



Consensus statement on childhood neuropsychiatric presentations, with a focus on PANDAS/PANS

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Child and Adolescent Psychiatry Faculty of the Royal College of Psychiatrists



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Glossary

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| ADHD | Attention Deficit Hyperactivity Disorder |
| ASD | Autism Spectrum Disorder |
| BPNA | British Paediatric Neurology Association |
| CBIT | Comprehensive Behavioral Intervention for Tics |
| CBT | Cognitive behavioural therapy |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders |
| EEG | Electroencephalogram |
| ERP | Exposure and response prevention therapy |
| ESES | Electrical status epilepticus in sleep |
| ICD-11 | International Classification of Diseases |
| IVIG | Intra-venous immunoglobulin |
| MDT | Multi-disciplinary team - <i>clinical teams from other specialties and allied professionals, such as teachers and/or social services</i> |
| NICE | UK National Institute for Health and Care Excellence |
| OCD | Obsessive compulsive disorder |
| PANDAS | Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections |
| PANS | Paediatric Acute-onset Neuropsychiatric Syndrome |
| RCT | Randomised Controlled Trial |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| UK-CNID | UK-Childhood Neuro-Inflammatory Disorders special interest group - <i>this group's interest is in the acquired inflammatory brain disorders</i> |

1. Purpose

Over the last year or so our BPNA members have experienced increasing referrals for review of possible underlying neurological disorders among children with acute neuropsychiatric presentations. In particular, they have been asked whether children may have features for PANS/PANDAS syndrome.

The aim of this consensus statement is to provide a UK focussed document to support British Paediatric Neurology Association (BPNA) members to provide best evidenced care when reviewing a child with acute neuropsychiatric presentations, including suspected PANS/PANDAS.

The statement and its key-points have been developed by the BPNA. Members from a range of different backgrounds have contributed, including paediatric neurology consultants with experience in managing children with acute psychiatric presentations and suspected PANS/PANDAS, members of the UK-Childhood Neuro Inflammatory Disorders (UK-CNID) special interest group and experts in neuro-developmental conditions.

We are also very grateful for the collaboration and active contribution to the statement from Child and Adolescent Psychiatrists with experience in managing these children.

2. Introduction

The British Paediatric Neurology Association (BPNA) is the professional organisation for doctors, nurses and allied health professionals, who look after children with neurological disorders in the UK and Ireland. Members include paediatric neurology, paediatric neurodisability, neuropsychiatry staff and allied clinical teams.

The BPNA is aware there has been increasing interest around two potential paediatric neuropsychiatric conditions termed Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Paediatric Acute-onset Neuropsychiatric Syndrome (PANS).

BPNA members acknowledge the distress and concern that childhood neuropsychiatric conditions raise; they have seen how the onset of symptoms, such as tics, psychiatric symptoms and stereotypical behaviour can be rapid and life changing. Children with these problems are often referred to BPNA members, to consider the differential diagnosis and advice on specialist neurological investigations. Sometimes patients are referred to BPNA members while waiting for mental health or neurodevelopmental review. The referrer or family may ask the BPNA member if the child could have PANS or PANDAS.

This statement aims to provide a balanced view of the issues raised by families and referrers to enable BPNA members to provide an opinion, be part of the multidisciplinary management for the children (i.e. review by clinical teams from other specialties and allied professionals, such as teachers and/or social services) and stay within their area of professional competence. It has also been written to promote discussion around the issues relating to PANDAS and PANS with other relevant stakeholders.

We have written a consensus statement rather than a guideline on PANDAS/PANS because our review of the literature indicates there is limited class 1 evidence (i.e. robust data from randomised controlled trials) to be used as a basis for developing a guideline (as typically used by professional bodies such as the UK National Institute for Health and Care Excellence (NICE)).

Given the increasing referrals and interest in this area, the BPNA recommends that members discuss any potential clinical service implications raised in this consensus statement with their employing Trust.

3. Background

In 1998, a group of clinical researchers at the National Institutes of Mental Health in the USA, described a group of 50 children who presented with acute onset obsessive-compulsive disorder (OCD) and/or tic disorders in a temporal association with streptococcal infection (Swedo, et al, 1998; Snider, et al, 2002). The authors emphasised the episodic, relapsing/remitting nature of the condition, with acute and dramatic onset of symptoms and associated with infection. They proposed the term Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) for the group.

Based on the relapsing-remitting course, acute onset and link with infection the authors suggested PANDAS could have a pathogenesis similar to Sydenham's chorea; with antibodies raised in response to Group A β -haemolytic Streptococcus (GAS) infection cross reacting with auto-antigens in the brain's basal ganglia or cortical structures, in-turn, leading to the behavioural and motor manifestations (Swedo et al, 1989; Swedo at al, 1993; Swedo et al, 1998). The proposed pathogenesis implied broader treatment options could be considered, including prophylactic antibiotics to prevent recurrent infection and immune-modulatory treatments to dampen potential inflammation (triggered by the infection). To date, subsequent research has been unable to confirm causal infection (rather than coincidental infection) or an inflammatory or autoimmune pathogenesis. Recently, a large multi-country study reported no significant association between GAS infection and tic exacerbation. Although, the study focussed on children with chronic tic disorders (Martino et al, 2021). In addition, no consistent biomarkers have been identified that accurately diagnose PANDAS or are reliably associated with brain inflammation (Dale RC, 2017; Hesselmark E and Bejerot S, 2017).

In 2012, the same group developed a modified term: Paediatric Acute-onset Neuropsychiatric Syndrome (PANS) to describe children with abrupt and dramatic onset OCD or eating disorders in combination with multiple psychiatric or neurological symptoms (Swedo et al, 2012). In this syndrome, illness did not have to be associated with infection. The authors suggested the trigger could be multi-modal (genetic, metabolic, infection etc). The authors highlighted that PANS is a diagnosis of exclusion: one of the diagnostic criteria is to exclude all other potential known causes.

Within the current International Classification of Diseases (ICD-11), although PANDAS is mentioned, no operational clinical diagnostic criteria for either PANDAS or PANS are defined. PANDAS/PANS are not classified or mentioned in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders), the handbook used by health care professionals in the United States and much of the world as the guide to the diagnosis of mental disorders. The diagnostic criteria proposed by Swedo's group for PANDAS and PANS are presented below (Appendix A).

OCD is a relatively common disorder (1-3% of the general population). It is regarded as a chronic disorder with fluctuation of symptoms, although episodic courses are described. OCD displays a bimodal age of onset: the first peak is around 8-12 years, the second peak is in late adolescence. Early onset OCD is characterised by a higher rate of co-morbidities including tics or Tourette syndrome. It shows a male predominance (nearly 25% of males with OCD have an onset before

10-years), more severe symptoms, poorer response to typical pharmacological treatment, and a poorer prognosis compared to later onset or adult OCD (Orefici et al, 2016).

There are a few longitudinal studies comparing clinical features or clinical course of PANDAS (or PANS) to chronic OCD or tic disorders. Authors concluded clinical features between groups were overlapping. Frequency of acute symptom exacerbations were not statistically different between PANDAS and chronic OCD patients (Kurlan et al, 2008; Bernstein et al, 2010; Leckman et al, 2011; Murthy et al, 2012).

4. Evidence base for treatment of PANDAS/PANS

There are no guidelines about PANDAS or PANS written or endorsed by bodies such as the National Institute for Health and Care Excellence (NICE), NHS England (or the devolved nations), the Royal College of Paediatric and Child Health, the Royal College of Psychiatrists or the BPNA. Guidelines that are currently available were written by the United States PANS research consortium, involving Swedo's team and the Stanford PANS team, following a meeting at the National Institutes of Health in the USA in 2014: an overview was published in 2015 (Chang et al, 2015). Three separate documents were published as pragmatic guidelines in 2017 which give an overview of psychiatric and behavioural interventions, discuss the potential use of immunomodulatory therapies and treatment of infections (Thienemann et al, 2017; Frankovitch et al, 2017; Cooperstock et al, 2017). Many recommendations in the guidelines amount to completing a high-standard neurological history and examination. The guidelines state that all treatments have risks and should constantly be evaluated; and that children should be managed by a multi-disciplinary team.

Links to the Stanford PANS website and related sites are available through the PANDAS/PANS UK charity website. When interest started to increase in the UK in 2018, a treatment guideline was drafted by a group: the UK PANDAS and PANS Physicians Network. This guideline was developed independently of the BPNA. To our knowledge, the guideline was not peer reviewed. The document was temporarily available via the PANDAS/PANS UK charity website and a private paediatric healthcare platform (e-hospital).

There is an evidence base for the treatment of obsessions, compulsions and tics, features associated with PANDAS and PANS. NICE has published treatment guidelines for OCD in children (over 8-years of age) and young people in the UK (NICE Clinical Guidance CG31). They recommend cognitive behaviour therapy (CBT), including exposure and response prevention (ERP) therapy. The guidelines also recommend medication, typically selective serotonin reuptake inhibitors (SSRIs), to be added or as an alternative to CBT. SSRI use is supported by randomised control trials (RCTs) demonstrating benefit over placebo among children and adults in reducing OCD symptoms. The seminal Paediatric OCD treatment study recruited a broad range of children with OCD, including early onset cases. Children experienced a significant reduction in OCD symptoms when receiving CBT alone, SSRI (sertraline) alone and a more significant reduction when receiving both compared to placebo (Paediatric OCD Treatment Study team, JAMA 2004). A recent longitudinal study of CBT again showed benefit for over 70% of paediatric OCD sufferers (Højgaard et al, 2017). We note the diagnosis and management of OCD in children and young people would typically be undertaken by CAMHS clinicians. Treatment of OCD would be outside the expertise of Paediatric Neurologists, but may occur in partnership with child and adolescent psychiatrists and other CAMHS clinicians for relevant cases. Decisions on treatment should follow NICE guidelines and be undertaken by CAMHS services

Two trials of CBT among PANDAS and PANS patients have also demonstrated significant reduction in OCD symptoms. Response rates to CBT were comparable to paediatric OCD. However, the studies were not RCTs and involved small patient numbers (Storch et al, 2006; Nadeau et al,

2015). There has been one self-reported (or parental) survey of CBT among PANDAS/PANS patients. Among those currently receiving CBT, the majority (73%) reported it as some-what or very effective (Calaprice et al, 2017). There have been no systematic studies of SSRIs specifically in PANDAS or PANS patients.

Although tics are a frequent symptom in PANDAS and PANS (occurring in 70% of cases) there are no published studies looking at behavioural or pharmacological treatment targeting tic reduction among these patients. However, there is an evidence base for treating tics. Comprehensive Behavioral Intervention for Tics (CBIT), including Habit Reversal Training, is recommended as a first-line intervention for youths with chronic tics. In a recent RCT, CBIT showed superiority to supportive treatment in both children (age 9-years upwards) and adults (Sukhodolsky et al, 2017). In the broader group of paediatric Tourette syndrome or chronic tic disorders, pragmatic guidelines recommend alpha-2 adrenergic agonists (e.g. clonidine or guanfacine) as first-line and antipsychotics (e.g. risperidone or aripiprazole) as second-line medications (Roessner et al, 2011; Murphy et al, 2013; Pringsheim T et al, 2019). A meta-analysis of RCTs for paediatric tic disorder treatment demonstrated a medium effect size for antipsychotics (including risperidone) over placebo and a modest effect size for alpha-2 adrenergic agonists (including clonidine or guanfacine) over placebo. The latter effect was better when patients with attention deficit hyperactivity disorder (ADHD), a co-morbidity which frequently occurs with tics, were included (Weisman H et al, 2013). These behavioural and pharmacological treatments are also discussed and recommended by the USA PANS research consortium (Thienemann et al, 2017).

Paediatric Neurologists do see children with tics and may be involved in their treatment. Where significant co-morbidities, like ADHD or OCD are present, management may occur jointly with CAMHS clinicians or be fully managed by a multidisciplinary CAMHS team.

A recent systematic review examined a range of treatments among PANDAS or PANS patients (abstracts, n=1087; published articles, n=162; Sigra et al, 2018), including CBT, SSRIs, antibiotics (penicillin, azithromycin), Non-Steroidal Anti-inflammatory Drugs, corticosteroids, intra-venous immunoglobulin (IVIG), plasma exchange and tonsillectomy.

Only four randomised control trials were identified (where patients were randomised to receive either the study treatment or placebo in a double blinded manner (where neither patient nor clinician knew which). Among the two trials comparing IVIG against placebo, one showed a statistical reduction in neuropsychiatric symptoms following IVIG treatment (n=9 patients treated) and the other did not (n=17 treated; Perlmutter et al, 1999 and Williams et al, 2016). Among two trials comparing azithromycin against placebo, again one showed a statistical reduction in OCD symptoms and other did not (Murthy et al, 2017 and Snider et al, 2005). All four trials enrolled small numbers of patients. In the study by Perlmutter and colleagues, they also compared plasma exchange to IVIG and placebo. However, patients did not receive the exchange in a blinded manner. In addition, some study patients received additional medication off-protocol. The methodological flaws and low patient numbers made interpretation of the 'true' effect of treatment challenging. The review authors concluded rigorously conducted research was scarce,

and most published studies had a high risk of bias. They recommended further well-designed trials were conducted.

Based on our review of the literature and published reviews (such as those above) the BPNA acknowledges that the entities currently known as PANDAS and PANS require further work regarding validity of diagnostic criteria and that treatment lacks strong evidence. Consequently, the BPNA supports further robust research being undertaken in this area to enable evidence based management to be formulated.

In contrast, component symptoms of PANS/PANDAS have an evidence-base for treatment.

5. Advice for BPNA members

Children referred to BPNA members for suspected PANS or PANDAS are likely to have multiple problems and/or co-morbidities (e.g. OCD, tics, ADHD, autism spectrum disorder (ASD) or other neurodevelopmental and/or psychiatric [including functional] disorders). They will need assessment by several specialist teams, such as Child & Adolescent Mental Health Services (CAMHS), Community Paediatrics, and other relevant therapists (e.g. psychologists, speech and language and/or occupational therapists).

Where questions remain, children and young adults with complex neuropsychiatric or developmental disorders should have access to a joint review between neurology, mental health and/or neurodevelopmental teams to make appropriate onward plans.

Ideally, care should be in a multidisciplinary setting and children should be managed in a team. Feedback from CAMHS colleagues report improved patient engagement and management effectiveness during joint working. We are also aware that children with suspected PANS or PANDAS also get referred through other paediatric specialities, such as general and community paediatrics, infectious disease, immunology and rheumatology, so liaison with these colleagues may also be required.

Where this is not possible, BPNA members should work in close liaison with speciality colleagues. However, the BPNA appreciates there can be significant challenges in access and timely integration with relevant specialities (see below). As neurologists we must weigh up carefully the benefits versus risks of treatments. We have to be very careful to stay within all areas of professional expertise, most importantly, akin to all clinicians, our main objective is “first do no harm”.

A key role of a neurologist is to assess for neurological conditions which can be associated with acute neuropsychiatric features, such as infectious encephalitis, autoimmune encephalitis, acute disseminated encephalomyelitis, neuropsychiatric systemic lupus, cerebral vasculitis, epileptic sleep disorders (such as electrical status epilepticus in sleep (ESES) or Wilson’s disease (Thienemann et al, 2017). Some of these conditions can be associated with acute (usually within two weeks) impairment of awareness or a regression in development or cognition (i.e. symptoms beyond acute onset or acute exacerbation of obsessions, compulsions or tics). Other indications for neurological review include the development of psychiatric features as part of a condition with a documented regression of skills (to exclude rare neuro-metabolic or genetic conditions), the presence of focal neurological signs or abnormalities on cranial imaging. Neurologists may also support recognition of neuropsychiatric and/or neuro-developmental conditions, such as Tourette’s syndrome, OCD and autism. Although, the formal diagnoses of the latter conditions should be made by CAMHS or neuro-developmental services.

The need for neurological investigation (e.g. imaging, lumbar puncture, EEG) will depend on individual case circumstances. In the absence of focal neurological signs or symptoms, there is no evidence that specialised investigations are required (Chang et al, 2017). The neurologists’ role should be to discuss and refer for appropriate evidence based treatments, as well as support

discussion around why some forms of treatment (including antibiotics, non-steroidal anti-inflammatory drugs, or immunomodulatory treatments such as IVIG) are not recommended when the evidence for infection or an immune mechanism is lacking. Feedback from CAMHS clinicians indicate such explanation can help engagement with other evidenced based treatments (see above).

Other aims of the multi-disciplinary team review include defining the mental health domains impacted, the degree of functional impairment and any safeguarding issues. For example, many children with tics have mild functional impairment due to the tics, but often have associated features such as low self-esteem, and adverse effects on friendships which significantly impact on their own and their family's wellbeing. Education about the conditions remains a major part of the clinicians' role. Working as a multi-disciplinary team ensures a child-centred approach; information from all settings (including education and social care) are sought and shared, reducing the risk of over or recurrent investigations or conflicting advice leading to a risk of physician or anxiety induced illness.

Prescribing and monitoring medications for specific mental health conditions observed in children presenting with possible PANDAS/PANS, such as OCD, anxiety, depression, ADHD and tics should be undertaken by Child and Adolescent Psychiatrists. There should be clear agreements of what improvement is to be expected over a set time-frame ahead of any treatment (and consider multiple informants and observers including education professionals). Where possible patient improvement should be monitored using standardised questionnaires of symptoms/signs (such as the Children's Yale-Brown Obsessive-Compulsive Scale). There should be clear discussion with the family and involving all team members on the risks/side effects of treatments, against possible benefit.

The BPNA does not recommend treatment with antibiotics or immune modulatory treatments (such as steroids or Intra-venous immunoglobulin) for suspected PANS/PANDAS cases. In exceptional cases where children require in-patient hospital admission due to acute deterioration in behaviour/cognition or repeated in-patient admission due to recurrent acute deterioration in behaviour/cognition not responding to the interventions described above (despite adherence), we recommend discussion about further treatment options with colleagues at a regional or national level (such as members of the BPNA UK-CNID specialist interest group or specialists with experience of diagnosing and managing mental disorders in tertiary child and adolescent mental health or neurodevelopmental services).

Furthermore, in support of care for children where immune-modulatory treatment is ongoing, but the treating clinician has changed, we recommend discussion with the family, ideally in a multidisciplinary setting, to agree forward management.

Given the increasing referrals and interest in this area, the BPNA recommends that members discuss the issues raised in this consensus document with their employing Trust to establish a local agreed management pathway for children referred with suspected PANDAS/PANS to make sure that children are assessed and managed by the appropriate multidisciplinary team. The

BPNA envisage this consensus statement as a stimulus to discuss issues related to the care of suspected PANS and PANDAS cases, such as appropriate and timely access to multi-disciplinary care, with stakeholders. The BPNA is committed to working in partnership with patient and family representatives, as well as other relevant professional organisations, to realise these ambitions.

6. Summary

The BPNA is aware of increased referrals to neurologists for children who have been identified as possible PANDAS and PANS cases. Since the original description of these subtypes of OCD, tic and other neuropsychiatric disorders (1998 and 2012 respectively), there has been no clear evidence these conditions have a definite immune basis. Studies have shown a clinical overlap with paediatric OCD and tic disorders, with reports indicating over two thirds of PANDAS and PANS children show a reasonable response to conventional mental health interventions for these conditions, including behavioural therapy. Even if the clinical history suggests that mental health symptoms emerged following infection, there is insufficient evidence to conclude treatments targeting inflammation or immune-modulation are effective. Such treatments have been associated with immuno-compromise and other side-effects. Their provision may also risk diverting the focus away from effective symptom-directed treatment. As with managing all challenging neurology cases, members are encouraged to discuss severely affected children with colleagues at a local, regional or national level.

BPNA members should make sure the child and family have access to an appropriate multi-disciplinary team, with specialists that manage children with mental health, neuro-developmental or movement disorders where needed, so that the impairing symptoms can be identified and defined and then known, effective treatments can be accessed and trialled. The BPNA will continue to support partnerships with relevant professional organisations to help develop integrated services for children with complex neuro-psychiatric problems.

7. Key Points

1. The BPNA sees a key role of a paediatric neurologist in suspected PANDAS/PANS children is to assess for underlying neurological conditions which can be associated with acute neuropsychiatric features (such as infectious encephalitis, autoimmune encephalitis, acute disseminated encephalomyelitis, neuropsychiatric systemic lupus, cerebral vasculitis or epileptic disorders).
2. Aligning with our charitable aims, the BPNA strongly promotes robust research being undertaken about acute psychiatric presentations to neurological services, such as suspected PANDAS / PANS. We would welcome review by NIHR and/or NICE to support this process and enable evidence based management to be formulated.
3. The BPNA recommends suspected PANDAS/PANS children should have access to a joint review between neurology, mental health and/or other appropriate teams. Where possible, the child should be seen in a multi-disciplinary setting and managed through a team. Partnership with mental health clinicians including Child and Adolescent Psychiatrists will support psychiatric symptom diagnosis, access to established effective behavioural and pharmacological treatments.
4. Prescribing and monitoring medications for specific psychiatric symptoms, observed in children presenting with possible PANDAS/PANS, such as OCD, anxiety, depression, and tics should be undertaken by Child and Adolescent Psychiatrists.
5. In the absence of adequate scientific evidence confirming benefits outweigh the risks, the BPNA does not currently recommend treatment of acute psychiatric disorders with antibiotics, non-steroidal anti-inflammatory drugs or immune modulatory treatments (such as steroids or intra-venous immunoglobulin (IVIG)) for suspected PANS/PANDAS cases, but strongly supports further research.
6. The BPNA recommends that members discuss the issues raised with their employing Trust and both local / tertiary CAMHS services, to establish a local management pathway for children referred with acute psychiatric disorders, including suspected PANDAS/PANS, to make sure that children are assessed and managed by an expert multidisciplinary team, with evidence-based treatments, in a timely fashion.
7. The BPNA strongly supports equity of access for expert opinions and therapies in a timely fashion for all communities across the UK.

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9. Resources

PANS PANDAS UK charity - www.panspandasuk.org

Provides links to the PANS consensus statement publications in the Journal of Child and Adolescent Psychopharmacology 2017.

Stanford PANS clinic USA – www.med.stanford.edu/pans

Accepts patients into research projects from other paediatricians. Lots of information on the website and links to the following:

www.nimh.nih.gov – Q&A's for families; PANDAS leaflet for families

PANDAS Physician Network (PPN) USA - www.pandasppn.org

Organisation for medical professionals. Host the PPN Guidelines for Diagnostics and Therapeutics developed by PPN committees.

Tourette's Action

<https://www.tourettes-action.org.uk/146-online-support-groups.html>

OCD Action

<https://ocdaction.org.uk/>

OCD-UK

<https://www.ocduk.org/support-groups/>

10. Appendix

| Diagnostic criteria for PANDAS and PANS (Swedo et al 1998; Swedo et al 2012) |
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| <p>Guidelines for diagnosing PANDAS include:</p> <ol style="list-style-type: none">1. Presence of OCD and/or tics, particularly multiple, complex or unusual tics2. Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)3. Acute onset and episodic (relapsing-remitting) course4. Association with Group A Streptococcal (GAS) infection5. Association with Neurological Abnormalities (motor hyperactivity/adventitious movements including chorea) |
| <p>Guidelines for diagnosing PANS; patients must have the following:</p> <ol style="list-style-type: none">1. An abrupt, acute, dramatic onset of obsessive-compulsive disorder or severely restricted food intake2. Concurrent presence of additional neuropsychiatric symptoms with similarly severe and acute onset from at least 2 of the following categories:<ul style="list-style-type: none">· Anxiety· Emotional Lability and/or Depression· Irritability, Aggression, and/or Severe Oppositional Behaviors· Behavioral (Developmental) Regression· Sudden Deterioration in School Performance· Motor or Sensory Abnormalities· Somatic Signs and Symptoms, including Sleep Disturbances, Enuresis, or Urinary Frequency3. Symptoms are not better explained by a known neurologic or medical disorder4. Age requirement – None |