (6%)	12/273 (4%)	1.40	0.51	3.84	0.51
Arm sensory disturbance	36/374 (10%)	12/99 (12%)	24/275 (9%)	1.44	0.69	3.00	0.33
Leg sensory disturbance	29/373 (8%)	9/99 (9%)	20/274 (7%)	1.27	0.56	2.89	0.57
GCS abnormal (<15)	110/382 (29%)	40/102 (39%)	70/280 (25%)	1.94	1.20	3.13	0.007
GCS<9	18/382 (5%)	9/102 (9%)	9/280 (3%)	2.91	1.12	7.56	0.03
Pupillary abnormalities	11/358 (3%)	5/98 (5%)	6/260 (2%)	2.27	0.68	7.63	0.18
Sensory neglect	5/377 (1%)	3/99 (3%)	2/278 (0.7%)	4.31	0.71	26.20	0.11
Other signs	32/381 (8%)	9/102 (9%)	23/279 (8%)	1.078	0.48	2.41	0.86
No focal signs	122/379 (33%)	20/100 (20%)	102/279 (37%)	0.43	0.25	0.75	0.003

Other signs included abnormal deep tendon reflexes, confusion, altered consciousness or slowed mentation, involuntary movements, papilloedema. GCS indicates Glasgow coma score; LCI, lower 95% confidence interval; n, number; OR, unadjusted odds ratios; and UCI, upper 95% confidence interval.

speech disturbance and signs of face, arm, or leg weakness, dysarthria, dysphasia, and inability to walk. No child with AIS presented with loss of consciousness or coma (GCS [Glasgow coma score] of <9). In contrast, factors significantly associated with mimic diagnosis on univariate analyses included presence of other symptoms and absence of neurological signs on examination (Table II in the online-only Data Supplement). Factors associated with HS diagnosis on univariate analyses included sudden onset of symptoms, vomiting, altered mental state, inability to walk, abnormal GCS, and coma. All children with HS were well in the week before presentation, whereas none presented with vertigo (Table III in the online-only Data Supplement).

Discussion

Significant delays to diagnosis of pediatric stroke, well beyond those reported in adults,[1–3,16,17] mean that children are unlikely to access time-critical treatments that have been shown to improve outcome in adults.[18] Prehospital factors contribute more to delayed diagnosis in adults,[19] but recent studies suggest that in-hospital factors are more important contributors to delayed diagnosis in children.[1–3] It is likely that poor recognition of stroke among pediatric physicians[2] or limited knowledge of neurologically relevant brain attack symptoms are contributing factors.

Triage nurses and emergency physicians play a critical role in the diagnosis of stroke because they are the first point of contact in ≈50% of adults with stroke.[19] Clinical differentiation of stroke from mimics is a crucial first step that influences decisions about type and urgency of investigations and selection of the most appropriate treatments. Assessment of patients with brain attack symptoms is challenging for non-neurologists, with accuracy of emergency physician diagnosis, before completion of investigations, ranging from 51% to 81%.[5–7,20–22] The low a priori probability of childhood stroke makes diagnosis even more challenging for pediatric ED staff.[9]

The key findings of this study are as follows: (1) there are differences in the clinical presenting features of childhood stroke and mimics and (2) factors that discriminate stroke from mimics differ by stroke subtype. Few studies have investigated the clinical features that distinguish stroke from mimics in adults. Exact time of onset,[7] abnormal vascular findings (such as hypertension, atrial fibrillation, and valvular heart disease),[7] and sudden-onset symptoms of face, arm, or leg weakness and speech[6] are associated with increased odds of stroke. Lateralized signs,[7] face, arm, or leg weakness, eye movement abnormalities, visuospatial neglect, hemiparetic or ataxic gait disturbance, sensory disturbance of the arm or leg,[6] and abnormal visual fields[6] are also associated with increased odds of stroke. In contrast, altered consciousness,[5,6] cognitive impairment,[7] dizziness, confusion, loss of consciousness, and seizures[5,6] are associated with increased odds of mimic diagnosis.

We found that 16 variables were associated with combined stroke or mimic on univariate analysis but only 5 remained significant on multivariable analysis. Being well in the week before arrival, inability to walk, and examination findings of focal face or arm weakness were associated with stroke diagnosis, consistent with those in the literature on adults. Visual

Table 3. Factors Independently Associated With Stroke and Mimic Diagnoses on Multivariable Regression Analyses

	OR	95% LCI	95% UCI	*P* Value
Demographic factors				
Well in the week prior	5.76	2.25	14.75	<0.0001
Mean age	0.95	0.89	1.01	0.07
Symptoms				
Sudden symptom onset	0.95	0.45	2.02	0.90
Focal weakness	0.57	0.23	1.45	0.24
Altered mental status	1.39	0.65	2.97	0.39
Speech disturbance	1.63	0.73	3.64	0.23
Other symptoms	0.28	0.10	0.77	0.01
Signs				
Face weakness	2.94	1.19	7.28	0.02
Leg weakness	0.44	0.13	1.57	0.21
Arm weakness*	8.66	2.50	30.02	0.001
Dysarthria	2.41	0.80	7.27	0.12
Dysphasia	1.33	0.31	5.75	0.70
Inability to walk	3.38	1.54	7.42	0.002
Abnormal GCS (<15)	1.03	0.48	2.25	0.92
GCS<9	1.79	0.35	9.30	0.49
No focal neurological signs	1.03	0.50	2.14	0.92

Other symptoms, in order of frequency, included pain or stiffness, lethargy, gait disturbance, fever, involuntary movements, nausea, and irritability. GCS indicates Glasgow coma score; LCI, lower 95% confidence interval; OR, adjusted odds ratios; and UCI, upper 95% confidence interval.

*The effect size for arm weakness needs to be interpreted with caution because of the wide 95% confidence intervals.

symptoms were not independently associated with stroke diagnosis, which may be explained by the different spectrum of disorders mimicking pediatric stroke. For example, visual disturbance is the most frequent type of aura in migraine, and migraine is the most common pediatric stroke mimic.[9] Sudden symptom onset was not independently associated with stroke. The lack of independent association between sudden symptom onset and stroke may be because of selection bias, because brain attack symptoms were defined as acute-onset focal brain dysfunction, or variable interpretation of the term's meaning among ED physicians.

Equally important were the findings that seizures and loss of consciousness were not independently associated with mimic diagnosis, and therefore, in contrast to adults, they are not useful discriminators for mimic diagnosis in children. The relatively frequent occurrence of seizures in childhood stroke is well described in the pediatric literature, with reported rates ranging from 11% to 52% for ischemic stroke[1,10–13,16,17,23] and from 37% to 41% for HS.[24,25] This contrasts with the low rates of seizures in adults, ranging from 0.5% to 11%.[6,7] Increased rates of seizures may reflect age-related cortical hyperexcitability or decreased inhibitory influences in the developing brain. Loss of consciousness, which has been noted in 18% to 41% of adults with mimics,[6,7] was also nondiscriminatory, occurring in low numbers of children in both groups. Differences in discriminatory factors between adults and children may also be related to the higher proportion of HS in children because presenting features differ by stroke subtype.[3,14] Thirty-six percent of children in our stroke cohort had HS, consistent with the 37% to 46% rates reported in population-based studies.[26–29]

Exploratory analyses suggest that factors that discriminate AIS from mimics are different from those that discriminate HS from mimics. In contrast to the analyses comparing all strokes to mimics, being well in the week before presentation was not associated with AIS, and face or arm weakness was not associated with HS. Understanding factors that discriminate ischemic or HS subtypes from mimics may assist the clinician in selecting the most appropriate neuroimaging modality to minimize delays and maximize diagnostic yield. However, magnetic resonance imaging has similar sensitivity to computed tomography for detection of hemorrhage, and recent studies have demonstrated feasibility of rapid magnetic resonance imaging screening protocols that avoid the need for anesthesia in young children.[4]

Our study has limitations. The wide 95% CIs in the multivariable analyses for some signs suggest that the effect sizes need to be interpreted with caution. We did not have data on exact time of onset, assess for presence of positive signs in other systems, or use standardized stroke severity scales. Therefore, we were unable to assess the value of other factors that have been shown to be discriminatory in adults.[7] The majority of our stroke group was identified retrospectively but we did not find significant differences in the presenting features when compared with the smaller prospective group. Relatively small numbers of children limited our ability to determine adjusted associations for the arterial ischemic and HS subgroups. Children with sinovenous thrombosis were excluded from the analyses and, therefore, they require further study. Accuracy of the clinical examination findings may have been influenced by level of experience of emergency physicians.[7] The discriminatory values of conventional stroke risk factors were not assessed because the causes of stroke differ from adults.[11,13] We did not assess the influence of discriminatory factors in AIS for anterior and posterior circulation. Finally, the study findings may not apply to children with in-hospital strokes, such as those with cardiac disease, because of differences in demographic factors, comorbid problems, such as infection, and presenting clinical features.

Development of ED brain attack protocols[4] and decision support tools to improve accuracy of stroke diagnosis by frontline emergency staff need to take into account differences between children and adults[30] and differences between ischemic stroke and HS subtypes. Further work is required to assess discriminatory factors for stroke compared with more common mimic diagnoses, such as migraine, and with less common but more serious diagnoses requiring rapid intervention, such as encephalitis, acute disseminated encephalomyelitis, and central nervous system tumors.

Acknowledgments

We acknowledge the assistance of Zhi Kai Chua and Michelle Lee with data entry.

Sources of Funding

Grant support received from the National Stroke Foundation, Melbourne, Australia; the Collier Charitable Fund, Melbourne, Australia; and the Murdoch Childrens Research Institute, Melbourne, Australia, to use research assistances to recruit subjects and enter data to the CRF.

Disclosures

None.

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Stroke and nonstroke brain attacks in children

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ABSTRACT

Objectives: To determine symptoms, signs, and etiology of brain attacks in children presenting to the emergency department (ED) as a first step for developing a pediatric brain attack pathway.

Methods: Prospective observational study of children aged 1 month to 18 years with brain attacks (defined as apparently abrupt-onset focal brain dysfunction) and ongoing symptoms or signs on arrival to the ED. Exclusion criteria included epilepsy, hydrocephalus, head trauma, and isolated headache. Etiology was determined after review of clinical data, neuroimaging, and other investigations. A random-effects meta-analysis of similar adult studies was compared with the current study.

Results: There were 287 children (46% male) with 301 presentations over 17 months. Thirty-five percent arrived by ambulance. Median symptom duration before arrival was 6 hours (interquartile range 2–28 hours). Median time from triage to medical assessment was 22 minutes (interquartile range 6–55 minutes). Common symptoms included headache (56%), vomiting (36%), focal weakness (35%), numbness (24%), visual disturbance (23%), seizures (21%), and altered consciousness (21%). Common signs included focal weakness (31%), numbness (13%), ataxia (10%), or speech disturbance (8%). Neuroimaging included CT imaging (30%), which was abnormal in 27%, and MRI (31%), which was abnormal in 62%. The most common diagnoses included migraine (28%), seizures (15%), Bell palsy (10%), stroke (7%), and conversion disorders (6%). Relative proportions of conditions in children significantly differed from adults for stroke, migraine, seizures, and conversion disorders.

Conclusions: Brain attack etiologies differ from adults, with stroke being the fourth most common diagnosis. These findings will inform development of ED clinical pathways for pediatric brain attacks. *Neurology*® 2014;82:1434–1440

GLOSSARY

CRF = case report form; **ED** = emergency department; **IQR** = interquartile range; **RCH** = Royal Children's Hospital.

Timely recognition of stroke is essential to ensure appropriate acute management. Four recent pediatric studies have confirmed significant diagnostic delays in the prehospital setting attributed to lack of community awareness and after arrival at hospital attributed to lack of recognition of stroke symptoms by attending physicians.[1–4] Diagnostic delays may relate to lack of consideration of stroke as a diagnosis in children presenting with acute focal neurologic symptoms or headache.

Stroke is now considered a medical emergency. Prehospital and emergency department (ED) management protocols have been developed to facilitate rapid transport to hospital, clinical assessment, and diagnostic neuroimaging. Thrombolysis is established as standard of care in adults presenting within a 4.5-hour time window.[5] Key to management in adults is a high probability of stroke in patients presenting with brain attack symptoms.[6–9] It is currently unclear whether adult brain attack protocols can be implemented in children because of limited understanding of the spectrum of symptoms and signs of brain attacks and lack of data about the

Supplemental data at Neurology.org

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probability of stroke. Only one previous study has described the conditions that mimic stroke in children referred to a pediatric stroke service while inpatients.[10]

Determining the causes of brain attacks in children presenting to the ED is a key first step for the development of a pediatric brain attack protocol. The primary aims of this study were to describe the presenting features, scope, and prevalence of conditions causing brain attack symptoms in children presenting to a tertiary pediatric ED. The secondary aims were to describe timelines of care and ED physician practice and to explore differences in the spectrum of conditions causing brain attacks in children and adults. We quantitatively synthesized published information about the spectrum of disorders causing brain attacks in adults through meta-analysis because there is no single reference summarizing the spectrum of mimics in adults presenting to the ED with suspected stroke. We hypothesized that the conditions causing brain attacks in children differ from adults regarding their scope and frequency and that there is a lower a priori probability of stroke.

METHODS

Design. This was a prospective observational study of consecutive children aged 1 month to 18 years presenting to the ED with brain attacks from June 2009 to December 2010. The Royal Children's Hospital Melbourne (RCH) is the tertiary pediatric referral center for the state of Victoria in Australia (population of 5 million). The annual ED census is 67,000.

Table 1 Demographics and prehospital management

Variable	No. (%)	95% CI, %
Males	137/301 (46)	40–51
Prospective data entry	132/301 (43.5)	38–50
Medical history relevant for stroke[a]	116/301 (39)	33–44
Sudden onset of symptoms	217/297 (73)	68–78
Woke with symptoms	54/292 (19)	14–23
Well in the week before presentation	218/300 (73)	67–78
Referred to ED by health professional	64/301 (21)	17–26
Transported to ED by ambulance	104/301 (35)	29–40
Assigned high triage category	75/301 (25)	20–30
Median age at presentation, y	9.8 (IQR 5.0–13.8)	

Abbreviations: CI = confidence interval; ED = emergency department; IQR = interquartile range.

[a] In order of frequency: history of headache or migraine (8%), malignancy, recent chemotherapy, seizures (all 6%), hematologic disorders, genetic syndromes, hypertension, infection (all 3%), and congenital heart disease, head and neck infection, arteriovenous malformation (all 1%).

Inclusion and exclusion criteria. Children with brain attack symptoms were recruited to the study. A brain attack was defined as focal brain dysfunction of apparently abrupt onset. Patients were identified on arrival at triage using a screening tool (figure e-1 on the *Neurology*® Web site at Neurology.org). The following symptoms were required for inclusion: weakness, sensory disturbance, speech disturbance, visual disturbance, altered conscious state, unexplained collapse, first febrile or afebrile seizure, headache with other symptoms, and dizziness or unsteadiness. These symptoms were chosen because they are common presenting features of stroke and they have been found to be useful in discriminating stroke from mimics in adult studies.[6,7] We included headache associated with vomiting in our definition because they can be symptoms of increased intracranial pressure or hemorrhage. We selected first seizure as an inclusion criterion because it is a common presenting feature of stroke in the pediatric population.[11] Patients needed to have persistent neurologic symptoms (headache, subjective visual or sensory disturbance) on presentation to the ED or presence of objective abnormal neurologic signs on examination by the ED physician. Children were excluded if they had (1) isolated headache without associated neurologic symptoms, (2) a history of witnessed head trauma, (3) a history of epilepsy, defined as 2 or more previous febrile or afebrile seizures, or (4) shunted hydrocephalus.

Study procedure. Data were collected in 2 ways. The research assistant was notified of eligible patients arriving in the ED during the hours of 9 AM to 6 PM daily on weekdays after screening by the triage nurse. Children who met inclusion criteria were followed during their ED stay, and data were directly entered into the case report form (CRF). The patient discharge list in the ED triage system was reviewed daily for children who presented on the previous day outside recruitment hours. Records of eligible patients were retrieved and data were entered to a CRF, often while the child was still in the ED or on the ward. This "dual" data-collection process was reviewed after 1 month, and the data collected were found to be of good quality, with no substantial differences resulting from the 2 collection processes. All patients who presented in the ED were triaged using the national Australian Triage Scale,[12] a rating of clinical urgency. Patients assigned a category of 1, 2, 3, 4, and 5 are to be seen immediately, within 10, 30, 60, and 120 minutes, respectively.

Definitions. The first neurologic examination by the emergency physician was used for the purpose of analysis. If this neurologic examination was not available, the examination of a subsequent ED physician followed by the consulting neurologist or neurosurgeon was used. ED diagnosis was assigned by the ED physician at the time of ED discharge, and final diagnosis was assigned by the study neurologist (M.T.M.) after review of all patient records, imaging studies, and other investigations. Arterial stroke diagnosis was defined as an acute neurologic deficit lasting 24 hours or more, and confirmation of ischemic parenchymal infarction on neuroimaging.[13] Nontraumatic hemorrhagic stroke was defined as an acute neurologic deficit lasting 24 hours or more, and presence of parenchymal blood or intraventricular blood on neuroimaging.[14] TIA required a known history of cerebrovascular disease, a clinical history typical of a vascular brain event with full resolution of symptoms within 24 hours, and absence of acute infarction on MRI.[13] Migraine was defined according to the International Headache Society.[15] Children not meeting these criteria were given a diagnosis of headache not otherwise specified. Bell palsy was defined as acute, idiopathic, unilateral lower motor neuron paralysis of the upper and lower facial muscles.[16] Demyelinating disorders included acute disseminated encephalomyelitis,[17] transverse myelitis,[18] and Guillain-Barré syndrome.

Medical history was defined as risk factors for pediatric stroke and included arteriopathies, cardiac disorders, chronic systemic conditions, infection, acute head and neck disorders, acute systemic conditions, prothrombotic states, chronic head and neck disorders, malignancy, migraine, atherosclerosis-related risk factors, and previous stroke/TIA.[19]

Table 2 Presenting symptoms and signs of pediatric brain attacks

	No. (%)	95% CI, %
Symptom		
Headache	169/301 (56)	50–62
Vomiting	109/301 (36)	31–42
Focal weakness	103/297 (35)	29–40
Focal numbness	74/295 (24)	20–30
Visual disturbance	67/297 (23)	18–28
Febrile or afebrile seizures	62/301 (21)	16–26
Altered mental status	60/299 (21)	16–25
Dizziness	60/297 (20)	16–25
Speech disturbance	50/298 (17)	13–22
Ataxia	42/297 (14)	10–19
Loss of consciousness	34/299 (11)	8–16
Faint	33/297 (11)	8–15
Vertigo	10/295 (3)	16–61
Other symptoms	61/300 (20)	16–25
Sign		
Focal weakness	93/301 (31)	26–36
Focal sensory disturbance	40/301 (13)	10–18
Speech disturbance	24/301 (8)	5–12
Leg weakness	45/297 (15)	11–20
Facial weakness	44/297 (15)	11–19
Arm weakness	43/297 (14)	11–19
Hand weakness	35/297 (12)	8–16
Ataxia	31/297 (10)	7–14
Inability to walk	29/293 (10)	7–14
Eye movement abnormality	26/295 (9)	6–13
Arm sensory disturbance	26/293 (9)	6–13
Leg sensory disturbance	20/292 (7)	4–10
Visual defects	21/295 (7)	4–11
Dysarthria	18/296 (6)	4–9
Facial sensory disturbance	11/291 (4)	2–7
GCS abnormal, <15	83/292 (28)	23–33
GCS score <9	12/292 (4)	2–7
Pupillary abnormality	7/280 (3)	1–5
Hand sensory disturbance	9/277 (3)	1–6
Dysphasia	9/301 (3)	1–6
Paralysis	2/297 (0.7)	0.8–2
Sensory neglect	1/296 (0.3)	0.8–2
Other neurologic signs	24/300 (8)	5–12
No neurologic signs	102/298 (34)	29–40

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale.

Statistical analyses. Statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and Stata 12 (StataCorp, College Station, TX). Presenting symptoms and signs of strokes and stroke mimics were analyzed descriptively. Analyses were performed on the total number of episodes and are presented as percentages with corresponding 95% confidence intervals.

Meta-analysis of adult studies. A meta-analysis of adult studies describing the spectrum and relative proportions of conditions causing brain attacks was performed. The OVID interface was used to search MEDLINE (1946 to week 1 of May 2013) and EMBASE (1974 to week 1 of May 2013) databases. Search terms included "cerebrovascular disorders," "time factors," "ischaemic attack, transient," "diagnosis, differential," "neurologic examination," "referral and consultation," "reproducibility of results," "emergency medical services," "emergency service, hospital," "ER or emergency room," "stroke," and "mimic." Details of the full search strategy are provided in appendix e-1. Summary effects (the probability of a particular diagnosis) for selected studies with corresponding 95% confidence intervals were obtained using the DerSimonian and Laird random-effects meta-analysis model. Between-studies heterogeneity was quantified by the I^2 index. The results of the adult meta-analysis were compared with probability of particular diagnoses in children.

Standard protocol approvals, registrations, and patient consents. This study was reviewed and approved by the Royal Children's Hospital Human Research Ethics Committee (HREC) as a clinical audit (HREC reference CA28127).

RESULTS During the 17-month data collection period from August 2009 until December 2010, 101,000 patients presented to the study ED and were screened on arrival at triage. Three hundred forty-two presentations were believed to be eligible for enrollment by the research assistant, and data were entered to the CRF. Each child's data (ED notes, CRF, and medical record) were reviewed by the study neurologist (M.T.M.), and 41 children were excluded. Therefore, 287 children with 301 consecutive presentations were included in the analysis. Data were prospectively entered to the CRF by the research assistant for 132 children (44%) who presented between 9 AM to 6 PM.

One hundred thirty children (45%) were male. Median age at presentation was 9.8 years (interquartile range [IQR] 5–13.3 years). The majority of families (79%) self-presented to the ED, but general practitioners were the most common referral source in the remainder (41 of 64 children). Only 35% of children were transported to the ED by ambulance. Median time from symptom onset to presentation was 6 hours (IQR 2–48 hours). On arrival in the ED, 25% were assigned higher (1 or 2) triage categories. Median time to assessment by an ED physician was 22 minutes (IQR 6–55 minutes) (table 1). A medical history of disorders relevant for stroke was identified in 116 children (39%), with history of

headaches or migraine (8.3%) and malignancy (6%) being the most common conditions.

The presenting symptoms and signs of brain attacks are presented in table 2. Headache was the most common presenting symptom followed by vomiting and focal weakness or numbness. Seventy-six percent of children had neurologic deficits at the time of assessment by the ED physician. Lateralized weakness was more common than sensory disturbance or speech disturbance. Abnormal Glasgow Coma Scale score was documented in 28% children, but very few had a score less than 9.

Investigations and management in the ED are presented in table 3. Neuroimaging was performed in 139 children (46%) and was abnormal in 63 (45%) of cases. Children with stroke comprised 17 (27%) of all cases with abnormal scans. CT was performed in 90 cases (30%) and was abnormal in 27% of cases. Eight children underwent CT imaging at other centers before arrival at RCH. The scan was abnormal in 3 children and normal in 5. CT was performed in 73 (89%) of the remaining 82 children while the child was still in the ED. MRI was performed in 92 children (31%) and was abnormal in 62% of cases. One child had MRI before arrival at RCH and only 15 (16%) of 91 MRIs performed at RCH occurred while the child was still in the ED. Median time to first scan at our institution was 270 minutes (IQR 149–672 minutes). Specialty consultation was requested in 62% of children, and 50% of children were admitted to hospital.

Table 3 ED management, results of investigations, and timeline of care

ED management	No. (%)	95% CI, %
Neuroimaging performed	139/301 (46)	40–52
Brain CT performed[a]	90/301 (30)	25–35
Brain MRI performed[a]	92/301 (31)	25–36
Neuroimaging abnormal	63/139 (45)	37–54
CT abnormal	24/90 (27)	18–37
MRI abnormal	57/92 (62)	51–72
ECG performed	35/301 (12)	8–16
ECG abnormal	5/35 (14)	5–30
Lumbar puncture performed	40/301 (13)	10–18
Lumbar puncture abnormal	15/40 (38)	28–54
EEG performed	38/301 (13)	9–17
EEG abnormal	23/38 (61)	43–76
Specialty consultation sought	187/301 (62)	56–68
Admitted to hospital	151/301 (50)	44–56
Outpatient follow-up postdischarge	233/301 (77)	72–82
Timeline of care	**Median time (IQR)**	**95% CI**
Time from symptom onset to arrival	6 h (2–43)	5–7.1 h
Waiting time to assessment	22 min (6–55)	19–27 min
Time to first RCH scan	270 min (149–672)	204–304 min
Time to CT[a]	162 min (97–141)	128–186 min
Time to MRI[a]	1,174 min (1,045–1,387)	515–1,808 min
Time to ED discharge	291 min (193–424)	268–317 min

Abbreviations: CI = confidence interval; ED = emergency department; IQR = interquartile range; RCH = Royal Children's Hospital.
[a] Seventy-three CT scans and 15 MRIs were performed while the child was still in the ED.

The 5 most common final diagnoses included migraine in 28%, seizures in 15%, Bell palsy in 10%, ischemic or hemorrhagic stroke in 7%, and conversion disorders in 6% (table 4).

Fifty original studies were selected for detailed review in the meta-analysis of adult studies. Three met the criteria for inclusion and are summarized in table 5.[7,9,10] Between-studies heterogeneity varied by diagnosis from 0% to 90% and was high for stroke, migraine, and conversion disorders, moderate for seizures and syncope, and low for other disorders. The 4 most common diagnoses in adults were stroke, seizures, systemic infection, and migraine. The 4 most common diagnoses in children were migraine, seizures, Bell palsy, and stroke. Relative proportions of conditions in adults (obtained with the random-effects meta-analysis) and children differed significantly for stroke, migraine, seizures, and conversion disorders (table 5, figures e-2 and e-3). Adult disorders such as transient global amnesia, dementia, vestibular disease, toxic metabolic disorders, systemic infection, and cardiac disease were not encountered in our pediatric study. In contrast, pediatric disorders including cerebellitis, Bell palsy, and drug intoxication were not described in the adult studies and therefore were not included in the meta-analysis.

DISCUSSION This report describes the spectrum of brain attacks in children presenting to the ED. The key finding in this study is that pediatric brain attacks present very differently from adults. First, there is a much lower likelihood of strokes in children, accounting for 7% of cases, in contrast to adults where stroke is the most common diagnosis, accounting for 73% of cases in the meta-analysis.[6,8,9] Second, the spectrum of disorders causing pediatric brain attacks differs from adults, with migraine being the most common diagnosis. While uncommon, stroke was still the fourth most frequent diagnosis. Third, we found that children are usually transported to the ED by their parents; therefore, prehospital emergency medical services–based protocols will miss many children with stroke.

We adopted similar inclusion criteria to adult studies to allow comparison with published adult data.[7,8] The distribution of stroke mimics in children differs from adults.[6,8,9] Migraine was the most common stroke mimic in children, accounting for more

Table 4 Pediatric brain attacks: Final diagnoses

Final diagnosis	Frequency (%)	95% CI, %
Migraine	84 (28)	22.9–33.3
Febrile or afebrile seizures	46 (15)	11.4–20
Bell palsy	29 (10)	6.5–13.5
CVD[a]	21 (7)	4.4–10.5
Conversion	18 (6)	3.6–9.3
Syncope	14 (5)	2.6–7.7
Headache NOS	12 (4)	2–7
Other encephalopathy	10 (3)	1.6–6
Cerebellitis	7 (3)	0.9–4.7
CNS demyelination	6 (2)	0.7–4.3
Peripheral nerve	5 (1.6)	0.5–3.8
CNS tumors	3 (1)	0.2–2.9
CNS infection	4 (1.3)	0.4–3.4
Drug intoxication	4 (1.3)	0.4–9.3
Cord demyelination	2 (0.7)	0.1–2.4
Other neurologic	18 (6)	3.6–9.3
Other non-neurologic	18 (6)	3.6–9.3
Total	301	

Abbreviations: CI = confidence interval; CVD = cerebrovascular disease; NOS = not otherwise specified.
[a] Arterial ischemic stroke 7 (2%), TIA 7 (2%), hemorrhagic stroke 6 (2%), cerebral sinovenous thrombosis 1 (0.3%).

than one-quarter of cases, in contrast to adults where it accounts for less than 3% of cases. This is not surprising because migraine is a common neurologic disorder of children and teenagers.[20,21] Transient global amnesia, dementia, vestibular disease, toxic metabolic disorders, systemic infection, and cardiac disease, reported in the adult studies, were not encountered in our pediatric study. In contrast, cerebellitis and acute disseminated encephalomyelitis, found in our study, were not reported in adult studies. Age-related variation has also been demonstrated in adults. In one study of 87 adults presenting with suspected stroke, 21% of adults younger than 50 years had a stroke mimic with the main diagnoses being conversion disorders and migraine. Mimics were very rare in the group older than 50 years, accounting for only 3% of cases.[22]

One previous study has described the spectrum and characteristics of stroke mimics in children.[10] The patient cohort consisted of children referred by primary medical and surgical teams to a dedicated pediatric stroke team for an opinion because of concerns about suspected stroke. One hundred forty-three cases of suspected stroke were identified over 12 months and 21% were found to be stroke mimics.

Our data set is more representative of children presenting to front-line emergency services where immediate decisions need to be made for imaging and decision-making before admission. Including children with brain attack symptoms, regardless of whether stroke was suspected by the triage nurse and ED physician, better reflects acute care practice. This methodologic difference explains the much higher proportion of mimics, accounting for 93% of all cases in our study, which we believe better reflects the true incidence of stroke mimics in children. Two-thirds of children in the previous pediatric study had nonbenign disorders, defined as a clinically significant structural abnormality on neuroimaging, requiring long-term treatment or associated with risk of long-term adverse outcomes.[10] If the same definition is applied to our cohort, 41% had nonbenign disorders.

Adult studies have shown that time from symptom onset to arrival at hospital is an important determinant of access to hyperacute treatments including thrombolysis.[23] Use of emergency medical services in adults is consistently associated with more rapid transport to hospital, triage, and treatment with tissue plasminogen activator.[24,25] We were not able to determine the reasons for the delay in seeking medical advice but there was low utilization of ambulance service in our cohort. Inappropriate help-seeking action, nonambulance transport, and nonabrupt onset of symptoms have been shown to delay stroke diagnosis in previous pediatric studies.[1,2] Only one-quarter of children were assigned a high triage category, which requires assessment within 10 minutes of arrival. Once again, this delay may be attributable to lack of physician awareness of stroke as a potential cause of acute neurologic symptoms.[3,4]

Similar numbers of children underwent CT and MRI, but CT was more likely to be performed while the child was still in the ED, suggesting greater accessibility. We did not set out to determine sensitivity of neuroimaging in our cohort because many patients were scanned after discharge from the ED, particularly those requiring MRI, but a previous pediatric study of stroke mimics reported better sensitivity of MRI.[10]

This study has limitations. The brain attack definition of apparently abrupt symptom onset is open to interpretation. Furthermore, this definition potentially missed children with TIAs because symptoms or signs can resolve within an hour. Even though this was a prospective observational study, a research assistant was not available after hours and therefore data were abstracted retrospectively for a substantial proportion of cases. However, data collection was often completed while the patients were still in the ED or on the wards, even for these patients. Exact time of onset could not be determined for some cases. Accuracy of the clinical examination findings may have been influenced by level of experience of ED medical staff. ED determination of final diagnosis was made by a single neurologist rather than a consensus panel. ED physicians were not required to list or rank a differential diagnosis as part

Table 5 Random-effects meta-analysis: Comparison of 1,117 combined adult brain attacks from 3 studies[6,8,9] with 301 pediatric brain attacks from current study

	Children		Adult meta-analysis	
Diagnoses	%	95% CI	%	95% CI
Conditions encountered in both groups				
Stroke	7	4.4–10.5	73.1	64.7–81.5
Migraine[a]	27.9	22.9–33.3	2.4	0–5.7
Seizures/epilepsy	15.2	11.4–20	4.3	2.3–6.2
Psychiatric	6	3.6–9.3	1.5	0.4–3.2
Syncope	4.7	2.6–7.7	1.7	0.7–2.8
Encephalopathy[a]	3	1.6–6	1	0–2.7
CNS demyelination[b] (n = 411)	2	0.7–4.3	0.2	0.01–1.3
PNS/mononeuritis[a]	1.7	0.5–3.8	2.1	0.9–3.1
CNS infection[b] (n = 411)	1.3	0.4–3.4	0.5	0.01–1.7
CNS tumors	1	0.2–2.9	2.1	0.5–3.6
Cord lesion[b] (n = 350)	0.7	0.1–2.4	0.9	0.2–2.5
Other neurologic[a]	6	3.6–9.3	0.6	0.1–1.2
Other non-neurologic[a]	6	3.6–9.3	2	0–4.4
Conditions not encountered in children				
Systemic infection	0	0–1.2	3.4	2.3–4.4
Toxic metabolic	0	0–1.2	2.3	1.4–3.3
Vestibular	0	0–1.2	1.7	0.9–2.4
Trauma[b] (n = 411)	0	0–1.2	1	0.3–2.5
Cardiac[b] (n = 411)	0	0–1.2	0.97	0.3–2.4
Joint/musculoskeletal[b] (n = 356)	0	0–1.2	0.8	0.2–2.4
Dementia/delirium	0	0–1.2	0.8	0.3–1.3
Subdural[a]	0	0–1.2	0.5	0–1
TGA[a]	0	0–1.2	0.5	0–1
Conditions not described in adult studies				
Bell palsy[c]	9.6	6.5–13.5	NA	NA
Headache NOS[c]	4	2–7	NA	NA
Cerebellitis[c]	2.3	0.9–4.7	NA	NA
Drug intoxication[c]	1.3	0.4–9.3	NA	NA

Abbreviations: CI = confidence interval; NA = not applicable; NOS = not otherwise specified; PNS = peripheral nervous system; TGA = transient global amnesia.
[a] Data available for 2 studies.
[b] One study, therefore random meta-analysis was not performed and 95% CIs are presented for the individual study.
[c] Not stated as diagnoses in adult studies and therefore removed from meta-analysis.

of the study. Therefore, we could not determine whether stroke had been considered in the differential diagnosis of the ED physicians involved. The study was conducted in a tertiary pediatric ED, and therefore, the results may not be generalizable to the broader pediatric population.

Our study shows that pediatric brain attacks differ from adults, with a much lower probability of stroke in children and a different spectrum of mimics. The data indicate that adult approaches will need to be modified for children because of a much lower probability of stroke as compared with mimics. In particular, adult stroke recognition tools will need to be modified for front-line staff in pediatric and adult EDs receiving children.[26]

AUTHOR CONTRIBUTIONS

Mark Mackay conceptualized and designed the study, designed the data collection instrument, coordinated, undertook, and supervised data collection, performed the statistical analyses, drafted the initial manuscript, and approved the final manuscript as submitted. Zhi Kai Chua and Michelle Lee undertook data collection, contributed to development of the data collection instrument, contributed to data analyses, and reviewed the manuscript. Adriana Yock contributed to the study design, contributed to development of the data collection instrument, supervised the research assistants, supervised data collection, contributed to data analyses, and reviewed the manuscript. Leonid Churilov contributed to statistical analyses, and critically reviewed, revised, and approved the final manuscript as submitted. Paul Monagle and Geoff Donnan contributed to the study design, contributed to data analyses, and critically reviewed, revised, and approved the final manuscript as submitted. Franz Babl contributed to the study design, contributed to development of the data collection instrument, supervised the research assistants, supervised data collection, contributed to data analyses, and critically reviewed, revised, and approved the final manuscript as submitted.

ACKNOWLEDGMENT

The authors thank the emergency department medical and nursing staff for their assistance.

STUDY FUNDING

Grant support received from the National Stroke Foundation, Melbourne, Australia, the Collier Charitable Fund, Melbourne, Australia, and the Murdoch Childrens Research Institute, Melbourne, Australia, to employ research assistants to recruit subjects and enter data to the CRF.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 2, 2013. Accepted in final form January 16, 2014.

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CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System

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SECTION ON HOSPICE AND PALLIATIVE MEDICINE, COUNCIL ON CHILDREN WITH DISABILITIES

Clinical Report – Reaffirmed With Reference & Data Updates November 2021

This Clinical Report has been reaffirmed with reference and data updates. New or updated references and datapoints are indicated in bold typeface. No other changes have been made to the text or content.

The AAP would like to acknowledge Julie Hauer, MD, FAAP, FAAHPM, and Amy Houtrow, MD, PhD, MPH, FAAP, for these updates.

Pain is a frequent and significant problem for children with impairment of the central nervous system, with the highest frequency and severity occurring in children with the greatest impairment. Despite the significance of the problem, this population remains vulnerable to underrecognition and undertreatment of pain. Barriers to treatment may include uncertainty in identifying pain along with limited experience and fear with the use of medications for pain treatment. Behavioral pain-assessment tools are reviewed in this clinical report, along with other strategies for monitoring pain after an intervention. Sources of pain in this population include acute-onset pain attributable to tissue injury or inflammation resulting in nociceptive pain, with pain then expected to resolve after treatment directed at the source. Other sources can result in chronic intermittent pain that, for many, occurs on a weekly to daily basis, commonly attributed to gastroesophageal reflux, spasticity, and hip subluxation. Most challenging are pain sources attributable to the impaired central nervous system, requiring empirical medication trials directed at causes that cannot be identified by diagnostic tests, such as central neuropathic pain. Interventions reviewed include integrative therapies and medications, such as gabapentinoids, tricyclic antidepressants, α-agonists, and opioids. This clinical report aims to address, with evidence-based guidance, the inherent challenges with the goal to improve comfort throughout life in this vulnerable group of children.

abstract

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Dr Hauer conceptualized and drafted the initial manuscript, reviewed and responded to questions and comments from all reviewers, and contributed to writing the final manuscript; Dr Houtrow contributed to the initial drafting and editing at all stages, including the final manuscript; and all authors approved the final manuscript as submitted.

To cite: Hauer J Houtrow AJ, SECTION ON HOSPICE AND PALLIATIVE MEDICINE, COUNCIL ON CHILDREN WITH DISABILITIES. Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System. *Pediatrics.* 2017;139(6):e20171002

The identification, assessment, and treatment of pain in children with severe neurologic impairment (SNI) is an important goal for clinicians involved in the care of such children. Meeting this goal is considered a significant challenge, even for clinicians with expertise in symptom treatment.[1]

The International Association for the Study of Pain indicates that "the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment"[2] (Table 1). There are many reasons why pain can be a significant burden for children with SNI, including their increased risk for sources of acute pain, with symptoms expected to resolve once a problem is identified and treated. An even greater challenge is recurrent or chronic pain experienced by many children with SNI, with risk including pain sources attributable to alterations in the central nervous system (CNS) that cannot be identified by diagnostic tests.

Given the complexity of identifying and treating pain in such children, pain goes unrecognized or inadequately treated all too often.[5–7] In 1 study of children with cerebral palsy who experienced pain, more than 90% had experienced ongoing recurrent pain for more than 1 year, yet only half were receiving any treatment directed at pain.[8] In children with progressive genetic, metabolic, or neurologic conditions with no cure, the 3 most common symptoms reported by parents were pain, sleep problems, and feeding difficulties, with symptoms often not well controlled.[9]

Recurrent pain can have a significant effect on all aspects of daily life, including sleep and family interactions, and can lead to distress, anxiety, depression, irritability, insomnia, fatigue, and negative coping behaviors in the child and family members. Because chronic pain can be an outcome of many factors, a holistic approach is often needed to relieve pain and the associated problems.[10]

SPECIFYING THE GROUP OF CHILDREN WITH SNI

Significant impairment of the CNS can be attributable to various etiologies and indicated by different developmental descriptors (Table 2). This clinical report focuses predominantly on children with severe to profound intellectual disability with resulting lifelong limitations in verbal communication. Most will have associated motor impairment (ie, cerebral palsy). This report is not specific to autism, because pain in this group has not been well studied, although many of the same principles may apply. The use of the term "nonverbal" reflects that most children referenced in this report are unable to verbally indicate the presence or location of pain, yet will have features that indicate pain. SNI will be used to refer to this group, reflecting severe impairment of the CNS.[11]

PAIN FREQUENCY AND SEVERITY ARE SIGNIFICANT IN CHILDREN WITH SNI

Medical tests, procedures, and surgery are thought to be a frequent source of pain in children with SNI,[12] yet in 1 study only 8% of all pain episodes were attributed to these sources.[13] Pain in some is chronic, occurring on a weekly to daily basis and persisting despite treatment of problems such as gastroesophageal reflux disease (GERD) and spasticity.[13–17] For example, pain was noted to occur weekly in 44% of children with moderate to profound cognitive

TABLE 1 Definitions

Pain	Defined by the IASP[2] as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment"
Pain behaviors	Observable features expressed by an individual in pain, with features specific to children with SNI indicated in Table 3
Nociceptive pain	Defined by the IASP[2] as "pain that arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors" Indicates tissue injury or inflammation
Neuropathic pain	Defined by the IASP[2] as "pain that arises from an alteration or disease in the somatosensory nervous system" Attributable to alterations in the peripheral nervous system or CNS, resulting in abnormal excitability
Dysesthesia	Defined by the IASP[2] as "an unpleasant sensation, whether spontaneous or evoked" with cases including hyperalgesia and allodynia
Hyperalgesia	Defined by the IASP[2] as "increased pain from a stimulus that normally provokes pain"
Allodynia	Defined by the IASP[2] as "pain due to a stimulus that does not normally provoke pain"
Agitation	Unpleasant state of arousal manifesting as irritability, restlessness, and increased motor activity[3] Features include loud speech, crying, increased movement, increased autonomic arousal, such as sweating and tachycardia, inability to relax, and disturbed sleep-rest pattern
Irritability	A disorder characterized by an abnormal responsiveness to stimuli or physiologic arousal; may be in response to pain, fright, a drug, an emotional situation, or a medical condition[4]
Neuroirritability	Might best be used to indicate children with SNI who have persistent or recurrent episodes with pain behaviors after assessment and management of potential nociceptive sources, suggesting the CNS as a source of persistent pain features

IASP, International Association for the Study of Pain.

TABLE 2 Neurodevelopmental Terminology and Causes of SNI

Term	Definitions and Comments
SNI	Used in this clinical report to indicate children with severe impairment of the CNS resulting in lifelong intellectual disability and limited verbal communication, often with coexisting motor impairment (eg, cerebral palsy) Causes include genetic, metabolic, neurodegenerative, structural malformation of the CNS, CNS infection, anoxic or traumatic brain injury, unknown
Intellectual disability	A disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social, and practical domains Also referred to as cognitive impairment; previously called mental retardation References indicated in this report are typically of children who have severe to profound intellectual disability with associated limitations in communication
Cerebral palsy	Nonprogressive impairment of the CNS affecting muscle tone and control of movement Not always associated with intellectual disability especially with milder forms, whereas those with severe impairment often have both
Autism	Neurodevelopmental disorder characterized by impairments in social interaction and communication and a pattern of repetitive behaviors and interests

impairment and almost daily in 41% to 42% of children with severe to profound impairment, assessed by using the Non-Communicating Children's Pain Checklist–Revised or the Pediatric Pain Profile.[13,14,16] In children with moderate to severe cerebral palsy, pain was noted by parents to occur "once or twice" to "a few times" in 44% and "fairly often" to "every/almost every day" in 21% over a 4-week period.[15] This information is in marked contrast to typically developing children, with only 12% identified in a large population-based survey to experience pain on a weekly basis.[18]

Pain intensity is also rated high in children with SNI. Children with developmental and neuromuscular disorders were identified as 1 of 3 subgroups with high pain scores, assessed by using the Individualized Numeric Rating Scale, in a retrospective cohort analysis of more than 1.5 million documented pain scores in a tertiary pediatric medical center during a 3-year period.[19] In children with severe cognitive impairment, the average pain intensity for all sources of nonaccidental pain was 6.1 on a 10-point scale (0 equaling no pain and 10 equaling the worst pain), with an average duration of 6 hours.[13] In those with less impairment, specifically the ambulatory group with accidental pain, the average pain intensity was 3.8, with an average duration of 46 minutes.[9] Along with pain severity, pain frequency is also noted to be higher in children with the greatest neurologic impairment.[8,13,15,20] For example, pain was reported to be present in 48% of the ambulatory children with cerebral palsy compared with 79% in the nonambulatory group.[8]

IDENTIFYING PAIN IN CHILDREN WITH SNI

The goals of pain assessment are to identify the presence of pain and to track the response to interventions for pain. To meet these goals, pain-assessment tools have been developed for use in children with SNI who cannot communicate their pain experience. Such tools can educate clinicians and empower parents in recognizing specific pain behaviors in a child. When using such tools, it is beneficial to recognize both the information they provide and the limitations in their use.

Pain Behaviors

Pain behaviors refer to the observable features expressed by an individual in pain (eg, facial grimacing). The observation of pain behaviors is considered a valid approach to pain assessment in those unable to self-report.[21] Pain behaviors that are specific to children with SNI have been identified in studies of such children after surgery and painful procedures and by asking parents and caregivers what they observe when they believe their child is in pain. Table 3 indicates the categories and

TABLE 3 Pain Behaviors in Nonverbal Children With SNI

Category	Examples
Vocalizations	Crying, whimpering, moaning, gasping, sharp intake of breath
Facial expression	Grimacing, frowning, furrowed brow, squinting, eyes wide open, clenched teeth, teeth grinding, distressed look
Consolability	Inability to be consoled and made comfortable
Interaction	Withdrawn, seeking comfort
Sleep	Disturbed sleep, increased or decreased sleep
Movement	Increase from baseline in movement of arms and legs, restless and fidgety, startles easily, pulls away when touched, twists or turns
Tone	Stiffening of extremities, clenching of fists, back arching, resists movement
Physiologic	Tachycardia, sweating, shivering, change in color, pallor, breath holding, tears
Atypical features	Blunted facial expression, laughter, breath holding, self-injurious behaviors

features identified on pain-assessment tools.[14,22–25]

Behavioral Pain-Assessment Tools

Behavioral pain-assessment tools for children with SNI are listed in Table 4.[14,22–25] Such tools assist with determining the presence of pain. The use of these tools involves a detailed review with parents, caregivers, and home-based nurses, so as to determine a child's baseline behaviors and changes from baseline when pain occurs. As examples, some children display less typical pain behaviors, such as laughing, a blunted facial expression, or self-injurious behavior.[14,17,22,26,27] Parents of children with SNI consider pain identification to be an uncertain process, although they rate themselves as accurate in identifying pain in their child and quickly identified pain behaviors specific to their child when given a pain-assessment tool.[13,27]

No one tool can be recommended over another. Of note, the revised Face, Legs, Activity, Cry, Consolability (r-FLACC) scale and the Individualized Numeric Rating Scale can be individualized by indicating behaviors specific to each child, with examples of pain behaviors provided.[22,23] This option, not present in other tools, is important for children with atypical pain behaviors. In such children, ratings on other pain tools can then be deceptively low.

Nurses and physicians rated the r-FLACC and Nursing Assessment of Pain Intensity (NAPI) as having an overall higher clinical utility based on complexity, compatibility, and relative advantage, in a comparison of these tools with the Non-Communicating Children's Pain Checklist-Postoperative Version (NCCPC-PV).[28] In several studies, nurses preferred the r-FLACC for its ease of use and pragmatic qualities, although not all tools were included for comparison.[28–30]

Other Considerations When Assessing Pain

In children with recurrent pain, assessment tools can be used to score worst and typical pain episodes, although it is important not to become overly dependent on numbers. Other information to review includes the frequency and duration of pain episodes. This information can assist in determining whether the frequency, duration, and severity of pain episodes have sufficiently decreased after a medication trial.

TABLE 4 Pain-Assessment Tools for Nonverbal Children With Neurologic Impairment

r-FLACC[22]
- Revised from the FLACC to include pain behaviors specific to children with cognitive impairment
- Like the FLACC, a 5-item pain assessment tool with a score ranging from 0 to 10
- Allows parents to individualize by adding behaviors specific to their child
- Option of indicating individualized behaviors can be beneficial for children with atypical pain behaviors and lack of other typical features, which may result in a false low score on other tools

INRS[23]
- A personalized pain-assessment tool for nonverbal children with intellectual disability, based on the parent's knowledge of the child, developed for use in the hospital
- Parents and caregivers identify behaviors that indicate no pain to the worst possible pain on a scale ranging from 0 to 10
- Moderate to strong correlation between INRS ratings and NCCPC-PV (see below) total scores
- Option of indicating individualized behaviors can be beneficial for children with atypical pain behaviors and lack of other typical features, which may result in a false low score on other tools

NCCPC-PV[24]
- 27-item pain-assessment tool for children with severe cognitive impairment
- Moderate to severe pain determined at a cutoff of ≥11 of 81
- In Breau et al,[24] this cutoff provided a sensitivity of 0.88 and specificity of 0.81
- Available for download for clinical use or use in research funded by not-for-profit agencies at http://pediatric-pain.ca/resources/our-measures/

NCCPC-R[25]
- 30-item pain-assessment tool designed for nonverbal children ages 3–18 y with severe cognitive impairment
- Moderate to severe pain determined at a cutoff of ≥7 of 90
- In Breau et al,[25] this cutoff provided a sensitivity of 0.84 and specificity of 0.77
- Revised from the NCCPC-PV (postoperative version)
- Available for download for clinical use or use in research funded by not-for-profit agencies at http://pediatric-pain.ca/resources/our-measures/

PPP[14]
- A 20-item pain-assessment tool for children with severe to profound cognitive impairment
- Scores of ≥14 were generally associated, by observers, with moderate or severe pain
- A cutoff of 14 provided a sensitivity of 1.0 and specificity of 0.91
- The tool is arranged to provide different scores to indicate a rating for "on a good day," "most troublesome pain," "second-most troublesome pain," etc
- Available to download from the Web, after registration at www.ppprofile.org.uk

Adapted with permission from Hauer, JM. *Caring for Children Who Have Severe Neurologic Impairment: A Life with Grace*. Baltimore, MD: Johns Hopkins University Press; 2013:52-53. FLACC, Face, Legs, Activity, Cry, Consolability; INRS, Individualized Numeric Rating Scale; NCCPC-PV, Non-Communicating Children's Pain Checklist–Postoperative Version; NCCPC-R, Non-Communicating Children's Pain Checklist–Revised; PPP, Pediatric Pain Profile.

These pain-assessment tools (Table 4) have been studied in children identified as having intellectual disability, with the majority also identified as having cerebral palsy. Most of the children in these studies have intellectual disability in the severe to profound range, with few in the mild to moderate range. There are limited studies assessing pain behaviors in children with autism and intellectual disability, although the features identified are similar to those in children with intellectual disability without autism.[31,32] In children who acquire a developmental age of 3 years or greater, age-appropriate pain-assessment tools, such as various faces pain scales, can be used.[33]

In addition to pain assessment after surgery, other reasons to assess for pain behaviors and consider the use of behavioral pain assessment tools include the following:

- When concerns are identified at routine comprehensive assessments: Parents can be asked at such visits, "Do you have concerns that your son is uncomfortable or agitated at times, or is he typically calm and easily comforted?"
- When a child is identified to have intermittent muscle spasms and changes in body position: Determine whether pain behaviors are associated with intermittent muscle spasms and movement or whether the child appears calm during such movement.
- When gastrointestinal symptoms, such as vomiting or feeding intolerance, are identified: Nociceptive sources (ie, pain attributable to tissue injury or inflammation) include GERD and cholecystitis and CNS sources include central neuropathic pain and autonomic dysfunction.

Assumptions and Beliefs That Interfere With Identifying Pain

When pain behaviors are observed, beliefs and assumptions can interfere with considering pain as the cause. Past beliefs that are not viewed as relevant included that some children with SNI were indifferent or insensitive to pain,[34] and explanations for irritability in children with SNI included psychiatric diagnoses such as bipolar affective disorder.[35]

Although some parents may bring concerns about a child's comfort to a clinician's attention, for other parents their own beliefs can reduce the consideration of pain, such as the perception that the observed features are a natural part of the underlying condition.[36] Parents may encounter uncertainty from clinicians as to the source and management of symptoms, poignantly indicated by parents who shared that their children with SNI had "learned to live with pain."[27] In addition, comfort measures, such as holding and rocking, can temporarily calm some children, with parents then assuming the responsibility of maintaining their child's comfort, even if this requires constant vigilance. Such a child may be viewed as not having pain, even though frequent holding to maintain comfort could indirectly indicate an abnormal state of excessive hyperarousal, possibly attributable to pain.

Clinicians may assume that increased tone and movement are a result of spasticity and dystonia, rather than investigating pain as a possible cause of these findings.[13–15,37] This assumption can occur when pain behaviors in children with SNI are not recognized to include alterations in tone, bodily position, and movement (Table 3). Descriptors on pain-assessment tools include "stiffens or spasms," "spastic," "tense," "rigid," "tremors," "marked increase in spasticity," "twists or turns," and "arches back."[14,22–25] In a study in 22 children with SNI and persistent pain behaviors, intermittent increased tone was the most common pain behavior category, with 86% (19 of 22) of the children having recurrent muscle spasms, although 20 of 22 children were already taking one or more medications for spasticity.[17] With decades of literature focusing on spasticity treatment of this population, it can be difficult to shift to a view that treatment directed at pain may be of greater benefit than another intervention directed at spasticity. The identification of other pain behaviors can guide consideration of an empirical pain treatment trial.

Various words are used to describe children with SNI in distress, including irritability and agitation (Table 1).[3,38] The term "neuroirritability" has been used in children with SNI to describe a sustained activated behavioral state associated with crying or agitation during which the child is not easily consolable despite reasonable measures.[4] Neuroirritability has also been used in the same manner as a diagnosis, although with no indication of the pathophysiologic mechanism.

It is helpful to distinguish such descriptive terms that are independent of etiology from the mechanisms that can cause the observed features. Consideration of language is important, because the use of such terms as "agitation" or "irritability" can inadvertently shift focus away from pain and thereby away from treatment directed at the mechanisms of action that result in pain. The use of the phrase "pain behaviors" is likely to be viewed as a problem in need of treatment, whereas agitation and

neuroirritability might be viewed as indicating an irritable nervous system with less urgency given to its management. Such terms might also focus away from medication trials directed at pain mechanisms and instead result in the use of adjuvant medications, such as benzodiazepines, neuroleptics, or other sedatives.

Occasionally, concerns about pain raised by the parent or caregiver of a child with SNI may appear to be out of proportion to the observed features. It is feasible that such surrogate reporters may have emotional experiences that alter their perception of pain in their child. Parent reporting of pain that is initially not observed in the child should be reviewed carefully before considering that the child is not in pain. Parents historically have too often been reassured that their child with SNI is not experiencing pain, likely reflecting the lack of studies on pain behaviors until more recently, and ongoing assumptions of what such features indicate. Consideration of parental emotional experience warrants expertise, such as from an interdisciplinary pediatric palliative care team, rather than reassurance that the problem is not pain.

SOURCES OF PAIN BEHAVIORS

The mechanisms that generate pain include any cause of tissue injury or inflammation (nociceptive pain) or abnormal transmission of pain signals attributable to injury, dysfunction, or altered excitability in the peripheral nervous system or CNS (neuropathic pain).

Sources of acute pain in children with SNI include everyday routine discomfort, such as muscle spasms or an uncomfortable position, and pain from a new nociceptive source, such as a fracture, urinary tract infection, or other sources (highlighted in the following section). New-onset pain behaviors may also be observed with any acute illness that can result in distress. As an example, pain sources identified by parents of children with SNI included "chest congestion" and "chest infection," likely reflecting respiratory distress.[13,14] Some problems with acute onset have features that include pain behaviors, such as medication toxicity and delirium.

When a child with SNI is identified as having recurrent pain behavior episodes, it is important to consider sources attributable to altered function of the CNS (Table 5). These sources, such as central neuropathic pain and autonomic dysfunction, can either be a source of pain or have features that include pain behaviors. Children with SNI are at risk of more than one of these problems to exist. A focus on 1 problem as the

TABLE 5 Problems of the CNS That Are Sources of Pain or Have Features That Include Pain Behaviors

Problem	Features and Comments
Central neuropathic pain	Symptoms include pain localized to the gastrointestinal tract, such as pain triggered by distention of the gastrointestinal tract (suggested by pain associated with tube feedings or intestinal gas, with relief after a bowel movement or flatus) Pain features can occur spontaneously and with no trigger, described by adults as "shock-like" Attributable to impairment of the spinothalamic tract and thalamus
Visceral hyperalgesia	Altered threshold to pain generation in response to a stimulus in the gastrointestinal tract Attributable to sensitization of visceral afferents as well as central sensitization in the CNS
Autonomic dysfunction (dysautonomia)	Features that suggest dysautonomia: skin flushing, hyperthermia, pain localized to the gastrointestinal tract, retching, bowel dysmotility, general discomfort, agitation, tachycardia, sweating, arching, stiffening Dysautonomia can be a source of discomfort, and pain can trigger the features that occur with dysautonomia
Dystonia	Involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both Children with secondary dystonia attributable to severe alterations of the CNS may also be at risk of central neuropathic pain Pain can trigger and worsen features of dystonia
Paroxysmal autonomic instability with dystonia	Involves features of both autonomic dysfunction and dystonia Indicates altered function of the CNS areas that regulate autonomic function and movement Pain can trigger and worsen the observed features
Spasticity	Velocity-dependent increase in muscle tone that results in muscles that are resistant to movement Spasticity is often not painful but can result in musculoskeletal pain over time
Muscle spasms	Sudden involuntary contraction of a muscle or group of muscles; associated features can include arching, stiffening, tremors, and clonus Pain behaviors can indicate pain from muscle spasms or indicate pain from another source as the trigger for muscle spasms
Delirium	Disturbance of consciousness with an acute onset over hours to days and a fluctuating course Features include disordered thinking, change in cognition, inattention, altered sleep-wake cycle, change in arousal, and psychomotor disturbances

source of observed pain behaviors could then limit consideration of other treatment strategies for the problems indicated in Table 5.

NEW-ONSET PAIN BEHAVIORS

Tissue injury with resulting stimulation of nociceptors can be a source of acute pain, generally with resolution when the injury heals.[10] This section reviews sources to consider when a child with SNI has an acute onset of significant pain behaviors.

Nociceptive Pain Sources

New acute pain can be a result of common childhood problems, such as otitis media, corneal abrasion, hair tourniquet, testicular or ovarian torsion, or appendicitis. Children with SNI are also at increased risk of GERD, gastric ulcer, acute pancreatitis (associated with valproic acid and hypothermia), cholecystitis (associated with tube feedings), urinary tract infection, nephrolithiasis (associated with immobility, topiramate, and the ketogenic diet), hip subluxation, fracture (osteoporosis risk attributable to immobility and certain antiseizure drugs), and dental pain.[39] Problems such as hip subluxation can be a source of symptoms in some and an incidental finding in others.

Evaluation for Nociceptive Pain Sources

No agreed-on standard nociceptive evaluation exists for children with SNI. Decisions will be guided by history and examination, the risk of missing a specific source, and the level of invasiveness of the diagnostic study.[39] History can determine when the last dental assessment occurred, whether symptoms are associated with movement (fracture or hip subluxation), whether the child has a ventriculoperitoneal shunt, and other details relevant to the potential sources. Older children with moderate intellectual disability may be able to point to the location of pain. A thorough physical examination involves examining the child unclothed. Details include determining whether pain behaviors are reproduced with movement of the gastrostomy tube and whether pain occurs with positioning or palpation of the extremities (Table 6). Parts of the examination should be isolated as much as possible to determine whether the pain response is consistently localized to 1 area. Allowing the child to calm down and relax when possible between areas of examination can minimize confounding information.

Baseline studies that may aid in the discovery of the source of pain include blood tests (basic metabolic panel, a complete blood cell count, alanine aminotransferase, total bilirubin, alkaline phosphatase, amylase, lipase), urine (urinalysis and culture), stool guaiac, gastric pH in a patient with a gastrostomy tube, and radiography or bone scan if a fracture is suspected.[40,41] A dentist, ideally with expertise in children with special health care needs, can complete a dental assessment if specific concerns are identified or if there has been no dental examination in the past year. If the initial evaluation is negative, empirical treatment of GERD is often initiated while considering other tests.

After this initial assessment of a child with no history of irritability and recurrent pain behaviors, further diagnostic evaluation would be warranted. This workup may include abdominal ultrasonography or computed tomography scan, upper gastrointestinal tract series, impedance study, and endoscopy, as directed by history and examination. In a child with a history of persistent irritability that has increased over time to a level of concern for the parent, it might be reasonable to initiate an empirical medication trial directed at the CNS sources of pain behaviors while considering further diagnostic studies that are invasive. Figure 1 provides suggested guidance for this decision-making process.

Medication Toxicity and Withdrawal

Many of the features associated with certain medication toxicities include painlike behaviors.[42,43] Examples include serotonin syndrome, with features including tachycardia, hypertension, sweating, hyperthermia, increased muscle tone, clonus, agitation, dilated pupils, and diarrhea.[42] Medications to consider include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), linezolid, tramadol, fentanyl, metoclopramide, ondansetron, dextromethorphan, and, in some instances, several such medications used in combination.[42] Another example with similar features is neuroleptic malignant syndrome

TABLE 6 Physical Examination as Part of Nociceptive Evaluation

Physical Examination Technique	Potential Nociceptive Pain Source
Inspection of eyes for tears and conjunctival injection	Corneal abrasion
Inspection of dentition, mouth, and throat	Dental caries and abscess, gingivitis, tonsillitis
Inspection and palpation of shunt catheter site	Ventriculoperitoneal shunt malfunction
Inspection and movement of gastrostomy tube	Gastrostomy tube tension associated with growth
Inspection and palpation of abdomen	Constipation, distention
Inspection of skin	Hair tourniquet or pressure ulcer
Inspection, palpation, and movement of extremities	Occult fracture
Palpation and range-of-motion of joints	Subluxation (especially hips)

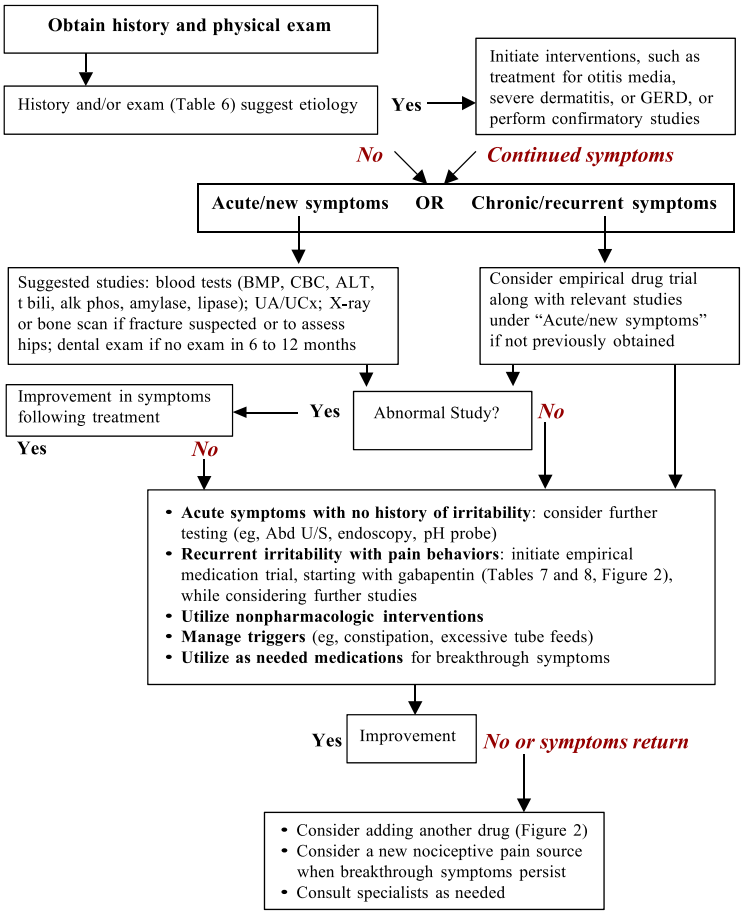

FIGURE 1

Decisions when pain behaviors are identified in children with SNI. Abd U/S, abdominal ultrasonography; alk phos, alkaline phosphatase; ALT, alanine aminotransferase; BMP, basic metabolic panel; CBC, complete blood count; t bili, total bilirubin; UA/UCx, urine analysis/urine culture.

attributable to dopamine antagonists, such as metoclopramide and risperidone.[43] Other problems that can present with pain behaviors include paradoxical drug reactions, including to benzodiazepines, anticholinergics, SSRIs, and neuroleptics. History can determine whether a medication was started days to weeks before the onset of symptoms.

Unintentional sudden cessation or a rapid decrease in the dose of certain medications can also present with painlike behaviors. Medications include benzodiazepines, baclofen, opioids, and TCAs. Withdrawal symptoms include excitation of the CNS (agitation, muscle spasms), activation of the sympathetic nervous system (tachycardia, hypertension, diaphoresis), and gastrointestinal symptoms (vomiting, diarrhea).

Delirium

Delirium is a disturbance of consciousness with an acute onset, over hours to days, and a fluctuating course. Features described in adults include disordered thinking, change in cognition, inattention, altered sleep-wake cycle, perceptual disturbances, and psychomotor disturbances.[44] Features of delirium are difficult to assess in children with SNI, with some features associated with pain in this group. Triggers for delirium include medications, pain, stress, illness, infection, and metabolic disturbances.

Delirium can be an important consideration in children in the ICU, with assessment tools being developed for use with children.[45,46] In 1 study of delirium in the PICU, 22 of the 111 patients were identified as having significant developmental delay. Use of the Cornell Assessment of Pediatric Delirium tool in this group had a low specificity of 51.2%, compared with a specificity of 86.5% in those without delay, with an overall specificity of 79.2%.[45] This study highlights the challenge of distinguishing problems that have overlapping presenting features in children with SNI.

CHRONIC RECURRENT PAIN

Chronic pain is continuous or recurrent pain that may involve a persistent noxious stimulus or persist in the absence of an identifiable pathophysiology. As noted earlier, some children with SNI have recurrent pain episodes rather than acute pain episodes that resolve after treatment of a nociceptive source. When a child with SNI first presents because of symptoms reaching a threshold for parental concern, history can identify the child with long-standing irritability and agitation as potential indicators of chronic pain.

Children with long-standing irritability may have had repeated tests and interventions for commonly recognized problems, such as treatment directed at GERD and spasticity. Chronic symptoms may be attributed to these problems, potentially limiting consideration of other coexisting pain sources as triggers. Children with SNI are also vulnerable to repeat testing over months in the search for a cause, with delayed

consideration of empirical medication trials directed at CNS sources (Table 5) that cannot be identified by diagnostic tests. Repeat testing exposes such children to potential harm from invasive testing and delayed pain management.

It is also possible to have an abnormal finding that is not the source of symptoms. Examples include a child with persistent symptoms after cholecystectomy, with improvement after starting gabapentin,[40] and 2 children identified by colonoscopy to have nonspecific colitis, with no improvement or escalation in symptoms after antiinflammatory treatment with significant improvement after the use of a TCA or gabapentin.[47] At times, empirical treatment can help avoid invasive testing and unclear findings from tests.

NEUROPATHIC PAIN (PERIPHERAL AND CENTRAL)

Neuropathic pain is attributable to damage or dysfunction of the peripheral nerves (peripheral neuropathic pain) or the CNS (central neuropathic pain). Neuropathic pain has some characteristics that are different from nociceptive pain. Pain descriptors in those able to report include burning, shocklike, shooting, prickling, or needlelike pain. Pain can be persistent or recurrent, including pain that occurs spontaneously with no known trigger. Neuropathic pain can be difficult to treat but is often managed with nontraditional analgesic drugs, such as antidepressants and anticonvulsants. Benefit from medications used for neuropathic pain may provide indirect evidence of this chronic pain source in children with SNI.[17,47–50]

Neuropathic pain can result in pain from a stimulus that does not normally result in pain (allodynia) or an increased pain response to a painful stimulus (hyperalgesia). Neuropathic pain is suggested in children with SNI by higher baseline pain ratings when they are not considered to be in pain and the significant intensity and duration of symptoms that were attributed to routine problems.[8,13,14,27,28,51] Examples that suggest hyperalgesia include constipation, with an average intensity of 6.2 out of 10 and a duration of 24.5 hours, and teething, with an average intensity of 5.2 out of 10 and a duration of 18.5 hours.[13]

Surgery can be a risk to the development of neuropathic pain. Persistent pain has been reported in 10% to 50% of adults after common surgeries, becoming severe in 2% to 10% of these patients.[52] One case series of 6 children with cerebral palsy identified neuropathic pain after orthopedic surgery of the lower extremities.[53] In addition, some diseases of the nervous system have associated painful peripheral neuropathy.

Central neuropathic pain can develop when injury or disease of the CNS involves the thalamus or spinothalamic tract.[54–56] Central neuropathic pain is best studied in adults with such problems as multiple sclerosis (MS) or after a cerebral vascular accident. Thalamic MRI findings have been reported with various conditions, including metabolic and genetic disorders (Leigh syndrome, Krabbe disease, Canavan disease, Alexander disease, gangliosidosis, neuronal ceroid lipofuscinosis, Rett syndrome), infections (cytomegalovirus, toxoplasmosis), osmotic demyelination syndrome, and hypoxic-ischemic injury.[57–60] This information suggests a risk for central neuropathic pain in children with SNI but does not indicate which child may develop symptoms attributable to this problem. The symptoms experienced with central neuropathic pain can be constant and involve sudden bursts of intense pain. Other symptoms include visceral pain associated with distention of the gastrointestinal tract and bladder, described by 1 adult as feeling "like my bowels will explode."[61]

Visceral Hyperalgesia

Visceral hyperalgesia is an altered threshold to pain generation in response to a stimulus in the gastrointestinal tract.[62] As a result, a normal stimulus, such as distention and pressure within the gastrointestinal tract, or minor tissue injury, such as from GERD, can result in significant pain. Injury or inflammation in the gastrointestinal tract is believed to cause sensitization of visceral afferent pathways, with resulting visceral hyperalgesia.[62,63] Visceral hyperalgesia may also be referred to as visceral dysesthesia, indicating an unpleasant sensation (Table 1).

Studies identify the gastrointestinal tract as 1 of the most common sources of recurrent pain in children with SNI, despite treatment of common sources such as GERD and constipation.[13–15,17,64,65] Pain attributed to the bowels is also noted to have a high pain intensity of 7.5 out of 10, second only to pain of unknown cause.[13] Such information suggests visceral hyperalgesia and central neuropathic pain as potential sources for recurrent pain behaviors in children with SNI.

Visceral hyperalgesia was identified as the source of gastrointestinal symptoms in 12 of 14 medically fragile children, most with cerebral palsy, with symptoms that persisted after medications for GERD and Nissen fundoplication.[63] Fewer were

identified to have impaired gastrointestinal tract motility. Of those, 7 had both impaired gastrointestinal tract motility and visceral hyperalgesia, and only 2 of the 14 children had a motility disorder as the sole problem identified.[63] In another study, gastrointestinal symptoms were noted in 14 of 22 children with SNI and persistent pain, all of whom were receiving treatment of GERD.[17] In both studies, medications used to treat visceral hyperalgesia and central neuropathic pain resulted in improvement in symptoms, including decreased vomiting and retching, improved feeding tolerance, weight gain, and change from jejunostomy to gastrostomy tube feedings.[17,63]

Nissen fundoplication and gastrostomy tube placement may be another risk to visceral sensitization of the gastrointestinal tract. Higher levels of pain in response to the same degree of gastric distention were identified after Nissen fundoplication.[66] In addition, parents of children with SNI have reported an increase in pain symptoms after the placement of a gastrostomy tube.[67]

Information from history can suggest visceral hyperalgesia and/or central neuropathic pain as potential sources of gastrointestinal tract symptoms in children with SNI. Questions include those that suggest a lower threshold to pain generation in the gastrointestinal tract and may include a history of pain associated with gastrostomy or jejunostomy tube feedings, bowel gas, and pain before a bowel movement, with relief after the passing of stool. Such pain sources may also be suggested by a decrease in symptoms when formula by feeding tube is substituted with an electrolyte solution or tube feedings are held while intravenous fluids are provided. Such information from history suggests a decrease in the threshold to the generation of painful symptoms from gastrointestinal tract stimulation.

Autonomic Dysfunction

Autonomic dysfunction is another potential source for pain behaviors in children with SNI.[8,68] Other terms include dysautonomia, autonomic storm, sympathetic storm, thalamic storm, and paroxysmal autonomic instability with dystonia. Features that suggest autonomic dysfunction include altered heart rate and body temperature; pale skin or flushing of the skin; retching, vomiting, and abdominal pain; sweating; and increased production of saliva.[69–71] Some features are the same behaviors associated with pain, and others can contribute to discomfort.

Seizures

For a child with persistent agitation and pain behaviors, EEG might be considered to determine whether movement associated with the events is attributable to seizures. EEG warrants careful consideration, because it is possible for a child to have results indicating seizure activity while simultaneously having a pain source that alters the threshold to seizures. Seizures in adults are not typically viewed as painful.[72] Discomfort can be experienced in the postictal period because of repeated movement or injury.

Spasticity, Muscle Spasms, and Dystonia

In children with SNI and recurrent pain behaviors, it can be unclear whether associated spasticity or dystonia are the direct cause of pain behaviors or if a chronic pain source is triggering any observed changes in tone and movement. When pain behaviors coexist with spasticity or dystonia, children with SNI may benefit from a multimodal approach, including interventions directed at chronic pain sources as well as spasticity or dystonia.

Spasticity is defined as hypertonia in which stretching the muscle at increasing speed results in higher tone or resistance to externally imposed movement.[73] Spasticity is often not painful, but over time it can result in painful musculoskeletal injury. In addition, intense muscle spasms can result in intermittent pain. Spasticity and muscle spasms can be increased by acute illness and pain. Dystonia is a movement disorder characterized by involuntary muscle contractions that lead to repetitive twisting movements and/or abnormal postures.[73] Like spasticity, dystonia is not typically painful, and pain from any source can increase movements associated with dystonia.

Hip Subluxation

Hip subluxation/dislocation is a potential source of chronic nociceptive pain. Because this problem is common in nonambulatory children with SNI, it may be an incidental finding in the evaluation for a pain source.[74] Interventions for this problem warrant consideration when positioning, transferring, bathing, dressing, and diaper care are difficult to conduct because of pain or limitations in range of motion.

More Than 1 Source of Pain May Coexist

Children with SNI are at risk of several sources of pain behaviors. A child may have GERD or spasticity as well as central neuropathic pain. Coexisting sources of pain may only be evident after symptoms improve, yet remain troublesome after the treatment of such problems. The presence of more than 1 source of pain may also be suspected by symptoms that are out of proportion to the problem, such as prolonged and

severe crying associated with constipation in a child with central pain. By considering more than 1 source, such children may experience symptom improvement sooner.

TREATMENT OF PAIN

Treatment of pain starts with a comprehensive evaluation, with an initial goal to identify and treat the cause whenever possible. Some sources, such as pain from a fracture, require temporary treatment of pain. The greater challenge is when pain behaviors have been identified as recurrent or chronic. General principles for pain treatment can serve as a guide throughout this process. Initial considerations include tailoring therapy to each child on the basis of the severity, frequency, and duration of episodes and the expected outcome after an empirical medication trial directed at potential chronic pain sources, along with close follow-up and availability throughout this process.[10]

A tool to guide medication selection, referred to as the analgesic ladder and originally applied to cancer pain, was developed by the World Health Organization (WHO) in 1986. It was revised recently for children from a 3-step to a 2-step ladder because of concerns that the previous second step[10] included codeine, a medication that is no longer routinely recommended given the recognized concerns with safety and efficacy related to genetic variability in metabolism.[75,76] Tramadol was also included in the second step, although the WHO suggests that the risks associated with strong opioids such as morphine are acceptable when compared with the uncertainty of response and risk associated with tramadol in children.[10]

The first step is used for mild pain and includes the use of nonopioid analgesics. The second step is used for moderate to severe pain and includes the use of opioid analgesics, starting with a lower dose for moderate pain. Adjuvant medications can be used at either step. These include medications such as anticonvulsants and antidepressants that can provide benefit for specific types of pain, such as neuropathic pain, or others that can enhance the benefit of medications used for pain treatment.

Other pain treatment principles guided by the WHO include "by the clock," "by the mouth," and "by the child,"[10] which indicates that treatment should be scheduled when pain is frequent, with rescue doses of analgesics or other appropriate medications available as needed. Medications should be given by the least-invasive route, such as enteral, buccal, or transdermal, and be tailored to the child's needs and response to treatment. Intramuscular injection is not an appropriate option for analgesia, given the other delivery options available.

It is unclear how well the WHO analgesic ladder applies to children with SNI, because it has not been studied in this population, but the principles of its use with patients with cancer apply. Children with SNI may be more likely to have chronic pain attributable to impairment of the CNS (Table 5), and not all central sources respond to opioids. Medications directed at these CNS sources of pain behaviors (Table 7) may have a preferential role in children with SNI before the use of an around-the-clock opioid. In recognition of these issues, an alternative to the WHO analgesic ladder was proposed for use in children with SNI and recurrent pain, indicated as the "neuro-pain" ladder.[50]

Because there is no standard approach to pain and symptom treatment in children with SNI,[48] empirical medication selection for persistent pain behaviors is best guided first by the safety of medications, with information on their efficacy for chronic sources of pain primarily guided by evidence in adults. The proposed neuro-pain ladder for children with SNI and persistent pain behaviors takes this approach, such as suggesting a gabapentin trial before a TCA or methadone.

Barriers to Pain Treatment

Fears commonly experienced when considering medications for pain, especially opioids, include harm, drug addiction, masking pain from a new problem, and giving up too soon on identifying a pain source. Fear of respiratory depression is 1 of the greatest barriers to opioid use. Knowing the intent of pain treatment can assist when considering this risk. For example, opioid use after surgery involves monitoring to identify and manage respiratory depression, meeting the intent to safely promote comfort and avoid any harm. In contrast, when the intention to relieve pain is the primary and overriding goal in a child with a life-limiting condition, accepting the low risk of respiratory depression is ethically permissible, along with forgoing monitoring at such a time. The risk of significant respiratory depression is low when following evidence-based dosing guidelines and slow titration, from a starting dose that is individualized to the patient. When available, expert consultation may be considered. Fears should not interfere with adequate symptom treatment. Rather, access to expertise or the advancement of one's own expertise through education can provide guidance on how to safely start opioids as well as other medications, monitor for effectiveness and adverse effects, adjust the dose as needed, and consider other treatment options when symptoms have not adequately improved.

TABLE 7 Medications for Acute and Chronic Pain

Medications	Evidence for Use	Comments
Gabapentinoids		
Gabapentin, pregabalin	Neuropathic pain, peripheral and central	Thought to inhibit excitation by binding to the α-2δ subunit of voltage-dependant Ca^{2+} ion channel in the CNS
	Visceral hyperalgesia	Side effects include sedation, nystagmus, tremor, swelling
Dysautonomia	Sedation can be minimized by increasing the dose gradually and then advancing more rapidly as tolerated	
Spasticity	No significant interactions with other drugs	
	No evidence that 1 is superior to the other for children who have SNI	
TCAs		
Nortriptyline, amitriptyline	Neuropathic pain, peripheral and central visceral hyperalgesia	Reuptake inhibition or serotonin and norepinephrine in the CNS, both inhibitors of pain transmission (also antagonists of 5HT-2, H-1, and Ach)
		Adverse effects include dry mouth, constipation, urinary retention, sedation, agitation, akathisia, and prolonged QTc syndrome (consider baseline ECG)
		Limit the use of other anticholinergic medications
		Side effects can be lessened by increasing gradually
		Caution when using with other medications that result in serotonin syndrome
		Serum level not necessary, although can document absorption
		Nightly lower dose may have benefit for sleep
Opioids		
Tramadol	Pain	Opioid receptor agonists, including μ-receptors
		Tramadol should not be used in children under 12 years or in those 12 to 18 years with altered respiratory status and should be used with caution in older patients with seizures or on drugs that cause serotonin syndrome
Morphine, other short-acting opioids	Pain	Morphine and other opioids safe when started with a standard dose, titrated to effect, and adjusted for renal impairment and respiratory depression, as examples
	Dyspnea	
	Autonomic storms	
Methadone	Neuropathic pain	Methadone has benefit of longer duration of action, but requires expertise in use
α2-Adrenergic receptor agonist		
Clonidine	Dysautonomia	Side effects include hypotension, bradycardia, sedation, although fewer side effects in children than in adults
	Spasticity	Side effects can be minimized by gradual dose increase
	May enhance pain management	Clonidine has the option of transdermal patch
	Nightly dose may have benefit for sleep	
Cannabinoids		
Dronabinol	Central pain in adults with multiple sclerosis	Cannabinoid receptor agonist (C-1 and C-2)
	Appetite stimulant	Limited studies in children
		Side effects include delayed gastric emptying, dizziness, anxiety, depression, irritability, restlessness, tachycardia, and dry mouth
Benzodiazepines as adjuvants		
Clonazepam	Autonomic storms	Not for pain treatment, used as adjuvants to enhance pain treatment
Lorazepam	Muscle spasms	Increase affinity of GABA for $GABA_A$ receptors
Midazolam	Myoclonus	Consider as-needed use for breakthrough symptoms in children on scheduled analgesics
	Seizures	Side effects include prolonged sedation and paradoxical reactions
		Use cautiously in combination with opioids
		Midazolam has rapid onset and shorter duration
		Tolerance develops with scheduled use

Ach, acetylcholine; C, cannabinoid; ECG, electrocardiogram; GABA, gamma-aminobutyric acid; H, histamine; 5-HT, serotonin.

The association of opioid use with end-of-life care can create the assumption that opioids hasten death. Opioids do not hasten death when used appropriately and can enhance comfort throughout life. In a case series of children with SNI on scheduled morphine for recurrent respiratory distress with associated

pain behaviors, 1 parent said, "I think [my son] has lived this long due to his improved comfort, [as] he used to struggle so much with each illness," a sentiment shared by several parents and primary nurses.[77] Once parents observe benefit from symptom treatment, clinician fear may continue and interfere with ongoing use of medications, adjustment in dosage, and additional trials when needed. Although physicians were aware of the benefit of opioids for severe dyspnea in adults, a significant gap remained between the benefit experienced by patients and family caregivers and physician fear over the use of opioids.[78]

Parental fear of addiction can be addressed by reviewing the difference between physical dependence and drug addiction. Parents can be informed of the need to slowly taper off of a medication so as to avoid withdrawal symptoms from a sudden stop or reduction in the medication's dose. In contrast, drug addiction refers to a psychological desire and dependence on a drug.

Another commonly held fear is that effective pain treatment will mask pain from a new pain source, but this does not occur, as noted in a case series of children with SNI when, at a time of effective symptom management of recurrent pain behaviors, urinary tract infections in 3 patients were identified by the onset of new pain behaviors.[17]

Acute Pain Treatment: Procedural and Postsurgical Pain

Pain-management techniques should be used for painful procedures. Strategies include medications along with nonpharmacologic interventions, such as music, distraction, and holding.[79] Medication delivery options for procedural pain management include topical, enteral, intravenous, intranasal, and inhaled medications.[80–82] There are numerous guidelines and policy statements for pain management,[80] yet pain during procedures for children is often undertreated.[82]

The management of postoperative pain ideally involves an interdisciplinary team of providers to assess and monitor pain and make adjustments as needed. The family can be engaged in all phases, from plan development through implementation and monitoring. The plan can include preemptive management of constipation that can be made worse by anesthesia and opioids.

Postoperative pain management, including the use of intravenous opioids in children with SNI, requires a team with expertise in safe pain management. Benzodiazepines may play an adjuvant role in the postoperative management of children with spasticity. For lower extremity orthopedic surgery, some physicians use botulinum toxin injections to help diminish the effects of postoperative spasticity, which is especially helpful in the child who is immobilized for several weeks.[83] Perioperative gabapentin may aid in reducing pain and opioid need after surgery, as noted in children undergoing spinal fusion.[84,85] Epidural analgesia is also a consideration for select patients.[86–88]

Chronic Pain Treatment

An empirical analgesic trial can be considered when pain behaviors continue.[21] There is no absolute "tipping point" when the severity, frequency, and duration of episodes with pain behaviors warrant an empirical medication trial versus further diagnostic testing. Consideration of central sources of symptoms with parents can minimize the assumption that testing will eventually identify the source to be treated, which may facilitate earlier initiation of a medication trial directed at the chronic pain sources that cannot be identified by diagnostic tests. Initiating an empirical medication trial while considering invasive tests, such as endoscopy or impedance study, can then avoid the need for such tests when symptoms improve. An empirical trial can also be considered before surgical interventions for GERD and spasticity with associated pain behaviors, potentially avoiding surgery if there is adequate improvement in symptoms.

Guiding principles for treatment of recurrent pain behavior episodes in children with SNI include frequency and duration of events. Infrequent episodes may be adequately managed with a medication used as needed, along with nonpharmacologic strategies. When episodes occur weekly, a scheduled medication can be considered, with the goal to minimize the frequency, duration, and severity of episodes. Occasionally, a child may have a monthly cycle of pain, such as a male with SNI described as having daily severe symptoms for 7 to 10 days each month for at least 4 years, with a significant benefit noted after several medication trials directed at neuropathic pain.[17]

Setting realistic goals can better prepare families throughout the process of treatment directed at chronic pain sources, reflecting the inability to "fix" the sources of chronic pain that arise from the impaired nervous system. One can acknowledge the hoped-for goal of improved symptom control while recognizing that the hoped-for benefit might not always be achieved.

Interventions for Pain

Interventions start with daily management of expected sources of

discomfort in children with SNI, such as repositioning. The ability to console the child with such interventions, along with other comfort strategies, indicates that routine needs have been met. In children with persistent pain behaviors despite such strategies, medications (Table 7) and nonpharmacologic strategies can be considered and used. Experts in pain treatment, such as pain or palliative medicine specialists, can be consulted when needed.

Nonsteroidal Antiinflammatory Drugs and Acetaminophen

Medications used for mild pain include acetaminophen and nonsteroidal antiinflammatory drugs.[10] Adverse effects with the chronic use of nonsteroidal antiinflammatory drugs include gastritis and gastrointestinal bleeding. Lack of benefit may indirectly indicate a problem more significant than a routine ache or pain. At such a time, an empirical trial directed at chronic pain sources can be considered. There is still an ongoing role for these medications given the benefit when used in combination.

Tramadol

The analgesic effect of tramadol includes weak μ-opioid agonist activity and weak reuptake inhibition of norepinephrine and serotonin.[89,90] The Food and Drug Administration (FDA) recently issued a warning indicating that tramadol should not be used to treat pain in children younger than 12 years and a warning against its use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of respiratory depression and death.[91] Some individuals, because of genetic variations, are ultrarapid metabolizers who convert tramadol more rapidly and completely to O-desmethyltramadol, the active form of the opioid, resulting in this risk. The WHO analgesic ladder for children recommends a strong opioid started at a lower dose for moderate pain rather than the use of tramadol.[10] In older patients, tramadol must be used with caution in those with a seizure disorder, receiving medications that are CYP2D6 and CYP3A4 inhibitors, and on medications that are associated with serotonin syndrome.[42,92]

Opioids

Opioid use requires knowledge of dosing, titration, adverse effects, and when to consider opioid rotation, information covered in greater detail elsewhere.[89,90] Opioid use in children with SNI includes the management of acute nociceptive pain, acute breakthrough pain that occurs despite use of scheduled medications for chronic pain sources, and intermittent autonomic storms or dyspnea.[77]

If an opioid is the only medication being used for frequent pain, it is best scheduled around the clock on the basis of duration of benefit, typically every 4 hours when given enterally, with a dose available as needed for breakthrough pain.[10] Monitoring will determine when the scheduled dose needs to be adjusted.

One limitation of opioid use for chronic pain in children with feeding tubes is the frequency of dosing required with short-acting opioids and fewer long-acting options. Options of longer duration include methadone solution or a fentanyl transdermal patch. The fentanyl patch should not be used to manage acute pain. Long-acting morphine pellet-filled capsules can be given by gastrostomy tube if the equivalent daily dose of short-acting morphine converts to the capsule doses available, by suspending the pellets in water and administering in a gastrostomy tube that is 16 F or larger, although care must be taken not to crush or dissolve the pellets.[93,94] This process is in contrast to long-acting tablets, which cannot be opened or crushed and therefore cannot be given in a feeding tube.

Methadone is the only long-acting opioid available as a liquid. The analgesic effects of methadone include μ-opioid agonist activity and *N*-methyl-D-aspartate receptor antagonist against glutamate, an excitatory neurotransmitter in the CNS, providing theoretical added benefit for children with SNI and chronic pain. Its use requires expertise, given its biphasic elimination and alterations in metabolism with other drugs.[95,96] Potential drug interactions include many medications used commonly for children with SNI, including phenobarbital, phenytoin, carbamazepine, ciprofloxacin, diazepam, metronidazole, and erythromycin.[95,96]

When opioids are used, adverse effects need to be anticipated and managed.[89,90] In children with SNI, the risk of respiratory depression can be minimized by attending to patient details, such as the presence of severe hypotonia and obstructive apnea, and determining whether other sedating medications were recently started. Constipation is best managed preemptively by initiating treatment that includes a stimulant laxative and is not limited to stool softeners or by increasing any treatment already in use for constipation.[89] Itching can also occur, a problem to consider if new agitation is noted. Management options include opioid rotation, ondansetron, and opioid antagonists. Antihistamines are not effective, because opioid-induced itching is not histamine mediated. Other adverse effects of opioid use include

sedation, usually transient, and urinary retention.

Not all children with SNI and severe pain behaviors will respond to opioids, as noted in case reports.[49,50] Short-acting opioids may be best used in the postsurgical period, when a pain source such as a fracture is expected to resolve, and on an as-needed basis for breakthrough episodes. When needed, experts in pediatric pain and palliative care can assist with the use of long-acting opioid forms.

Gabapentinoids

Gabapentin and pregabalin are the most commonly used anticonvulsants for neuropathic pain. Evidence, mostly in adults, indicates benefit for many of the chronic pain sources reviewed earlier, including peripheral neuropathic pain,[97–100] central neuropathic pain,[54–56,100] visceral hyperalgesia,[63,101–103] autonomic dysfunction,[69,104] and spasticity.[105] Gabapentin is approved by the FDA for use in postherpetic neuralgia in adults, adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy, and adjunctive therapy in the treatment of partial seizures in pediatric patients 3 to 12 years of age. FDA-approved indications for pregabalin include postherpetic neuralgia in adults and diabetic peripheral neuropathy. The use of gabapentin and pregabalin for the treatment of potential pain sources in children with SNI is off-label, as is commonly the case in pediatrics.

Gabapentinoids are considered first-line medications for neuropathic pain in adults.[98–100] Several case reports and 2 different case series of children with SNI indicated a reduction in pain behavior episodes as well as an improvement in muscle spasms, feeding intolerance, and sleep after treatment with gabapentin.[17,47–50,106]

The analgesic mechanism is not fully understood, although gabapentinoids are noted to bind to presynaptic voltage-gated calcium channels in the dorsal horn, reducing the release of excitatory neurotransmitters such as glutamate and substance P.[107] Pregabalin has an advantage of twice-daily dosing in older children, although there is less information regarding its use compared with gabapentin in children. Pregabalin also has linear pharmacokinetics compared with gabapentin's decreasing bioavailability at higher doses, although there are no data to indicate whether differences in absorption are clinically significant in children. Both require dose reductions in children with renal insufficiency and appear to be similar in their adverse-effect profiles, including no known drug-drug interactions.[98,99]

Given the limited evidence in treating persistent and recurrent pain behavior episodes in children with SNI, gabapentin may be reasonable in a first-line empirical trial on the basis of its safety and theoretical benefit for central pain sources (Fig 2). Clinicians routinely involved in the care of children with SNI can pursue knowledge in its use, including starting dose, titration, initial goal dose, and potential adverse effects (Table 8). Gabapentin dosing in children indicates that children younger than 5 years need a 30% higher dose, with doses up to 72 mg/kg per day (3600 mg/day) reported.[17,108,109] In adults, doses up to 3600 mg/day are used, although doses greater than 2400 mg/day may have incrementally less benefit. To provide an adequate empirical trial, such information is important when determining the initial dose to achieve.

TCAs

Nortriptyline and amitriptyline have been used to treat peripheral neuropathic pain,[101–103] central neuropathic pain,[54,56,100] and visceral hyperalgesia.[63,101] Their mechanisms of action include presynaptic reuptake inhibition of norepinephrine and serotonin, resulting in the modulation of descending inhibition from the CNS.[100] Both also have anticholinergic properties, with subsequent adverse effects including sedation, constipation, and urinary retention, along with possible benefit because of decreased secretion production. Adverse effects can be lessened with a slow titration to the initial goal dose. Nortriptyline has a lower anticholinergic effect, although it is unclear whether this is clinically significant in children. TCAs should be used cautiously with other medications that can result in serotonin syndrome. Other risk factors include potential cardiac dysrhythmia, including prolonged QT interval. For these reasons, TCAs require expertise in their use.

Nortriptyline and amitriptyline are considered first- or second-line treatment of neuropathic pain in adults.[98–100] They have the benefit of once- or twice-daily dosing. Given the lack of evidence in children with SNI and potential adverse effects, a TCA might be a reasonable second-line medication after a trial with a gabapentinoid in such children with recurrent pain behaviors (Fig 2). A TCA can be started while continuing gabapentin, an approach supported by 1 study that identified greater benefit with the combination of gabapentin and nortriptyline over either 1 given solely for neuropathic pain in adults.[110]

Medication Combinations for Neuropathic Pain

The combination of 2 or more medications for neuropathic pain may improve analgesic efficacy and reduce overall adverse effects if

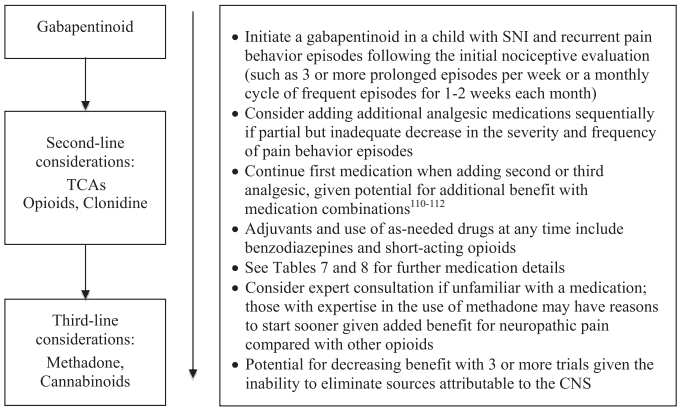

FIGURE 2
Suggested guidelines for pharmacologic management of recurrent pain behavior episodes.[50,98–100,110–112]

synergistic benefit allows for dose reductions.[111,112] Combinations studied for neuropathic pain include gabapentin plus nortriptyline, gabapentinoid plus opioid, and TCA plus opioid. General principles when considering a combination include selecting medications with the following: (1) maximal efficacy, the fewest adverse effects, and minimal adverse interactions with other drugs; (2) minimal adverse drug interaction with each other; (3) different adverse-effect profiles; (4) different mechanisms of action; and (5) different sites of action.[111] Figure 2 provides suggested guidelines to a stepwise approach by using such evidence as well as information from the neuro-pain ladder and guidelines from adults with neuropathic pain.[50,98–100]

Clonidine

Clonidine is an α2-agonist used in the treatment of spasticity[113] and autonomic dysfunction.[114] It also has potential mild analgesia through the inhibition of substance P release.[115] Clonidine may have a role in symptom treatment of children with SNI when associated problems include significant hypertonia or when features suggest autonomic dysfunction. Clonidine also has a suggested benefit in reducing pain perception during gastric and colonic distension.[116] Adverse effects of sedation and hypotension can be lessened with a gradual increase to the initial goal dose. Children with SNI who are unable to stand independently will not have the risk of orthostatic hypotension and associated fall. In children with associated sleep disruption, it can be used at nighttime to enhance sleep and to minimize problems such as muscle spasms that can disrupt sleep. Clonidine should not be discontinued abruptly because of the risk of rebound hypertension.

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered first- or second-line therapy for adults with neuropathic pain.[98–100] Studies are predominantly in adult patients with peripheral neuropathic pain, with fewer studies for central pain. Studies in children are limited to adolescent patients with depression. SNRIs include venlafaxine immediate release, which can be crushed and given by feeding tube, and duloxetine, which cannot be crushed, because it is an extended-release capsule. SNRIs have a greater benefit for neuropathic pain than SSRIs, with SSRIs indicated as fourth-line therapy for neuropathic pain in adults. The reuptake inhibition of norepinephrine is thought to be beneficial against neuropathic pain, a property shared by SNRIs and TCAs but not with SSRIs.

Antiseizure Medications: Other

Antiseizure drugs are used in adults with neuropathic pain, including valproic acid, carbamazepine, oxcarbazepine, lamotrigine, and topiramate. Studies in adults with peripheral neuropathic pain showed mixed results, and there are few studies in adults with central neuropathic pain. Overall, they are considered third- or fourth-line treatment of peripheral and central neuropathic pain in adults.[98,100] Their role in children with SNI and persistent pain behaviors is unclear.

Cannabinoids

Dronabinol is the synthetic form of δ9-tetrahydrocannabinol, an active compound of the cannabis plant. Dronabinol has been studied in adult patients with MS and traumatic brain injury.[117] Benefit for central pain and spasticity has been shown in patients with MS.[100,117] Other cannabinoid therapies used in adults include nabilone, a synthetic cannabinoid, and nabiximols, a cannabis extract that is available in the United Kingdom and other countries but not in the United States.[100,118] Such therapies are suggested as third-line treatment of neuropathic pain in adults.[100,118] In a recent policy statement, the American Academy of Pediatrics opposed the use of medical marijuana outside the regulatory process of the FDA but recognizes that marijuana may be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate.[119] Although the data in adults indicate benefit for chronic neuropathic pain as well as

TABLE 8 Analgesic Dosing Guidelines and Suggested Titration Schedules

Gabapentin
- Days 1–3: 2 mg/kg (100 mg maximum), enterally, 3 times daily
- Days 4–6: 4 mg/kg, enterally, 3 times daily
- Increase every 2–4 days by 5–6 mg/kg per day until the following[97]:
  1. Effective analgesia reached (may be noted at 30–45 mg/kg per day)
  2. Side effects experienced (nystagmus, sedation, tremor, ataxia, swelling)
  3. Maximum total dose of 50–72 mg/kg per day reached (2400–3600 mg/day)
  4. Younger children (<5 years) may require a 30% higher mg/kg per day dosing, such as a total dose of 45–60 mg/kg per day[17,108,109]
  5. Half of the total daily dose may be given as the evening dose if symptoms occur mostly in the evening and overnight
  6. Titrate more rapidly for severe pain or as tolerated, titrate more gradually if sedation noted

Pregabalin
- Days 1–3: 1 mg/kg (50 mg maximum), enterally, every night
- Days 4–6: 1 mg/kg, enterally, twice daily
- Increase every 2–4 days up to 3 mg/kg per dose, enterally, given 2 or 3 times daily (maximum 6 mg/kg per dose)

Amitriptyline or nortriptyline
- Days 1–4: 0.2 mg/kg (10 mg maximum), enterally, every night[97]
- Days 5–8: 0.4 mg/kg, orally, every night
- Increase every 4–5 days by 0.2 mg/kg per day until the following[97]:
  1. Effective analgesia, side effects (constipation, dry mouth, urinary retention, sedation), or dosing reaches 1 mg/kg per day (50 mg/day maximum)
  2. Consider ECG before further dose escalation up to 1.5–2 mg/kg per day (100 mg/day maximum); higher rate of side effects with higher doses including anticholinergic
  3. Consider plasma level if concerns with gastrointestinal tract absorption
  4. Consider twice-daily dosing of 25%–30% in the morning and 70%–75% in the evening

Clonidine
- Days 1–3: 0.002 mg/kg (0.1 mg maximum), enterally, every night
- Days 4–6: 0.002 mg/kg, enterally, twice daily
- Days 7–9: 0.002 mg/kg, enterally, 3 times daily
- Increase every 2–4 days by 0.002 mg/kg until the following:
  1. Effectiveness noted or side effects develop
  2. Titrate more rapidly if tolerated
  3. Average dose in 1 study (for spasticity): 0.02 mg/kg per day[113]
  4. 0.002–0.004 mg/kg every 4 hours as needed for breakthrough episodes that suggest autonomic storm events (suggested by facial flushing, muscle stiffening and tremors, hyperthermia)

Data from refs 17,50,96–100,108,109,113. ECG, electrocardiogram.

spasticity in patients with MS, no studies have been performed on the use of medical marijuana in children. The American Academy of Pediatrics supports the research and development of pharmaceutical cannabinoids and supports a review of policies promoting research on the medical use of these compounds.[119]

Benzodiazepines

Benzodiazepines are commonly used in children with SNI for spasticity, dystonia, seizures, dysautonomia, agitation, and sleep. Tolerance can develop with daily, prolonged use. Increasing the dose as tolerance develops may increase the risk of adverse effects. It can become difficult to separate out potential sedation or paradoxical effects, such as agitation and irritability, from problems attributable to the impaired CNS.[120,121]

There are times when the benefit of daily use of a benzodiazepine may outweigh the disadvantage of tolerance and other concerns, such as the use of clonazepam for certain seizure types. For other indications, such as for intermittent muscle spasms, autonomic storms, or prolonged seizures, benzodiazepines might be ideally used as needed. Other considerations include drug-drug interactions with midazolam, diazepam, and clonazepam as a result of metabolism by the P450 enzyme system.[122–124] In contrast, lorazepam is metabolized by conjugation. Children started on clonazepam should be monitored for the development of significant saliva production and bronchial secretions, possibly a greater risk in younger children.[125,126] Midazolam is highly fat soluble, which can result in accumulation over time. Continuous use in the hospital can result in accumulation and prolonged sedation.[127] These considerations for midazolam are relevant to children with SNI, given the greater percentage of fat for body weight.[128,129]

Sudden cessation should be avoided, because withdrawal can occur. Withdrawal can result in such symptoms as jitteriness, agitation, anxiety, increased heart rate, muscle cramps, disrupted sleep, gastrointestinal upset, and heightened sensitivity to light and sound. One review of benzodiazepine tapering after long-term use suggested a taper over 8 to 12 weeks, such as decreasing by 10% of the original dose every 7 days.[130] If persistent pain behaviors in a child with SNI are successfully managed after other medication trials, tapering of a benzodiazepine can be considered.

Antipsychotics

Used for agitation and delirium, it is unclear what role antipsychotics, including atypical antipsychotics such as risperidone, have in the management of persistent pain behaviors in children with SNI. Evidence in adults is lacking, with adverse effects needing to be considered before use as an add-on therapy for pain.[131] Antipsychotics should not be used as the sole therapy when children with SNI

have persistent pain behaviors. When used, adverse effects are an important consideration.

Antipsychotics, as well as SSRIs, have been used in children with self-injurious behaviors with variable benefit. Self-injurious behaviors are also identified as pain behaviors (Table 3). Recent literature has suggested neuropathic pain as a trigger for observed self-injurious behaviors.[132,133] Medications directed at central sources of pain are options to consider before the use of antipsychotics and SSRIs.

Management of Chronic Problems: Spasticity, Dystonia, Hip Subluxation, and Visceral Distention

The treatment of spasticity includes baclofen, a γ-aminobutyric acid agonist.[113,134] The major adverse effect of sedation can be minimized by titrating the dose slowly. There is also concern that baclofen can potentiate seizures in children with cerebral palsy.[135] Other medications for spasticity include tizanidine, clonidine, and dantrolene.[113,134] Benzodiazepines for spasticity may best be reserved for intermittent or short-term use.[134]

Intramuscular injections of botulinum toxin for focal spasticity can have benefit for associated pain in some children with cerebral palsy.[136,137] In studies in adults, botulinum toxin had some efficacy for neuropathic pain with localized symptoms.[138]

The placement of an intrathecal baclofen pump allows for the delivery of continuous and/or pulse doses. The reduction in spasticity with intrathecal baclofen is well documented, with limited evidence regarding pain relief.[139] Complications with intrathecal baclofen include malfunction, infection, overdose, and withdrawal.[140] Selective dorsal rhizotomy is another surgical option for spasticity, although it is best suited for children with spastic diplegia who are ambulatory and cognitively intact.[141]

Interventions for dystonia include medications and surgically placed devices. Such interventions are less effective in children with secondary dystonia than those with primary dystonia, likely reflecting the coexistence of other problems of the CNS.[142,143] Medications include baclofen, trihexyphenidyl, and carbidopa/levodopa, yet only baclofen has FDA-approved dosing for children.[142] Benzodiazepines, neuroleptics, muscle relaxants, and presynaptic dopamine-depleting medications have all been used with varying success.[143] Intramuscular botulinum toxin and intrathecal baclofen are also options. A randomized trial of intrathecal baclofen for dystonic cerebral palsy, including its impact on pain, is ongoing.[144] In a subset of patients with significant dystonia, implantation of a deep-brain stimulator into the globus pallidus can be considered.[142]

Nonpharmacologic strategies to lessen the effects of spasticity and dystonia include brace and positioning, passive stretching, massage, and warm baths. When pain behaviors are associated with spasticity and dystonia, medication trials for chronic pain sources can be considered before pursuing surgical interventions.[17,143]

Interventions for hip subluxation/dislocation that results in pain or limitations in movement include botulinum toxin injections around the hip joint to improve range of motion and comfort.[137] Surgical interventions can also provide symptom relief.[145–148] The consideration for surgery ideally involves an interdisciplinary team of providers and shared goal setting with the family, given the potential risks and lengthy recovery period for some children, including pain for up to 6 months.[146]

Management of Symptoms Attributable to Visceral Distention

Children with SNI may be noted to have symptom escalation before a bowel movement or with urinary retention. As discussed in the sections on central neuropathic pain and visceral hyperalgesia, this symptom escalation may reflect an altered threshold to symptom generation at times of visceral distention. Some children will have adequate symptom benefit from interventions that lessen distention, including the management of constipation that results in a daily bowel movement, the use of a suppository during times of persistent symptoms to determine whether colonic distention is a trigger (ie, resolution of symptoms after a bowel movement), and the use of intermittent urinary catheterization. Bowel medications for consideration include polyethylene glycol, lactulose, senna, suppositories, and enemas.[150] The nonpharmacologic strategies reviewed next can also be beneficial. When symptoms associated with visceral distention occur weekly after such interventions, the use of a scheduled medication directed at neuropathic pain/visceral hyperalgesia may lessen the frequency, severity, and duration of associated symptoms.

Nonpharmacologic Strategies That Improve Comfort

Nonpharmacologic interventions are an important part of symptom management for all children with SNI. Simple strategies include tight swaddling, cuddling, rocking, repositioning, and massage.[89] Supportive equipment, such as seating systems and supportive pillows, can minimize positional

pain. Other interventions include warm baths, weighted blankets, and music. Audiotherapy has also been shown to decrease pain postoperatively in pediatric patients.[150] Complementary and integrative therapies can include essential oils, Reiki, and acupuncture, with evidence of efficacy being notably limited in this population.[151] A trusting relationship with families can enhance the disclosure of alternative medicines being used, which can be relevant to drug interactions or sources of symptoms. An example is the risk of serotonin syndrome with St John's wort, ginseng, and tryptophan, when used in combination with other drugs.

Vibratory stimulation is reported as being beneficial for some with chronic pain.[152–154] Products available include vibrating mats and pillows. Parents may also observe their child appearing relaxed and comfortable when using high-frequency chest-wall oscillation vest therapy for mucous mobilization. Other sensory techniques include transcutaneous electrical nerve stimulation when neuropathic pain can be well localized.[155] The potential benefit of vibratory stimulation and transcutaneous electrical nerve stimulation is based on the gate-control theory of pain in which a nonpainful stimulus can enhance the inhibition of nociceptive transmission.[154,155]

Distention of the gastrointestinal tract is an important consideration, given the lower threshold to symptom generation in some children.[17,61–63,66] Strategies for symptoms triggered by gastrointestinal tract distention include gastrostomy tube venting, equipment that allows venting during feedings, and a decrease in the total volume of fluids and nutrition given by feeding tube, which is important given the risk of overestimating metabolism and fluid needs. The greatest risk factors for overestimating energy expenditure by 30% or greater in children with SNI include chronic hypothermia, limited movement of extremities, placement of an intrathecal baclofen pump, successful pain treatment with a reduction in intermittent muscle spasms, and declining health with declining activity.[17,128,156–160] Fluid needs can also be overestimated, given that metabolic expenditure accounts for more than half of fluid estimation, with fluid estimation based on weight then overestimating what is required to maintain hydration. Increased insensible fluid loss, such as that attributable to intermittent hyperthermia, sweating, or a tracheostomy, is also a consideration when estimating fluid needs.

Specific Considerations With Different Neurodevelopmental Disorders

This report focuses on children with severe intellectual disability who lack verbal communication, but there are some specific conditions that warrant mention. Children with cerebral palsy and pain will often have worsening muscle tensing and spasms during pain episodes. In contrast, children with intellectual disability and autism would not be expected to have pronounced muscle spasms with pain. These differences can affect the utility of different pain-assessment tools. In addition, there have been few studies specifically looking at pain assessment in children with autism. Such children may have behavioral features that complicate the process of pain assessment. In general, the same principles of pain assessment will apply to all children with intellectual disability, with or without cerebral palsy or autism. Pain assessment includes identifying individual baseline characteristics as well as features that suggest pain, as noted by those most familiar with the child. In such children with chronic recurrent pain behaviors, pain treatment will require an empirical trial along with use of nonpharmacologic strategies (Figs 1 and 2). Children with less impairment of the CNS (eg, mild intellectual disability without cerebral palsy) likely have a lower incidence of pain sources attributable to the CNS. In children with autism, nonanalgesic medication categories have been studied for the management of distressing behaviors that overlap with pain behaviors, including SSRIs, antipsychotics, naltrexone, and clonidine. As noted earlier, neuropathic pain has been suggested as a trigger for self-injurious behaviors, a feature more commonly seen in those with autism and severe intellectual disability.[132,133] Other considerations and interventions, including a search for triggers and behavioral management strategies, are clearly warranted for this complex problem. In children with intellectual disability and pain, these subgroups are important considerations with the assessment and treatment of pain as well as with future studies.

BROADER PAIN-MANAGEMENT STRATEGIES AND CONSIDERATIONS

Although pain can often be improved by implementing the interventions discussed previously, the optimal treatment of pain in children with SNI often requires considerable time and effort to achieve and is most likely accomplished if the overall treatment of pain for the child is guided by some broader management strategies and considerations. Optimal pain treatment includes care coordination with various providers involved with the child's medical

home. Specialty involvement regarding potential sources and pain-management strategies may include neurology, physical medicine and rehabilitation, complex care, gastroenterology, orthopedics, pain, palliative care, and hospice teams. Individualized pain-assessment tools and care plans can be made available across different locations of care. One clearly designated team, ideally with pain-management expertise, can oversee this process and can serve as the contact for questions and concerns as they arise.

Initiating and Monitoring Empirical Trials

Initiating a medication trial and monitoring the outcome benefit from a rigorous process. Information to consider includes the following: (1) response to previous medications, (2) interaction with other medications, (3) initial dose, (4) the need for titration to minimize adverse effects, (5) the minimal initial dose and time frame of the trial, and (6) adverse effects.[161] Table 8 provides guidelines that use this information and can be individualized. Monitoring will determine whether there is adequate benefit and, if not, if a second medication with a different mechanism of action directed at chronic pain sources will be added (Fig 2). If a medication will be discontinued, those to be tapered before discontinuing include gabapentinoids, TCAs, opioids, benzodiazepines, and baclofen. Ideally, when several medications are to be tapered, 1 is tapered at a time.

Monitoring requires the availability of a team with adequate expertise to answer questions and to address new changes in pain episodes. As new symptoms occur, consideration of new nociceptive pain sources can be balanced with a review of medication dosing and additional medication trials directed at sources of chronic pain. This team can also oversee other important aspects of care, such as encouraging a family to store medications such as opioids in a safe location, ideally in a locked cabinet, to reduce the risk of accidental overdose by other children and to discourage the diversion of opioids for illicit use. Diversion might also be considered if the expected benefit does not occur with escalating doses.

Care Plans in the Home for Breakthrough Pain Episodes

Chronic symptoms attributable to the impaired CNS can be modified but not eliminated. Breakthrough pain episodes should be anticipated, with care plans developed to assist families and home nurses in the moment. Families, caregivers, and nurses are integral to this process, including monitoring the benefit of such plans. Care plans can be tailored through trial and error as interventions that are beneficial are identified. A care plan may include the following information, with examples provided in the Appendix:

- presenting symptoms (describe the child's specific pain behaviors);
- initial routine interventions (check for wet diaper, reposition);
- initial nonpharmacologic strategies (considerations include removing orthotics that may cause temporary discomfort, swaddling, rocking, using a fan, placing headphones with favorite music, massaging legs, placing on a vibratory mat, and other strategies that have been identified as effective);
- interventions for triggers such as gastrointestinal tract distention (use as-needed suppository or enema if no stool in 1 day, vent gastrostomy feeding tube, hold feedings for 2 hours, hold feedings and give electrolyte replacement overnight, reduce total feedings/fluids);
- use of as-needed medications (options include as-needed antacid, acetaminophen, ibuprofen, morphine, clonidine, or benzodiazepine); and
- when to call (call the clinic during the day or the on-call clinician after hours if symptoms persist despite use of the interventions outlined, provide numbers to call).

Care plans can empower families with home-based options while retaining the option for direct assessment in the clinic, emergency department, or hospital. If the frequency and severity of events increase, the dose of scheduled medications can be reviewed and options for additional empirical medication trials can be considered.

Intractable Symptoms

Many children with SNI and recurrent pain will have improvement in symptoms after medication trials. The hoped-for benefit can be acknowledged with families while also preparing them for the possibility that some will have less benefit than desired. Case reports also suggest a risk of a return of symptoms without a source, speculated to indicate further neuronal apoptosis in the CNS.[40] Language at such times can include, "I hope for as much benefit from this next trial, although I also want you to be prepared that we might not have the hoped-for benefit. What is important to you as we consider these possibilities?"[162]

Many of the sources of chronic symptoms cannot be fixed; rather, medications can modify the symptoms that are generated by altering the imbalance of inhibition and excitation in the CNS. There is also a balance between further testing along with seeking a better outcome from multiple medication trials, with consideration that the problems and associated symptoms are intractable, analogous to

intractable epilepsy. Although not studied in children with SNI and chronic pain behavior episodes, decreasing benefit may occur from more than 3 medication trials directed at chronic pain sources.

These considerations are important for parents so as to minimize overtesting at a time of diminishing benefit. Palliative care and hospice teams can provide support and guidance throughout this process.[163] Suggested language includes, "I know that comfort is an important goal. I worry that it has been difficult to meet this goal or that it will only be possible with increased sedation. What are your thoughts?"[162] Discussions may result in a shared conclusion to redirect goals and decisions, such as accepting sedation to meet the goal of comfort and reconsidering the role of further testing, resuscitation, and hospitalization.

Symptom Treatment Throughout Life

Children with SNI deserve symptom identification and treatment throughout life. Waiting until a child is thought to be dying often delays symptom treatment, because it is often not possible to predict when a child with SNI is dying. It is also possible that a child with SNI will do better than expected if pain is significantly lessened, reflecting the harmful effect from the chronic release of stress hormones. Some children may also have improved respiratory function and a decrease in metabolic expenditure when muscle spasms triggered by pain are lessened, given the potential for altered position or respiratory effort attributable to muscle tensing.[77] Palliative care and hospice teams can assist with complex symptom management, including at the end of life.

SUMMARY

Available evidence supports the following points for consideration:

1. Children with severe impairment of the CNS, often referred to as children with SNI, have a significantly elevated frequency and severity of pain episodes compared with typically developing children.
2. Features that are observed when a nonverbal child with SNI is experiencing pain are referred to as pain behaviors. These features are summarized in Table 3.
3. These features are well established, with pain-assessment tools (Table 4) available to assist with pain monitoring in the hospital, such as after surgery, as well as to track response to interventions for chronic pain.
4. Nonpharmacologic interventions are an important part of routine symptom management.
5. Pain-management strategies should be used for painful procedures.
6. Postsurgical pain management benefits from an interdisciplinary team approach.
7. Children with SNI and acute pain have an increased risk of certain nociceptive pain sources. The goal is to identify and treat the cause of pain when possible.
8. Pain that reaches a threshold of concern for a parent may reflect long-standing discomfort without a source, with the child often referred to as agitated or irritable. Chronic pain sources attributable to the impaired CNS can be considered while also assessing for a new acute pain source as a reason for escalating symptoms.
9. Recurrent pain behavior episodes in children are typically best treated by using an empirical approach, with the goal to lessen the frequency, duration, and severity of episodes.
10. Lack of benefit from a medication trial should not be viewed as evidence that pain is not present.
11. Benefit from an empirical trial directed at central causes of pain behaviors can lessen the need for invasive testing in search of a nociceptive source.
12. Most evidence for treating chronic pain sources in children with SNI is derived from the adult literature. High-level evidence exists for the treatment of central neuropathic pain in adults, a source for consideration in children with SNI and persistent pain. First- and second-line trials (Fig 2) include gabapentinoids and TCAs.
13. Case series and reports of children with SNI and persistent pain behavior episodes suggest benefit from medications directed at central neuropathic pain, visceral hyperalgesia, and autonomic dysfunction, including gabapentin and TCAs.
14. Neuropathic pain that persists after 1 medication trial can benefit from medication combinations with different mechanisms of action.
15. Other medications include acetaminophen and nonsteroidal antiinflammatory drugs for mild pain and opioids for moderate to severe pain. Not all children with SNI and chronic pain behaviors will respond to opioids.
16. Pain behaviors often include alterations in tone, body position, and movement. When a child with muscle spasms or dystonia is also identified to have pain behaviors, a chronic pain source can be the trigger for intermittent changes in tone and position. Some children will have improvement after a medication directed at potential central sources of pain.
17. Management of coexisting problems, such as medications directed at spasticity and dystonia, can also improve comfort.
18. If symptoms persist after such medication trials, some children may benefit from

invasive interventions, including botulinum toxin injections and an intrathecal baclofen pump.
19. Bowel distention can trigger pain attributable to central neuropathic pain or visceral hyperalgesia. Management of constipation can lessen this trigger.
20. Overestimation of feeding and fluid requirements can be a trigger for symptoms in some, especially those with limited energy expenditure.
21. Breakthrough symptoms can be anticipated, with care plans developed to assist families and home nurses in the moment and tailored through trial and error as beneficial interventions are identified.
22. Potential CNS sources, such as central neuropathic pain and autonomic dysfunction, cannot be eliminated. Medications can decrease symptoms by increasing inhibition or decreasing excitation in the CNS. Many children will have a decrease in symptoms with drug trials, some will not experience the degree of benefit desired, and symptoms originating from the CNS can return or persist.
23. Palliative care teams can bring interdisciplinary expertise to assist with symptom management and family support, especially when symptoms remain intractable after first-line interventions.

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APPENDIX: HOME CARE PLAN EXAMPLES FOR BREAKTHROUGH SYMPTOMS

Example 1: Child With Benefit From Morphine When Symptoms Persist After Other Interventions

Features that suggest pain/discomfort in the child include crying, tears, stiffening of extremities, tremors, facial flushing (redness), sweating, and facial grimacing. Actions when such features are noted:

1. Routine comfort measures: reposition, check diaper, etc
2. Remove ankle foot orthotics
3. Vibrating mat or pulmonary vest (when features persist)
4. Use fan if warm to the touch or facial flushing noted
5. If pain considered mild, give as needed ibuprofen
6. If no improvement or if moderate to severe pain noted, give as needed morphine sulfate
7. If no improvement within 20 to 30 minutes with 1 medication, give other medication (ie, if ibuprofen given and no improvement within 20 to 30 minutes, then give morphine)
8. Call team if symptoms persist

Example 2: Child With Symptoms Attributable to Gastrointestinal Tract Distension and With Movement That Is Not Always a Seizure

Protocol for events with back arching and/or muscle tremors: consider triggers for these events in addition to considering a seizure.

1. Start with the following interventions:
   - Reposition
   - Vent gastrostomy tube
   - If no stool during the day
   - Give scheduled suppository if not yet given that day
   - Give as needed enema if suppository already given

2. Give ibuprofen if not already given
3. Consider giving antacid if not already given
4. Place in calm, dark environment
5. If event includes facial flushing (redness) and appearing agitated
   - Give as needed clonidine
6. If event involves rhythmic movement of extremities to suggest seizure
   - Give rectal diazepam; repeat if seizure activity persists for >15 minutes

It is not critical to determine the "chicken and the egg" (eg, is the event a seizure with increased heart rate versus discomfort as a trigger for muscle tremors); allow judgment and experience to guide the order of medication use when it is not possible to know with certainty while considering and eliminating sources that can trigger such events.

Example 3: Child With Symptom Relief From Gut Rest

For pain of ≥4 on pain scale:

1. Give clonidine 0.2 mg via gastrostomy tube
2. If no stool that day, give milk of magnesia, 30 mL (used as an antacid and for constipation)
3. If no stool in 1 day, give fleet enema
4. If no improvement, give morphine sulfate, 0.5 mL (10 mg) buccal

Other interventions at times of discomfort and pain:

1. Bath for comfort
2. Vent gastrostomy tube if any abdominal distention, gagging, or retching
3. Other options include as-needed milk of magnesia, acetaminophen, and ibuprofen as ordered

For persistent pain despite as-needed medications (notify team the next day):

1. Give electrolyte solution at 50 mL/hour in place of regular formula feedings × 24 hours
2. Give acetaminophen scheduled every 6 hours × 24 hours

Example 4: Younger Child Receiving Gabapentin and Clonidine, With Benefit From Vibratory Mat and Clonazepam for Breakthrough Symptoms

Interventions for persistent crying or toning:

1. Use the following 3 interventions, in no particular order:
   - Swaddling: use large bath towel or blanket, flex legs up toward abdomen, swaddle tightly
   - Vibratory mat, maximum of 15 minutes on followed by minimum of 15 minutes off
   - Weighted blanket, 30 minutes on followed by minimum of 30 minutes off
2. If no benefit from the above, use as-needed dose of clonazepam (suggested starting dose of 0.005-0.01 mg/kg)

ABBREVIATIONS

CNS: central nervous system
FDA: Food and Drug Administration
GERD: gastroesophageal reflex disease
MS: multiple sclerosis
r-FLACC: revised Face, Legs, Activity, Cry, Consolability
SNI: severe neurologic impairment
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
WHO: World Health Organization

DOI: https://doi.org/10.1542/peds.2017-1002

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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REVIEW

Recommendations for the Management of Initial and Refractory Pediatric Status Dystonicus

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ABSTRACT: Status dystonicus is the most severe form of dystonia with life-threatening complications if not treated promptly. We present consensus recommendations for the initial management of acutely worsening dystonia (including pre–status dystonicus and status dystonicus), as well as refractory status dystonicus in children. This guideline provides a stepwise approach to assessment, triage, interdisciplinary treatment, and monitoring of status dystonicus. The clinical pathways aim to: (1) facilitate timely recognition/triage of worsening dystonia, (2) standardize supportive and dystonia-directed therapies, (3) provide structure for interdisciplinary cooperation, (4) integrate advances in genomics and neuromodulation, (5) enable multicenter quality improvement and research, and (6) improve outcomes. © 2024 International Parkinson and Movement Disorder Society.

Key Words: dystonia; status dystonicus; childhood-onset movement disorders; deep brain stimulation; clinical pathway

Introduction

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions leading to repetitive twisting movements, abnormal postures, or both.[1,2] Dystonia severity often fluctuates along a spectrum from mild and tolerable to severe and life-threatening. Status dystonicus (SD), the most severe

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Relevant conflicts of interest/financial disclosures: A.F. has received grants/research support from Boston Scientific, DMRF – Canada, and Medtronic, and honoraria/consultation fees from Abbott, Boston Scientific, Ipsen, Medtronic, and Merz. D.E.-F. has received speaker honoraria from The Movement Disorders Society and the Taiwan Society of Child Neurology, and consulting fees from Guidepoint LLC, the University of Texas, the Telethon Foundation, and the German Center for Neurodegenerative Diseases (DZNE). C.G. has received honoraria/consultation fees from Medtronic and Ipsen.

Received: 3 November 2023; **Revised:** 7 March 2024; **Accepted:** 11 March 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29794

form of dystonia, is a medical emergency with significant morbidity, including metabolic derangement, respiratory/bulbar dysfunction, fractures, and pain.[3,4] Children in SD often require care in the intensive care unit (ICU) for sedative infusions, airway management, and other lifesaving procedures. Up to 12.5% of severe cases of SD result in death.[5]

Although SD is more common in pediatric dystonia, precise data on its prevalence and incidence in children are lacking.[3,6] Previous literature distinguished SD as dystonia in which the child cannot tolerate lying still or sleeping, and displays end organ changes (eg, rhabdomyolysis and acute kidney injury).[7,8] SD may emerge insidiously from a precursor entity, termed pre–status dystonicus (pre-SD; Table 1), which involves worsening dystonia without end organ involvement or airway compromise.[8,9] Refractory SD is distinguished as SD that persists despite attempted drug therapy and displays one or more life-threatening complications. SD is frequently observed in children with pre-existing dystonia secondary to neurodevelopmental syndromes, ranging from acquired causes (eg, dyskinetic cerebral palsy) to monogenic disorders (eg, DYT-*TOR1A*, *GNAO1*-related disorder,[10] *KMT2B*-related disorder,[11] or *ARX*-related disorder).[12] SD often ensues in the setting of triggers, including intercurrent illness, fever, dehydration, pain, and discomfort.[6,7] Rarely, SD can present as the first significant movement disorder manifestation of a variety of conditions, including genetic forms of dystonia, inherited metabolic disorders (eg, glutaric aciduria type 1,[13] Lesch–Nyhan syndrome,[14] pantothenate kinase–associated neurodegeneration),[15] or infectious/inflammatory central nervous system disorders (eg, infectious or autoimmune encephalitis).[16]

Worsening dystonia can be difficult for clinicians to recognize and treat. Even once established, it is often challenging to swiftly implement the next steps in management. Despite previous publications that provide tools for assessing severity and recommendations for general management,[7,8,17] there is still a need for comprehensive and systematic guidelines to treat SD in children. To address this unmet need, interdisciplinary working groups at The Hospital for Sick Children (Toronto, ON, Canada) and Boston Children's Hospital (Boston, MA, USA) undertook a literature review, evaluated institutional experiences, and developed clinical pathways. These pathways underwent a multistep consensus process, refining them based on multidisciplinary input provided by relevant teams, stakeholders, and patient safety and quality improvement initiatives (Supporting Information Data S1).

We present the resultant pathways designed to guide the evaluation and management of pre-SD, SD, and refractory SD in both inpatient and ICU settings. We sequentially outline our consensus recommendations, with the goals of (1) facilitating timely recognition and triaging of patients to a suitable level of care, (2) standardizing supportive and dystonia-directed therapies, (3) establishing structured monitoring protocols, (4) incorporating recent advances in genomics and deep brain stimulation (DBS), (5) enabling quality improvement initiatives and (6) enhancing patient outcomes.

TABLE 1 *Definition of relevant terminology in the spectrum of status dystonicus*

Term	Definition
Pre–status dystonicus	A child demonstrating worsening dystonia but without end organ involvement or airway compromise. They may be able to achieve intermittent sleep in this phase; however, it could be fragmented or easily disrupted by dystonia. Generally grades 2–3 on the DSS.
Status dystonicus	Worsening dystonia over 20 min, characterized by discomfort, tachycardia, and diaphoresis, with the presence of one or more end organ metabolic decompensations (hyperthermia, major electrolyte abnormalities, renal failure, myoglobinuria, or elevated serum CK level). Generally grade 4 on the DSS.
Refractory status dystonicus	Status dystonicus that persists despite attempted drug therapy and displays one or more life-threatening complications (bulbar weakness, compromised upper airway patency, exhaustion/pain, metabolic imbalances, renal or respiratory failure). Refractory status dystonicus generally requires care in the ICU setting. Generally grades 4–5 on the DSS.
Resolution of status dystonicus	Dystonia that has improved to grade 1 or 2 on the DSS for a sustained period of time (eg, >24 h), in the absence of infusions. Often this allows for de-escalation from ICU level of care.

Note: Major electrolyte abnormalities are defined as hyperkalemia >5.5 mEq/L. Renal failure is defined as serum creatinine >1.5× baseline and urine output <0.5 mL/kg/h for 6–12 h. Respiratory compromise is defined as the need for respiratory support in the form of continous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or intubation/mechanical ventilation.
Abbreviations: DSS, dystonia severity scale; CK, serum creatine kinase level; ICU, intensive care unit.

Recommendations for Pediatric SD

Tools for Assessing and Monitoring Dystonia Severity

Managing SD hinges on two key principles: (1) early recognition and (2) prompt treatment. Early recognition

facilitates timely management, effective communication within the care team, and appropriate triaging. This aspect aligns with other acute neurological emergencies, such as stroke or status epilepticus. The unique challenge in SD lies in its gradually worsening and fluctuating initial phase, distinguishing it from more binary presentations such as seizures. In addition, we acknowledge that there are nuances in the phenomenology of SD and other hyperkinetic movement disorder emergencies (eg, complex hyperkinetic crises in *GNAO1*-related disorder or *N*-methyl-D-aspartate receptor encephalitis, which can also encompass severe chorea). Our approach applies broadly because first steps are the same before treatment, which can later be tailored toward the leading phenomenology and etiology. Accurate assessment and close monitoring of dystonia severity are crucial to gauge progression, guide treatment decisions, and evaluate response to interventions. Beyond video recordings and informal reports from families, we propose two standardized strategies: the Dystonia Severity Scale (DSS) and the sleep–wake dystonia diary.

Dystonia Severity Scale (DSS)

The assessment of dystonia severity commonly relies on the use of the DSS, previously published by Lumsden et al in 2013.[7,8] For the purpose of the current consensus recommendations, we have adapted a modified version of the DSS, with appropriately mapped treatment guidelines, in Figure 1. The use of the DSS facilitates clinical decision-making among members of the care team. A common theme in prior literature has been the lack of clearly defined criteria for when a patient is in "pre-SD," "SD," or "refractory SD." We recognize that because of the fluctuating nature of the condition, this is a continuum rather than discrete stages. For ease of communication, we developed definitions of when a patient should be considered in each of these categories (Table 1).

Sleep–Wake Dystonia Diary

To streamline tracking of SD, we recommend a sleep–wake dystonia diary. Although a previous version of this listed five stages,[7,8] our clinical experience suggests that this poses a challenge for families and nursing staff to maintain. Instead, we propose simplifying the patient's state to three categories: (1) asleep, (2) awake and settled, and (3) awake and unsettled (Supporting Information Data S2). The diary is kept bedside and reviewed during rounds, akin to seizure count charts in epilepsy monitoring units. The diary may become integrated into the electronic medical record, allowing prompt correlations with vital signs and the medication administration record. The diary provides valuable information for assessing effects of medications/sedatives and escalation or de-escalation of care. Finally, the tool fosters cooperative care alliances by empowering caregivers.

Acute Dystonia Clinical Pathway

Next, we outline key components of the Acute Dystonia Clinical Pathway, a comprehensive approach to pre-SD or SD (DSS grades 3 and 4) across outpatient, emergency department, and inpatient ward settings (Fig. 2).

Step 1: Determine Dystonia Severity

The initial approach focuses on triaging dystonia severity based on the DSS (Fig. 1) and on conducting a focused history/physical examination (Supporting Information Data S3). If there is respiratory distress and/or significant metabolic derangement, a critical care team evaluation should be prioritized. Next, management along the "ABCD" mnemonic should be initiated without delay and should be revisited frequently: *a*ddress triggers, *b*egin supportive care, *c*alibrate sedation, and administer *d*ystonia-specific medications.[18] These steps should be implemented concurrently.

Step 2: Understand Baseline Dystonia; Search for and Address Triggers for Worsening Dystonia

This step builds on the focused history to identify the underlying etiology of dystonia and acute triggers, performing a comprehensive physical examination, and ordering relevant laboratory tests to identify triggers (Fig. 1, Supporting Information Data S3). Identifying triggers is vital, because about two thirds of SD cases are triggered by common factors, many of which occur in a hospital setting.[4,6,19,20] The history should also include asking about any personalized dystonia action plan and pertinent details about prior medications, including medications that may worsen dystonia (eg, neuroleptics) and recent medication changes.

Step 3: Initiate Supportive Measures

Supportive care should be initiated concurrently with the patient's evaluation (Fig. 2).[8,18] Multiple factors can worsen dystonia, which may lead to an unfortunate cycle where dystonia triggers pain, hyperthermia, dehydration, and metabolic compromise, provoking further dystonia and causing ongoing decompensation. Repeated evaluation of metabolic markers (creatine kinase level, renal function) and search for infection/musculoskeletal pain/constipation and ongoing triggers are important. Care should be taken to position the patient optimally and minimize handling that may exacerbate dystonia. Antipyretics, analgesics, and antimicrobial therapy should be provided as appropriate.

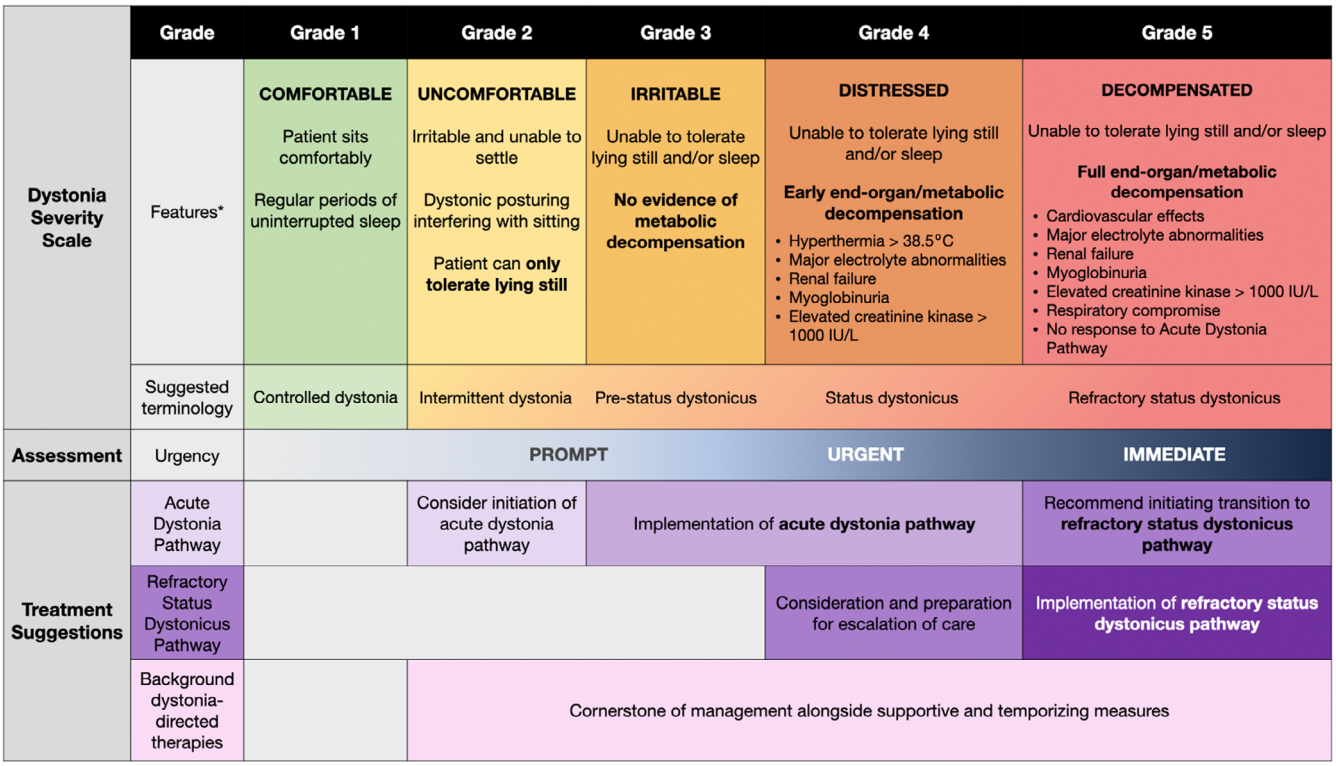

FIG. 1. Dystonia severity scale. The scale is used as a supplemental tool to determine severity of dystonia for the purposes of triaging pathway initiation. We have added additional parameters to indicate when the acute dystonia pathway versus refractory status dystonicus pathway (or escalation of care) should be considered, as well as when clinicians should consider modifying maintenance medications. Major electrolyte abnormalities are defined as hyperkalemia >5.5 mEq/L. Renal failure is defined as serum creatinine >1.5× baseline and urine output <0.5 mL/kg/h for 6–12 hours. Respiratory compromise is defined as need for respiratory support in the form of continous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or intubation/mechanical ventilation. This scale was adapted from Lumsden et al (2013, 2017).[7,18] [Color figure can be viewed at wileyonlinelibrary.com]

Ensuring adequate intravenous hydration and enteral or parenteral nutrition are of great importance.

Step 4: Initiate Pharmacologic Measures

In addition to supportive care, pharmacological intervention is usually needed. This involves the administration of medications to reduce dystonia and promote sedation/sleep (Table 2). We propose a stepwise approach, starting from least to most sedating medications.

Diphenhydramine is recommended as the initial medication in the pathway. It has rapid availability and a favorable safety profile (Table 2). It is used as a rescue therapy for acute dystonic reactions secondary to antidopaminergic agents and, therefore, is familiar to nonneurologists.[21] If dystonia persists for 10 minutes after intravenous administration or 20 minutes after oral administration of diphenhydramine, the next medication should be administered. Diphenhydramine should not be repeated.

As the second/third-line pharmacological interventions, we suggest enteral diazepam or clonidine (without regard to order). Diazepam is an intermediate-duration benzodiazepine that is commonly used to treat dystonia. Clonidine is a nonrespiratory depressant sedative that acts as a central α_2-receptor agonist and is often effective in controlling or preventing breakthrough dystonia.[18,22-24] If the response remains insufficient after the first dose, we propose moving on to whichever one was not tried (either diazepam or clonidine) as step 3. If available, a fourth-line option is chloral hydrate (Fig. 2, Table 2). Chloral hydrate is the most potent sedative in the acute dystonia pathway and is administered enterally or rectally.[25] Response should be reevaluated after 10–20 minutes, and if dystonia remains inadequately controlled (ie, DSS grade 3), both clonidine and diazepam (as well as chloral hydrate, if applicable) should be repeated as outlined in Figure 2. The pathway can be repeated from the beginning if dystonia returns after 6 hours.

After these acute treatments, a decision regarding the level of care and the need for further treatment escalation should be made. For patients with a presentation consistent with DSS grade 2 (pre-SD, Fig. 1), conservative management may be continued. For patients with DSS grade 3 (SD, Fig. 1), management on the general ward is appropriate unless medical comorbidities,

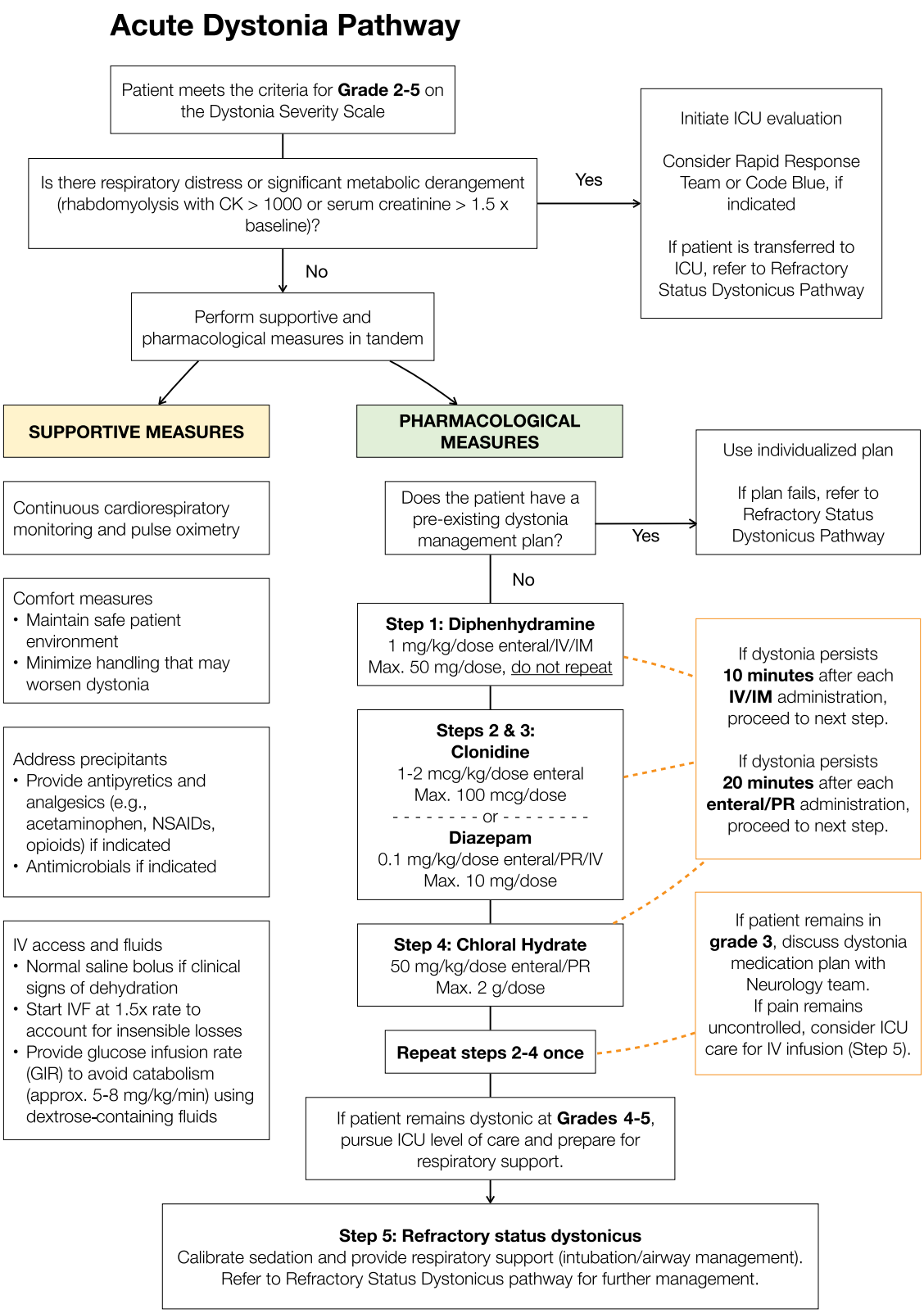

FIG. 2. Acute dystonia pathway. Acute Dystonia Clinical Pathway is a comprehensive approach to pre–status dystonicus and status dystonicus across outpatient, emergency department, and inpatient ward settings. Critical treatment steps should progress along "ABCD" mnemonic and should be revisited frequently: *a*ddress triggers, *b*egin supportive care, *c*alibrate sedation, and administer *d*ystonia-specific medications. These steps should be implemented concurrently. CK, serum creatine kinase level; ICU, intensive care unit; IV, intravenous; IVF, intravenous fluid; NSAID, nonsteroidal anti-inflammatory drugs; PR, per rectum. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 *First-line medications*

Agent and Recommended Dosing (Route)	Mechanism of Action	Duration of Action	Maximal Doses in 24 h[a]	Safety Concerns with Short-Term Use	Comments
Diphenhydramine, 1 mg/kg/dose (max. 50 mg), (enteral, IM)	Anticholinergic and sedative effects via inverse agonism of central H1 receptors	4–6 h	Do not suggest repeated doses	Anticholinergic effects, agitation and delirium, paradoxical excitation	Suggested because of its widespread availability and good safety profile.
Clonidine,[b] 1–2 μg/kg/dose (max. 100 μg) (enteral)	Nonrespiratory sedative via agonism of central α_2-adrenergic receptors	3–5 h	6–12	Hypotension, bradycardia, sedation	Titrate to effect/side effect. More frequent dosing, ie, every 2 h, can be advantageous. Once a stable dose is reached, can be converted to transdermal patch. IV clonidine is available in some regions of the world.
Diazepam, 0.1 mg/kg/dose (max. 10 mg) (enteral, PR, IV)	Sedative and muscle relaxant via GABA-A receptor agonism	60–120 min for sedation, despite long biological half-life	4–6	Cardiorespiratory depression with high doses, paradoxical reactions (rare), drooling	Titrate to effect. Enteral to IV conversion is 1:1.
Chloral hydrate, 50 mg/kg/dose (max. 2 g) (enteral, PR)	Sedative effects because of its active metabolite trichloroethanol via unknown mechanism	4–8 h	4	Excessive somnolence, dependency with chronic use	Not available in the United States.
Dexmedetomidine, 0.5 μg/kg/h (max. 2 μg/kg/h) (IV)	Anesthetic and sedative effects via agonism of α^2-adrenergic receptors	60–240 min after continuous infusion	N/A as continuous infusion	Cardiorespiratory depression, hypotension, tachyphylaxis, withdrawal after prolonged use	Titrate to effect.
Midazolam, 0.1 mg/kg/h (max. 2 mg/kg/h) (IV)	Sedative and muscle relaxant effects via GABA-A receptor agonism	N/A as continuous infusion	N/A as continuous infusion	Cardiorespiratory depression, paradoxical reactions (rare)	Titrate to effect.

Note: All medications listed are used off-label in children.
[a]Maximum number of doses per day is meant as a guide only. Individualized treatment plans are based on patient response, dosing of any existing maintenance medications, and usual safe daily maximum doses of each medication.
[b]Intranasal dexmedetomidine may also be used if clonidine is not available.
Abbreviations: max., maximum; IV, intravenous; IM, intramuscular; N/A, not applicable; PR, rectal.

nursing needs, or uncontrolled pain dictate a higher level of care. Patients who remain at DSS grade 4 or 5 meet the criteria for refractory SD, and care should be escalated. At this point, treatment should follow the Refractory Status Dystonicus Pathway presented later and in Figure 3.

Step 5: Developing an Individualized Dystonia Action Plan

Because patients may respond differently to various medications, and many patients with SD have significant medical complexities and a history of prior medical trials, we encourage the creation of an individualized

"Dystonia Action Plan" (Supporting Information Data S4). This includes the medications and specific order of medication that works best for an individual patient, analogous to seizure action plans in children with epilepsy.

Step 6: Adjusting/Initiating Baseline Dystonia-Directed Therapies

If the pathway is being used repeatedly, it is prudent to initiate or modify existing dystonia-directed therapies (Supporting Information Data S5). This often requires individualized approaches and should be guided by movement disorder specialists. Available agents often take days to weeks to take effect and therefore are added with the acute dystonia pathway acting as a bridge. This usually involves medications that are commonly recalled by another ABCD mnemonic: *a*nticholinergics (trihexyphenidyl), *b*aclofen, *c*lonidine/*c*lonazepam and other benzodiazepines (eg, diazepam), and *d*opamine (dopaminergic medications such as levodopa, versus tetrabenazine and other dopamine-depleting agents).[19,24,26] Medications should be chosen based on etiology/phenomenology, potential side effects, comorbidities, or other medications (Supporting Information Data S5).

Finally, efforts should be made to determine the underlying cause of dystonia if not already well established. This includes relevant biochemical studies, neuroimaging (including DBS planning sequences to establish feasibility of this possible treatment early on), as well as genetic investigations (commonly dystonia multigene panels or whole-exome/genome sequencing). Determination of the precise etiology can have profound implications for treatment and serves as a starting point for counseling, anticipatory guidance, and research. Although a consideration of DBS is appropriate for any patient in SD or any patient with severe or recurrent worsening dystonia despite medical therapy, we highlight that some forms of monogenic dystonia or hyperkinetic movement disorders with prominent dystonia display a superior response to DBS, indicating that it should be pursued early and rapidly in this setting (Fig. 3).[27]

Refractory Status Dystonicus Pathway

Refractory SD is characterized by a DSS grade of 4 to 5 with an inadequate response to initial pharmacological measures, namely, the acute dystonia pathway (Fig. 2), or the patient's personalized dystonia action plan (Supporting Information Data S4). The proposed management of refractory SD is constructed using the same ABCD principles discussed previously (Fig. 3). If not done previously, it is important to interrogate any intrathecal baclofen pump or deep brain stimulator to rule out withdrawal or hardware malfunction. The treatment should then progress along three axes: (1) calibration of sedating medications as a temporizing measure to control dystonia and prevent secondary complications, (2) initiation of dystonia-directed therapies, and (3) optimization of ICU supportive care.

Step 1: Calibrate Sedative Infusions

Sedative infusions provide relief and mitigate life-threatening risks of refractory SD. When administering sedative infusions, it is crucial to closely monitor and support the patient's cardiorespiratory status, and intervene if necessary. As such, this should be done in an intensive care setting. For first-line infusion, we propose dexmedetomidine (Fig. 3). A continuous infusion of dexmedetomidine allows for rapid titration with a relatively low risk of hypotension and other cardiovascular side effects.[28] Intravenous clonidine can be used as well, if available, and has shown to be safe in this setting.[22] If dexmedetomidine or intravenous clonidine prove insufficient, we recommend escalation to a continuous intravenous infusion of midazolam. Midazolam possesses muscle relaxant effects, and its short half-life expedites titration to effect. In rare cases, if dystonia continues to be refractory, a temporary initiation of nondepolarizing paralytics should be considered. In addition, a short course of propofol infusion (<12 hours to mitigate the risk of propofol infusion syndrome) may be considered as a second temporizing measure.[29]

In addition to continuous infusions, children with SD often undergo periodic worsening, which may be related to pain, discomfort, or the fluctuation of their underlying condition. In these cases, we propose reverting back to the patient's own dystonia action plan or the acute dystonia pathway. We suggest administering as needed medications (clonidine and diazepam) if the patient shows generalized dystonic posture/movements lasting more than 15 minutes, with associated discomfort/pain, and autonomic changes such as hyperthermia, tachycardia, or diaphoresis (Fig. 3).

The duration of sedation and intubation should be determined through periodic evaluations while simultaneously initiating and titrating dystonia-directed therapies. This approach allows for the gradual adjustment of sedation and ventilation based on the patient's response to treatment. The use of the acute dystonia pathway, along with the dystonia sleep–wake diary, can inform the appropriate adjustment of maintenance medications. If the patient requires continuous sedative infusions for a prolonged period of time, a "bridge" to intermittently scheduled enteral forms, commonly clonidine and diazepam, should be pursued. These agents have a synergistic effect with the aforementioned infusions and can gradually replace them over time.

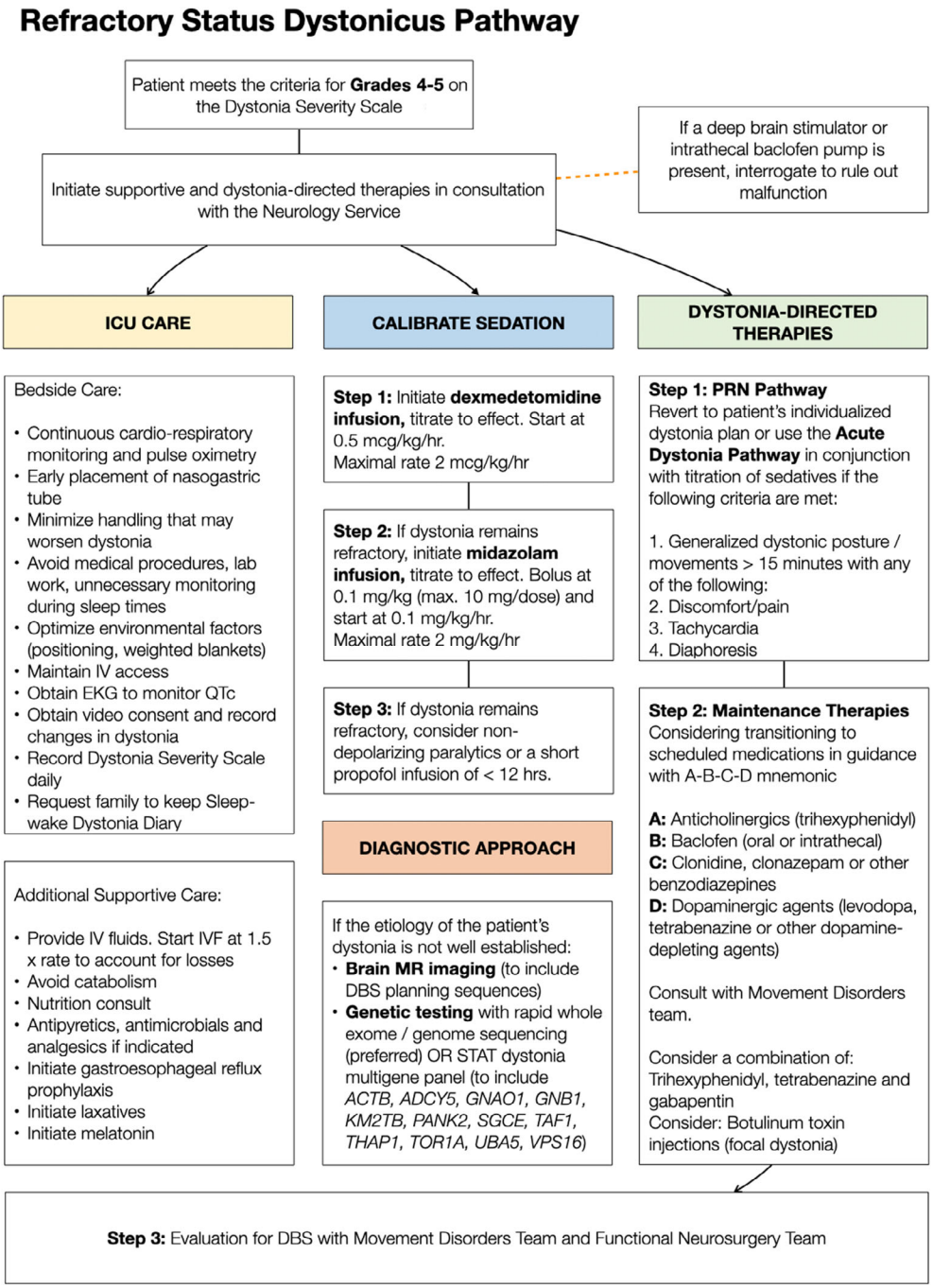

FIG. 3. Refractory Status Dystonicus Pathway. Refractory status is characterized by a Dystonia Severity Scale grade of 4 to 5 with an inadequate response to the acute dystonia pathway or the patient's personalized dystonia action plan. Treatment should then progress along three axes: (1) calibration of sedating medications as a temporizing measure to control dystonia and prevent secondary complications; (2) initiation of dystonia-directed therapies; and (3) optimization of intensive care unit supportive care. IV clonidine, where available, may be considered in place of IV dexmedetomidine. DBS, deep brain stimulation; EKG, electrocardiogram; IV, intravenous; IVF, intravenous fluid; MR, magnetic resonance; PRN, as needed. [Color figure can be viewed at wileyonlinelibrary.com]

Step 2: Dystonia-Directed Therapies

Although dexmedetomidine and midazolam may effectively control SD, such infusions are not suitable for long-term care and impede transfer out of the ICU. Thus, we recommend a transition to scheduled medications with antidystonic effects. This may involve a transition to bolus dosing of enteral clonidine/diazepam or the addition of other maintenance medications with antidystonic properties (Supporting Information Data S5). These medications may be personalized and should be guided by movement disorder specialist consultation, with pharmacy support, accounting for the

nature of the patient's underlying condition and existing medication regimen/side effects. In addition to the medications highlighted in Figure 3, another medication to consider is gabapentin as a nonopioid analgesic. Members of our group have found success with a combination of trihexyphenidyl, tetrabenazine, and gabapentin to leverage multiple mechanisms. It is important to note that children generally tolerate significantly higher doses (per body weight) of antidystonia medications than adults, and higher doses may be required to achieve symptom relief. Careful monitoring for significant anticholinergic side effects (ie, severe constipation, urinary retention, hyperthermia) or cardiac complications (ie, QTc-interval prolongation) is important (Supporting Information Data S5). Following the intensive treatment phase, sedative medications can be weighted toward higher evening doses to support sleep–wake cycle improvement.

Step 3: Supportive Care

Supportive care remains an important pillar throughout the management of acute dystonia, including refractory SD. Careful monitoring of vital signs and laboratory values is crucial, as well as maintenance of vascular and enteral access. Assessment of hydration/nutritional status should be conducted carefully to address deficiencies. Appropriate medications, if indicated, should be provided to manage fever, infections, gastroesophageal reflux, constipation, and pain. Care should be taken to avoid procedures during sleep times. Optimizing environmental factors, such as maintenance of a day–night schedule, positioning, and the use of weighted blankets, can help alleviate symptoms, avoid delirium, and provide comfort to the patient. A relatively long ICU course should be anticipated, and social work support should be provided.[30,31]

Step 4: Integration of Neuroimaging and Rapid Genomic Testing

As discussed earlier, if the etiology of the patient's dystonia is not well established, it is crucial to pursue both expedited genetic testing and neuroimaging (Fig. 3).

Step 5: Consideration of DBS and Other Surgical Measures

Although DBS was traditionally considered a last resort treatment for SD, we advocate for early consideration of DBS within 3 to 5 days of requiring intravenous infusions or once refractory SD is established. Before proceeding with DBS, it is important to conduct family and team meetings to provide counseling and build consensus. Relative exclusion criteria for DBS include young age, low weight, high risk for infection, medical instability, concerns regarding adequate follow-up, or unrealistic caregiver expectations. It is noteworthy that DBS is increasingly performed safely in young children, even as young as 2 to 3 years of age. In most cases, bilateral stimulation of the globus pallidus pars internus is the preferred target; however, subthalamic nucleus stimulation has been performed when globus pallidus pars internus stimulation is unsuccessful or not feasible because of anatomic restrictions.[31] We recommend a one-stage procedure for DBS implantation (implantation of brain electrodes and pulse generator in the same surgery) with stimulation initiated within 24 hours. Specific details regarding programming in this setting have been published recently.[31] Generally, this involves a monopolar review to ensure absence of adverse effects and then delivering double or single monopolar stimulation with the ventral contacts acting as the cathode, at set parameters of 60 μs for pulse width, 130 Hz frequency, and 2 mA or 2 V amplitude. Settings should be optimized every 1 to 3 days depending on the response. The effects of DBS may become evident within a few days, although the full benefit may take several weeks to manifest.[31] DBS has largely supplanted ablative procedures, such as pallidotomy or thalamotomy, for the treatment of refractory SD. If an intrathecal baclofen pump is already in place, bolus dosing or rate adjustments should be considered. If not, insertion of a spinal intrathecal baclofen pump or even intracerebroventricular baclofen therapy can be evaluated.[32] The decision to proceed to DBS versus intrathecal/intraventricular baclofen therapy is institution and patient dependent.

Educating and Empowering Multidisciplinary Teams

As part of the implementation of this guideline, our teams have employed educational outreach. Combined with the publication of the clinical pathways, this has anecdotally heightened awareness and increased confidence in management of dystonia in all care settings. We observed that the pathways enable clinicians to promptly recognize and initiate treatment without awaiting a neurology consultation, akin to what is established for other neurological emergencies, for example, status epilepticus.

Discussion

SD is a life-threatening movement disorder emergency. The condition is often first managed by pediatricians, emergency physicians, or intensive care providers who may have limited background in identifying and treating dystonia. Subsequently, these patients are cared for by many teams (neurologists, intensivists, movement disorder specialists, palliative care physicians, physical medicine and rehabilitation physicians, and

neurosurgical teams, as well as pharmacists, dieticians, physical/occupational/speech therapists, and social workers). To address a lack of systematic clinical recommendations and clear defining criteria for SD, we have proposed a stepwise approach to the assessment and treatment of worsening dystonia. We anticipate that this will standardize assessment/triage, provide guidance to the team looking after these patients, and improve outcomes.

The supportive therapies listed in our guideline expand prior publications.[7,8,18] Given that high-quality studies in the acute pharmacological management of pediatric dystonia are lacking, our guideline is based largely on expert consensus, previous literature/reported use, side effect profiles, and institutional factors. We recognize that this means that the pathway may require adjustment over time as evidence develops. In addition to making consensus recommendations for a general treatment approach, we also advise against other interventions that have been proposed previously, such as the use of haloperidol, dantrolene, or prolonged treatment with propofol. The interventions suggested in the pathway are generally familiar to pediatric providers and neurologists alike. We hope that, with appropriate education, families would be able to adopt some in the home setting (analogous to rescue medications for seizures). We acknowledge that not all the medications proposed in our pathway, and in the specific order, will work for all patients. There may be nuances in choice of medication depending on local availability and the goal of therapy. The medical team, patients, and families should therefore opt to create a personalized dystonia action plan over time (Supporting Information Data S4–S7).

As knowledge about various genetic forms of dystonia evolves, personalized therapies may move into focus. International collaborations will allow better tracking of the natural history of SD in these disorders, as well as their response to medications and DBS. For a growing list of monogenic hyperkinetic movement disorders with significant dystonia, including DYT-*TOR1A*,[33] DYT/CHOR-*GNAO1*,[34] or DYT-*KMT2B*,[11] we strongly recommend consideration of DBS early in the course of the disease. DBS should also be considered in any patient with refractory SD, regardless of the etiology.

The most striking limitation of our guideline is the scarcity of evidence in the field, which necessitated the reliance on expert consensus rather than evidence. We acknowledge that the proposed pathways assume a healthcare setting typical of large academic pediatric hospitals in North America. Although many suggestions and principles will be applicable to healthcare systems around the world, some may not. Accessibility to the recommended medications and DBS may pose a hurdle. In resource-limited settings, additional medications or interventions, such as carefully dosed phenobarbital or a pallidotomy, will have a different relative importance. The pathway offers room for customization to accommodate patient-specific needs and variations in resource availability.

Finally, the guideline primarily focuses on acute therapy, with limited guidance on transitioning to maintenance regimens and the specific strategies to employ during this phase. This omission is attributed to the highly individualized nature of such transitions, which depend on factors such as the patient's clinical condition, triggers (eg, infections), availability of enteral feeding and medications, prior and concurrent medications, medication interactions, and the distribution of dystonia. In the latter instance, adjunct therapies such as botulinum toxin injections should be considered. Given the lack of evidence in this domain, it is crucial to develop and assess outcome measures to track the impact of the proposed interventions. We hope this guideline will spark international, collaborative, prospective multicenter initiatives. Potential metrics to measure the pathway's effectiveness include the setting in which the pathway is used (usage in emergency department, ward, and ICU), initiation and supportive care measures on the first day of admission, effective tracking of sleep–wake dystonia diary by family and nursing staff, number of times the pathway is used and length of time between subsequent steps, peak creatine kinase level, length of hospital stay (divided into ward/ICU, respectively), admission to the ICU, need for intubation, need for intravenous sedative infusions, need for paralytic agents, time to completion of genetic testing, differences of effectiveness of the guideline based on the underlying etiology (patients with acquired cerebral palsy vs. inherited etiologies), number of cases referred for DBS, changes in baseline dystonia medications, and disease severity (resolution of SD vs. death, pre-SD baseline vs. post-SD severity using Burke-Fahn-Marsden Dystonia Rating Scale[35]). Alongside this, it will be important to document diagnoses, prior instances of SD, baseline medications, and whether the creation of an individualized dystonia action plan prevents recurrence of SD.

Conclusion

This review presents a comprehensive consensus approach to managing the challenging spectrum of pre-SD to refractory SD in children. Over the past two decades, SD has gained increasing recognition as a neurological emergency associated with significant morbidity and mortality. Recognizing the dearth of evidence in this domain, the proposed recommendations draw on expert consensus, emphasizing the importance of swift interventions and medications while minimizing side

effects. The overarching goal is to expedite the recognition and treatment of SD in children by enhancing the quality of care provided and establishing standardized terminology. Adopting a unified approach will facilitate multidisciplinary collaboration, ultimately contributing to evidence that can lead to improved care for children with SD.

Acknowledgments: We thank our colleagues of the Neurocritical Care Consult Service at Boston Children's Hospital for feedback, as well as those at SickKids who contributed to the development of the local pathway, including those from pediatrics (Dr. Shawna Silver, Dr. Catherine Diskin, Dr. Tanvi Agarwal, Kathleen Andres) and intensive care (Dr. Gail Annich). We also thank nurse practitioner Meena Kadiwal for providing a prior version for the dystonia action plan.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

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Supporting Data

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Author Roles

Conception and design of the study: C.G. and D.E.-F. Acquisition and analysis of data/feedback: L.M.V., Z.Z., G.T., K.Y., L.W., R.S., A.T., E.E., S.M., A.F., W.T.N., S.S., M.M., H.G., B.M., M.K., K.L.L., C.G., and D.E.-F. Drafting a significant portion of the manuscript or figures: L.M.V., K.Y., V.Q., C.G., and D.E.-F. Editing the manuscript: all authors.

Financial Disclosures

Darius Ebrahimi-Fakhari. Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: University of Texas Southwestern, German Center for Neurodegenerative Diseases, and Guidepoint LLC. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: Speaker honoraria from The Movement Disorders Society and the Taiwan Society of Child Neurology. Royalties: Cambridge University Press. Patents: US Patent No. 63/503,262, Compounds for treating hereditary spastic paraplegia. Grants: D.E.-F. has received research grants from National Institutes of Health, National Institute of Neurological Disorders and Stroke, CureAP4 Foundation, CureSPG50 Foundation, Spastic Paraplegia Foundation, Tom Wahlig Foundation, Un raggio di Sole per Martina, Manton Center for Orphan Disease Research, BCH Office of Faculty Development, and BCH Translational Research Program and Astellas Pharmaceuticals. Other: None. Elicia Estrella: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Alfonso Fasano: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: Honoraria/consultation fees from Abbott, Boston Scientific, Ipsen, Medtronic, and Merz. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: A.F. has received grants/research support from Boston Scientific, DMRF – Canada, and Medtronic. Other: None. Hernan Gonorazky: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Carolina Gorodetsky: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: Medtronic and Ipsen. Royalties: None. Patents: None. Grants: None. Other: None. Monica Kleinman: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Kerri L. LaRovere: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Shannon Manzi: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Brian McAlvin: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Mahendranath Moharir: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Weston T. Northam: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other:

None. Vicente Quiroz: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Rasha Srouji: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Scellig Stone: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Amy Tam: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Gabriel Tse: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Lindsey M. Vogt: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Laura Wang: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Kathryn Yang: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None. Zainab Zaman: Stock Ownership in medically-related fields: None. Intellectual Property Rights: None. Consultancies: None. Expert Testimony: None. Advisory Boards: None. Employment: None. Partnerships: None. Inventions: None. Contracts: None. Honoraria: None. Royalties: None. Patents: None. Grants: None. Other: None.