NeoNATE
Neonatal Neurology

# Pre-course Activities & Reading

BPNA
British Paediatric Neurology Association

# Contents



*** Please read before workshops at the NeoNATE course**

## Appendices

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Paper 2: Murray DM et al. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed*. 2008; 93: F187-F191

Paper 3: Uria-Avellanal C et al. Outcome following neonatal seizures. *Seminars in Fetal & Neonatal Medicine*. 2013; 18(4): 224-232

Paper 4: van Rooij LG et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomised, controlled trial. *Pediatrics*. 2010; 125: e358-66

Paper 5: Connolly D, Hart AR. The Basics of MRI.

Paper 6: de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 2010; 95: F220-F224

## 1. Introduction

Thank you for booking your place on the NeoNATE (Neonatal Neurology Assessment Treatment Education) course. We hope the course will be thought-provoking and will help improve the care given to neonates with neurological problems.

We have included some pre-course material in this pack. This work includes some articles or other reading, followed by some questions or activities to help keep your interest and improve your learning.

You may feel you don't need to do every part of the pre-course material. That's fine! The NeoNATE course is for neonatologist, neurologists, advanced neonatal nurse practitioners, allied health professionals, and all of those training in the above. Some sections will be too basic for you. The purpose of the reading is to make sure everyone has the basic knowledge at the start of the course, so we can then discuss things in more depth on the day.

Please pick and choose the sections that will be helpful. Ignore those that are too basic.

The parts of the pre-course material that relate directly to the workshops are marked with a "*". Please look at these sections to help the course run smoothly. These are essential.

The NeoNATE course is designed to relate directly to the BPNA Paediatric Neurology Distance Learning course: Unit 2 Neonatal Neurology. We can't possibly give you all the information you need in two days - it's an enormous topic! If you do want to learn more, feel free to ask us about this unit.

We hope you enjoy the course and appreciate any feedback you may have.

## 2. What is an epileptic seizure?

### 2.1 Introduction

This section will introduce you to the basics of what epileptic seizures are, what epilepsy is and some of the terminology used.

### 2.2 Learning objectives

By the end of this section, you will understand:

- What a seizure is
- What an epileptic seizure is
- What acute symptomatic seizures are and how they differ from epilepsy
- The ILAE classification system for epilepsy
- That challenges of epileptic seizure recognition in neonatal epilepsy
- Which movements are likely to be epileptic and which may or may not be.
- The basic physiology of neonatal epileptic seizures
- How common anti-epileptic drugs work
- The long term outcome following neonatal epileptic seizures
- Be able to weigh up the pros and cons of treating neonatal epileptic seizures
- Why it is important to think about vitamin therapies

### 2.3 Terminology – the good, the bad and the ugly

In neurology circles, terminology is used precisely. Unhelpful, old-fashioned terms have become obsolete.

Outside of this setting, the terminology is used confusingly.

Terms like convulsions, fit, grand mal, petit mal are all obsolete. They should not be used by clinicians.

A *"seizure"* is

Any sudden attack from whatever cause. Thus, an apnoea, a headache, or a stroke may be "seizures" in a strict sense of the word.

*An epileptic seizures is*

A seizure that arises because of paroxysmal, excessive synchronous firing of neurones

The crucial difference is that an epileptic seizure has occurred as a direct consequence of epileptic activity within the brain.

Many events are seen in neonates that are not epileptic seizures, including some in neonates who have brain injury. Examples include:

- Tonic stiffening in children with HIE due to brainstem release
- Stiffening due to hypoxia
- Stiffening due to gastro-oesophageal reflux disease
- Benign neonatal sleep myoclonus

The outward manifestation of epileptic and non-epileptic seizures may be identical, particularly in neonates. What is important in determining whether these events are epileptic or not is the mechanism giving rise to them.

**Key point:** Not everything that jerks, shakes and wobbles is an epileptic fit!

If everything that jerked and shook was an epileptic seizure, there are many neurologists who would need diazepam as soon as they took to a dance floor!

*Epilepsy*

is recurrent, unprovoked epileptic seizures

*Provoked epileptic seizures*

(often called acute symptomatic seizures) have a cause such as hypoglycaemia, HIE, or electrolyte imbalance. If the underlying cause is treated the seizures go away.

*Activity 1:*

This section will help determine whether different movements or clinical features are epileptic seizures or not.

The chart below has some common terminology used in neurology. Have a go at defining what the words mean. Use the back of the previous page to scribble your ideas. Then think whether it is usually, sometimes or rarely epileptic. We will come back to this later.

| ***Terminology*** | | ***Is it epileptic…?*** | | |
|---|---|---|---|---|
| | | **Usually** | **Sometimes** | **Rarely** |
| Jerking | Myoclonus | | | |
| | Clonic jerking | | | |
| | Clonus | | | |
| | Tremor | | | |
| | Jitteriness | | | |
| Stiffening | Generalised tonic episodes | | | |
| | Focal tonic episodes | | | |
| | Dystonia | | | |
| | Spasticity | | | |
| | Rigidity | | | |
| | Contracture | | | |
| | Epileptic spasm | | | |
| Other | Startles | | | |
| | Pedalling / cycling | | | |
| | Thrashing | | | |
| | Boxing / swimming | | | |
| | Nystagmus | | | |
| | Eye rolling | | | |
| | Lip smacking | | | |
| | Tongue thrusting | | | |

## *Commentary 1:*

Here are some definitions for you.

**Jerking:**

***Myoclonus*** is "repeated, often non-rhythmical, brief shock-like jerks caused by sudden, involuntary contraction or relaxation of one or more muscles." Myoclonus looks like extremely fast jerks, each lasting around 100 microseconds or less, often affecting the limbs. They can be single or multiple jerks affecting different parts of the body in sequence (ie, sometimes the arms, then the legs, or multiple limbs at once). When they occur in clusters, they lack the repetitive rhythmical nature of clonic seizures.

***Clonic seizures*** are repetitive, large amplitude, rhythmical jerks of the limbs, face or axial muscles. They can be focal, multifocal or hemiconvulsive. The frequency of jerks is around 1-3 per second, and slows towards the end of a seizure.

Clonus involves involuntary muscle contractions and relaxations in the muscles around a joint owing to brain or spinal cord injury above the level of the contracting muscle. It can be stopped by a change in the position / posture of a joint.

***Tremor*** is an involuntary generalised movement that is rhythmical, oscillating around a fixed axis. It is caused by alternating contractions of agonist and antagonist muscles.

***Jitteriness*** is recurrent tremor, which can be reduced by tactile stimuli, holding, or flexing the affected body part. It does not affect the face, nor is it associated with eye deviation or autonomic / cardio-respiratory changes.

**Stiffenings:**

***Tonic*** episodes involve stiffening of the muscles for more than a few seconds. It can be focal (one or a few parts of the body, including the extraocular muscles leading to eye deviation) or generalised (all limbs and axial muscles).

***Dystonia*** is a movement disorder in which sustained or intermittent, involuntary contraction of muscles leads to abnormal postures, twisting or repetitive movements. Classically, movement disorders like dystonia resolve during sleep.

***Spasticity*** is a velocity dependent increase in tone, often with the feeling of a catch. Good range of movement can be found with slow passive movements, but rapid movements yield a sudden increase in tone.

***Rigidity*** involves stiffness / resistance in a joint during fast and slow passive movement that is not related to the angle of the joint. It is a result of contraction of agonist and antagonist muscles, and is seen when the direction of movement is changed suddenly. Unlike dystonia, the limbs do not return to odd postures when passive movement has stopped. Movement in distal muscles doesn't affect the rigid joint posture.

***Contracture*** a joint that cannot be moved fully because of a structural joint abnormality or wasted / shortened muscles, most likely from lack of use and movement.

***Epileptic spasms*** (previously called infantile spasms) involve contraction of the axial and proximal muscles. Each one lasts around a second - they are shorter than tonic seizures but longer than clonic or myoclonic jerks. In the sitting position, you may see flexion of the neck, trunk, shoulders, elbows, hips and knees. In the lying position, one mother described it to us as if her baby was attempting bench presses or sit-ups. Sometimes the neck extends rather than flexes. The terminology Salaam attack is no longer recommended.

**Other movements:**

***Startles*** are jumps, jerks, Morro reflexes or apnoea that are brought on by a stimulus, such as a loud noise or being touched when not expected.

***Pedalling / cycling –*** a rhythmical, cyclical movement of the legs that looks like a person riding a bicycle.

***Thrashing*** – semi-purposeful looking movements of arms and legs, sometimes with the head moving from side to side, of large amplitude and often long lasting. They lack the rhythmical nature of many types of epileptic jerks, like clonic seizures.

***Swimming / boxing –*** pedalling but involving the upper limbs. In boxing, extension of the arms at the shoulders and elbows may be seen as if trying to punch an opponent. Swimming may involve the upper and lower limbs.

**Nystagmus –** rapid jerky involuntary movements of the eye, often with a slow and a fast phase. May be horizontal or vertical.

**Eye rolling** – different from nystagmus in the quality of movement, but slower movement of the eyes often in an arc that do not become “stuck in one place” because of tonic stiffening of the extraocular muscles.

***Lip smacking*** – rubbing the lips together or licking the lips as if removing sugar after eating a doughnut!

***Tongue thrusting –*** sticking the tongue out forcefully. This should be distinguished from tonic tongue movements in which the movement is relatively quick and rhythmical.

***We will look at whether they are epileptic or not in the next section.***

## 2.4 Diagnosing epileptic seizures

*Activity 2:*

| | |
|---|---|
| | We are going to look at EEG studies into which movements are epileptic or non-epileptic.<br><br>Please read Paper 1: Mizrahi EM. Clinical and neurophysiologic correlates of neonatal seizures (provided at the end of this activity book) and then answer the following questions. |
| 1) | In the introduction on Page 1, reference is made to Volpe's classification of neonatal seizures. What are the categories used? |
| | |
| 2) | In Mizrahi's previous study, what proportion of "clinical seizures" had no EEG so were not epileptic? What proportion of seizures on EEG had no clinical signs? |
| | |

| 3) List the movements that were epileptic and non-epileptic in Mizrahi's studies. | |
|---|---|
| **Epileptic** | **Non-epileptic** |
| | |

*Commentary 2:*

Volpe's classification for the paper (and the 5th edition of his textbook) suggest the following are seizures:

- Clonic
  - Focal
  - Multifocal
- Tonic
  - Focal
  - Multifocal
- Myoclonic
  - Focal
  - Multifocal
  - Generalised
- Subtle
  - Eyes (tonic horizontal deviation of eyes with or without jerking), sustained ocular opening with fixation
  - Oro-buccal-lingual (chewing)
  - Other (limb movements - pedalling, stepping, thrashing arms boxing, apnoea, autonomic features)

Mizrahi showed that many of these, particularly subtle seizures, were not associated with EEG changes and were unlikely to be epileptic. Instead, he felt they were more likely to be brainstem release phenomena.

Interestingly, 60% of clinical seizures were not associated with EEG change. Over-diagnosis can occur! Only 5% were seizures on EEG without clinical features.

Here's a summary of what is likely and not likely to be epileptic seizures:

**The movements that are frequently epileptic seizures include:**

- Generalised myoclonic jerks
- Myoclonic jerks of the diaphragm leading to frequent hiccups
- Clonic jerking of the limbs that does not improve with holding or moving the affected joint, particularly if associated with autonomic features and tonic eye deviation
- Rhythmical clonic thrusting of the tongue, especially is associated with other clonic movements of the limbs and / or tonic eye deviation
- Focal tonic seizures, especially if associated with eye deviation
- Tonic eye deviation without limb involvement when associated with autonomic features, often occurring after rapid eyelid fluttering
- Epileptic spasms
- Electrical epileptic seizures on EEG without clinical features

**Movements that should not be assumed to be epileptic seizures or treated without further investigation include:**

- Cycling
- Pedalling
- Swimming
- Thrashing of limbs
- Movement of head from side to side
- Sucking
- Lip puckering
- Grimacing
- Tongue protrusion
- Blinking without tonic eye deviation
- Roving eye movements
- Nystagmus
- Generalised tonic stiffening

**Movements that are not likely to be epileptic seizures include:**

- Tremor / jitteriness
- Clonus
- Myoclonus only seen in sleep
- Dystonia
- Startle with or without tonic stiffening (hyperekplexia)

***Compare your answers to Activity 1 to the summary above.***

*Activity 3:*

| | |
|---|---|
| | This activity will help you understand the scale of the problem with diagnosing and misdiagnosing epileptic seizures in neonates.<br><br>Read Paper 2: Deidre Murray's paper from 2008 entitled: Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures (provided at the end the end of this document).<br><br>Now answer these questions: |
| 1) | Of the 526 epileptic seizures caught on EEG, what proportion had clinical features on video? |
| 2) | 177 clinical events were noted by doctors and nurses and were thought to be epileptic seizures. What proportion had an EEG change? |
| 3) | What proportion of events thought to be clinical epileptic seizures had no EEG change? |
| 4) | Out of the total 526 epileptic seizures on EEG what proportion were correctly diagnosed by clinicians and nurses? |
| 5) | What are your thoughts on this data? |

## *Commentary 3:*

The answers are as follows:

1) Of the 526 epileptic seizures caught on EEG, only 179 (34%) had clinical features. The rest were electrographic only. This is a massive proportion, and much higher than in Mizrahi's study. Therefore, most of the time we are unaware a neonate is having epileptic seizures.

2) Of the 177 events that were thought to be epileptic seizures by neonatal staff, only 48 (27.1%) had EEG change. Over diagnosis is rife in our neonatal units!

3) Therefore, just to reinforce the point, 72.9% of events suspected (and possibly treated as epileptic seizures) were not.

4) Only 9% of all the captured neonatal seizures were correctly diagnosed

The statistics are startling. Most epileptic seizures do not have any clinical correlate and are likely to be missed. Most of what we treat as epileptic seizures are not epileptic. Most of the clinical events that we could detect are missed.

Education on what is and what is not likely to be an epileptic seizure is important (hence the course) but our diagnosis rate is still likely to be low.

24 hour EEG is not feasible in neonatal units – it's too expensive and the neurophysiology expertise and support is not available for such a massive task.

aEEG (cerebral function monitoring) is imperfect at detecting epileptic seizures.

If in doubt – ask for an EEG.

## 2.5 Treating neonatal epileptic seizures*

Think about your neonatal unit. What is the protocol for treating epileptic seizures? Most units still start with phenobarbitone. What they do afterwards differs. There are few studies directly comparing the effectiveness of these drugs in neonatal seizures. The evidence is poor.

One study[1] has shown that phenobarbital as a first line drug successfully treats 43% of neonatal seizures. Phenytoin first line treatment stops 45% of neonatal seizures. If they are both given in a neonate, the success rate is 57%. This is pretty poor!

Part of the reason for the drugs being ineffective in neonatal epileptic seizures relates to the unique neurophysiology of neonatal seizures and the mechanism of action of the drugs. We will study that next.

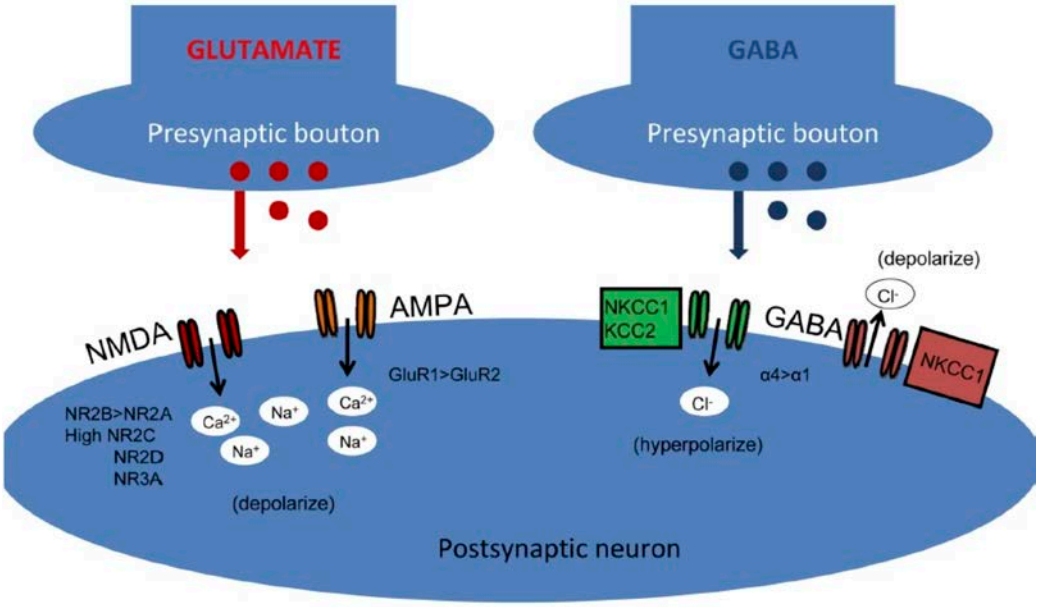
Here is a basic summary of why the neonatal brain is hyperexcitable and more likely to have epileptic seizures.

There are different types of neurones in the brain using different neurotransmitters. In the mature brain:

- Glutamate neurones are excitatory
- GABA neurones are inhibitory

[1] Painter MJ et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *New England Journal of Medicine*. 1999; 341(7): 485-9

Look at this diagram *(from Jensen 2009)*.




The neonatal brain has more excitatory glutamate neurones than at any other time of life. These work via NMDA and AMPA receptors.

It also has more synapses and the dendritic density is higher than in a more mature brain. This makes it more excitable.

GABA neurones are usually inhibitory in the mature brain, ie they reduce the likelihood of epileptic seizures. In the neonate, though, they are also excitatory. There are a number of reasons for this:

*Mature brain*

- In the mature brain the concentration of Cl within the postsynaptic neurone is relatively low
- The balance and movement of Cl occurs through channels. The NKCC1 channel moves Na, K and Cl into the neurone. KCC2 channel helps Cl move out of the neurone
- When GABA is released, Cl moves into the neurone where its concentration is low
- The movement of Cl into the neurone hyperpolarises it
- A hyperpolarised neurone is less likely to generate an action potential and “fire”. GABA is inhibitory

*Neonatal brain*

- The channels than manage the movement of Na, K and Cl in the brain are immature
- There are relatively high numbers of NKCC1 channels. These allow the movement of Na, K and Cl into the post synaptic neurone
- The KCC2 channel is immature or absent
- Cl therefore accumulates in the post synaptic neurone, ie the concentration is higher inside the neurone than outside
- When GABA is released the Cl moves out of the cells to where its concentration is less
- The post synaptic neurones becomes more excitable
- GABA becomes excitatory

This is all very simplistic. There is more data in the neonatal neurology unit of the BPNA Distance Learning Course, or you could read the following articles:

**Useful References**:

Glass H. Neonatal Seizures – advances in mechanisms and management. Clin Perinatol. 2014; 41: 177-90

Nardou R et al. Mechanisms and effects of seizures in the immature brain. Semin Fetal Neonatal Med. 2013; 18 (4): 175-84.

## *Activity 4:*

| Summarise the main points that you have just learned below. |
|---|

*Activity 5:*

Below is a list of anti epileptic drugs. Can you document the main ways these drugs exert their anti-epileptic effect? (Wikipedia is a useful resource)

| Drug | Mechanism of action |
|---|---|
| Diazepam | |
| Phenobarbitone | |
| Phenytoin | |
| Lidocaine | *Very hard to find – don't spend hours looking!* |
| Levetiracetam | |
| Sodium Valproate | |
| Topiramate | |
| Midazolam | |

*Commentary 5:*

| Drug | Mechanism of action |
|---|---|
| Diazepam | Binds to GABAa receptors to increase inhibitory effect of GABA |
| Phenobarbitone | Binds to GABA receptors to prolong the opening of channels and thus GABA effect |
| Phenytoin | Binds to sodium channels, allows sodium to flow out of the post synaptic membrane. Reduces possibility of action potentials forming |
| Lidocaine | Bind to Na channels |
| Levetiracetam | Unknown, binds to synaptic vesicle glycoprotein SV2A, inhibits presynaptic ca channels |
| Sodium Valproate | Blocks sodium channels, weak blocker of enzymes that deactivate GABA |
| Topiramate | Voltage gated Na channels blocker<br>AMPA and kainite receptor blocker<br>Blocks calcium channels<br>GABA receptor – enhances Cl channels<br>Carbonic anhydrase inhibitor |
| Midazolam | Binds to GABAa receptors to increase inhibitory effect of GABA |

When you understand how the drugs work, it becomes clear why they are ineffective in neonatal seizures.

Topiramate has the potential to be useful. But at the time of writing an IV drug is not available for clinical use. One is in development.

Drugs that affect the NMDA receptor include Nitric Oxide and Xenon, both of which have been noted to stop neonatal seizures. But other NMDA blockers have proved neurotoxic in animal studies.

Perampanel is a new drug that works on the AMPA receptor and is licensed for focal seizure control as an add-on drug in older children and adults. There is no IV preparation and none is likely to be developed because of difficulties with dosing.

When we weigh up the risks versus the benefits of treating neonatal seizures, there are two questions to ask. These are:

a) What is the effect of not treating neonatal seizures?

b) What is the effect of anti-epileptic drugs?

The next two activities will look at this further.

*Activity 6:*

***This provides the basis of one of our workshops.****

To inform discussion at one of the course workshops, please read the following and make notes on the blank pages that follow:

*Paper 3:* **Uria-Avellanal C** et al. ***Outcome following neonatal seizures***. *Semin Fetal Neonatal Med*. 2013; 18(4): 224-232

*Paper 4:* **van Rooij LG** et al. ***Effect of treatment of subclinical neonatal seizures detected with aEEG: randomised, controlled trial.*** *Pediatrics*. 2010; 125:e358-66

And the following two abstracts:

**Bittigau P** et al. ***Antiepileptic drugs and apoptosis in the developing brain.*** Ann N Y Acad Sci. 2003; 993: 103-14

*Abstract*

Epilepsy is the most common neurologic disorder in young humans. Antiepileptic drugs (AEDs), used to treat seizures in children, infants, and pregnant women, cause cognitive impairment, microcephaly, and birth defects by unknown mechanisms. We tested whether common AEDs cause neurodegeneration in the developing rat brain. Rats aged 3-30 days received phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid. Histologic examination of the brains revealed that these drugs cause widespread and dose-dependent apoptotic neurodegeneration in the developing rat brain during the brain growth spurt period. Apoptotic neurodegeneration was triggered at plasma drug levels relevant for seizure control in humans. Antiepileptic drugs lead to reduced expression of neurotrophins and decreased concentrations of the active forms of ERK1/2, RAF, and AKT. beta-Estradiol, which stimulates pathways that are activated by neurotrophins, ameliorated AEDs-induced apoptotic neurodegeneration. Our findings present one possible mechanism to explain cognitive impairment and reduced brain mass associated with pre- or postnatal exposure of humans to antiepileptic therapy.

**Sulzbacher S** et al. ***Late cognitive effects of early treatment with phenobarbital.*** *Clin Pediatr*. 1999; 38(7): 387-94

*Abstract*

We previously reported that IQ was significantly lowered in a group of toddler-aged children randomly assigned to receive phenobarbital or placebo for febrile seizures and there was no difference in the febrile seizure recurrence rate. We retested these children 3-5 years later, after they had entered school, to determine whether those effects persisted over the longer term and whether later school performance might be affected. On follow-up testing of 139 (of the original n = 217) Western Washington children who had experienced febrile seizures, we found that the phenobarbital group scored significantly lower than the placebo group on the Wide Range Achievement Test (WRAT-R) reading achievement standard score (87.6 vs 95.6; p = 0.007). There was a nonsignificant mean difference of 3.71 IQ points on the Stanford-Binet, with the phenobarbital-treated group scoring lower (102.2 vs 105.7; p = 0.09). There were five children in our sample with afebrile seizures during the 5-year period after the end of the medication trial. Two had been assigned to phenobarbital, and three had been in the placebo group. We conclude there may be a long-term adverse cognitive effect of phenobarbital on the developmental skills (language/verbal) being acquired during the period of treatment and no beneficial effect on the rate of febrile seizure recurrences or later non febrile seizures.

Notes

Notes

## 2.6 What is epilepsy?

Epilepsy is recurrent, unprovoked epileptic seizures.

Most epileptic seizures in neonates are not epilepsy - they are provoked / caused by something like hypoglycaemia or HIE.

Epilepsy does occur in neonates but is rare. This section will help you understand what is meant by epilepsy and how it is classified.

By the end of this section you will understand:

- That epilepsy is a group of conditions – *the epilepsies*
- Understand the classification system of epilepsy
- Be able to use the DESSCRIBE technique for classifying epilepsy

### *Activity 7:*

| A child presents to your clinic with a cough. Take a few minutes to think about the different causes of coughs. There are many! How do you differentiate between these potential causes? |
| --- |
| |

*Commentary 7:*

The answer is good old-fashioned medicine. You take a history, noting what the cough is like, what brings it on, when it happens and the family history. Then you examine the patient. You might order tests, like a chest x-ray. Eventually, you get a diagnosis. That diagnosis helps you advise the family on the prognosis.

Epileptic seizures are a clinical sign, like a cough. There are many causes – some with a good prognosis, some with bad prognosis.

**Epilepsy is therefore not one condition. It is a group of different conditions. They are "the epilepsies".**

An epilepsy syndrome is a group of features commonly seen together. This includes the types of seizures, the EEG results and the family history.

Making an epilepsy syndrome diagnosis can help you search for the right cause, the best treatment and give the most accurate prognosis to families.

There are many different epilepsy syndromes. Some common, some rare. Some easy to treat successfully, some impossible to treat. Some will resolve with time, some will last for life. Some will be associated with learning difficulties, emotional and behavioural problems, some will be associated with normal outcome.

The ILAE produce an "axial classification" for epilepsy, summarised below.

| Axis of classification | Name | What does that mean in English? | How this fits with the BPNA DESSCRIBE system |
|---|---|---|---|
| Axis one | Ictal phenomenology | Description of the event using the correct terminology | D |
| Axis two | Seizure type | The type of seizure, including the affected side / part of the body | ES |
| Axis three | Epilepsy syndrome | Derived from the type of seizures, the age, past medical history, family history and EEG findings | S |
| Axis four | Aetiology | The cause | C |
| Axis five | Disability | Associated difficulties | RIBE |

This can be quite hard to remember. The BPNA has developed a memorable tool in its PET (Paediatric Epilepsy Training) courses. Neonatal epilepsy is no different from epilepsy in older children or adults. So, it makes sense to use the same tool here.

**"DESSCRIBE"**

**D**escription?
**E**pileptic or non epileptic episodes?
**S**eizure type(s)?
**S**yndrome?
**C**ause
**R**elevant….
**I**mpairments ….
**B**ehaviour and emotional
**E**ducational issues

## *Activity 8:*

*Without turning back*, complete the following table about the DESSCRIBE classification.

| ***Letter*** | ***What does the letter stand for?*** | ***What does this mean? What axis of the ILAE classification does this relate to?*** |
|---|---|---|
| **D** | | |
| **E** | | |
| **S** | | |
| **S** | | |
| **C** | | |
| **R** | | |
| **I** | | |
| **B** | | |
| **E** | | |

## *Commentary 8:*

Now turn back to see if you were right! We will be discussing the neonatal epilepsy syndromes on the course, so make sure you understand the DESSCRIBE classification before then.

## 3. Central or peripheral?

### 3.1 Introduction

When assessing a neonate neurologically, it's worth thinking about where in the nervous system the signs are coming from. Is it central or peripheral? This is particularly important for the assessment of the floppy or stiff baby.

### 3.2 Learning objectives

By the end of this section you will:

- Know what constitutes the central and peripheral nervous system
- Have a framework to build your assessment around
- Know the clinical features of a central or peripheral condition, particularly with reference to a floppy baby

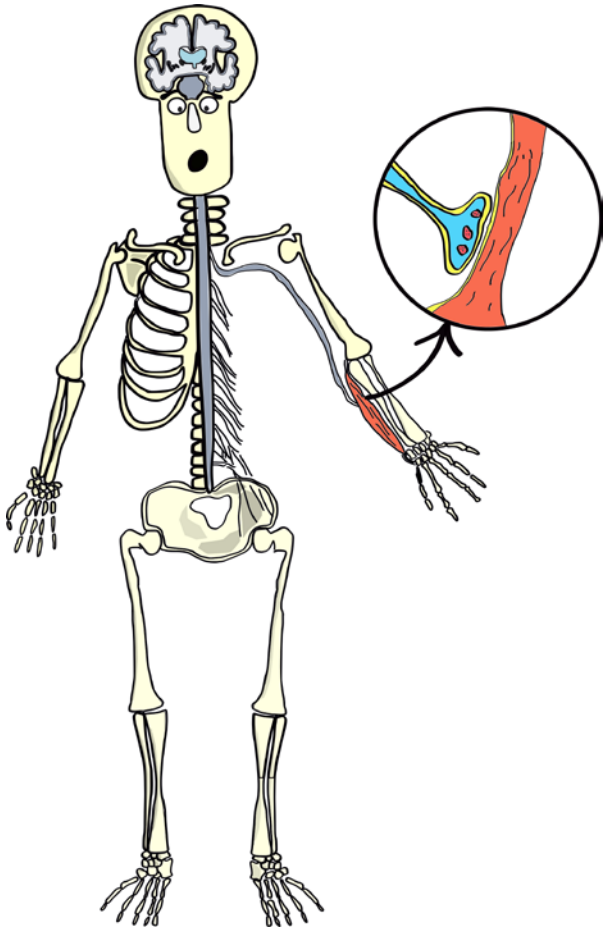
### 3.3 The basics of central and peripheral features

The nervous system is enormous.
It covers the:

- Cerebral cortex
- Deep grey matter (basal ganglia and thalami)
- The cerebellum
- Brain stem
- Spine
- Peripheral nerves
- Neuromuscular junction
- The muscles…

These are shown in the skeleton on the right.

It is silly, of course, but the cartoon does highlight the different areas of the nervous system that may be affected. Some people may find it useful if they are visual learners.



*Activity 9:*

Think back to your university days. You should have been taught about the symptoms and signs of upper and lower motor neurone findings. In particular, think about how it may affect a neonate.

List them in the table below.

| **Upper motor neurone (Central)** | **Lower motor neurone (Peripheral)** |
|---|---|
| | |

*Commentary 9:*

This neuroanatomical approach is particularly useful when you have to assess a floppy baby.

We have listed some of the features of central and peripheral pathologies in a couple of acronyms.

**Central (brain) – think STRONG!**

**S**ystemic signs
**T**iredness / encephalopathy
**R**eflexes present (brisk)
**O**FC size (macro or microcephaly)
**N**europhysiological abnormalities or epileptic seizures
**G**enetic features / dysmorphia

As you can tell from the acronym, these babies may be floppy but their power is normal. They are strong!

**Peripheral (nerves, neuromuscular junction, muscle) – think WEAK!**

**W**eak or absent reflexes
**E**xpression / myopathic face
**A**lert
**K**in / maternal features

As you can tell from the acronym, floppy babies with a peripheral cause are weak!

# 4. What is MRI?

## 4.1 Introduction

No one doubts the importance of cranial ultrasound imaging in neonatal care. It is invaluable, and not only for the ability to bring the scanner to the sick neonate's cot.

There is plenty of available training on cranial ultrasound. Many courses exist that and we cannot deal with this topic in such a short time. Our colleagues in Cambridge provide one particularly excellent course (see www.cambridgeperinatalgroup.org).

The growth or MRI in both clinical medicine and research is staggering. And yet, the teaching on the basics of MRI is limited. This section aims to plug that gap, without demeaning cranial ultrasound in any way.

Simple things about MRI, like the terminology, can be baffling. MRI meetings can just become an opportunity to snooze in the dark! But it can provide lots of useful information that is invaluable in the care of a neonate.

What's more - everyone thinks MRI is safe. In some ways, that's correct!

***There are no known side effects from MRI***

But, there are potential side effects. Most of this relates to the magnet and metallic objects being taken into the scanner room.

So, the phrase above can be changed to:

***There are no known side effects from MRI…***
***But there are side effects, potentially lethal, from an idiot in an MRI scanner room***

## 4.2 Learning objectives

By the end of this section you will understand:

- Some basic principles of MRI physics
- The safety aspects of MRI
- The planes used (axial, coronal, sagittal)
- Some of the terminology used
- Some of the sequences and what they are useful for

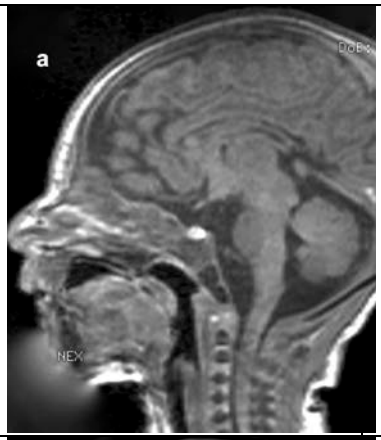
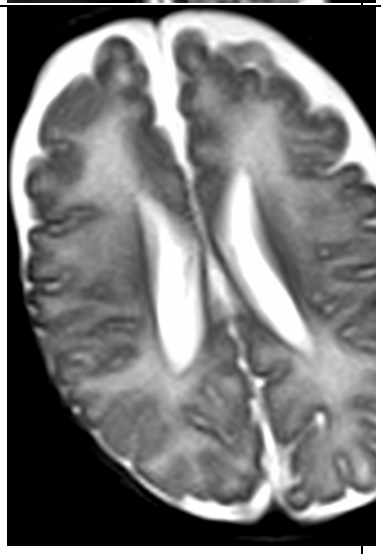
### 4.3 Your starter for ten! The MRI quiz

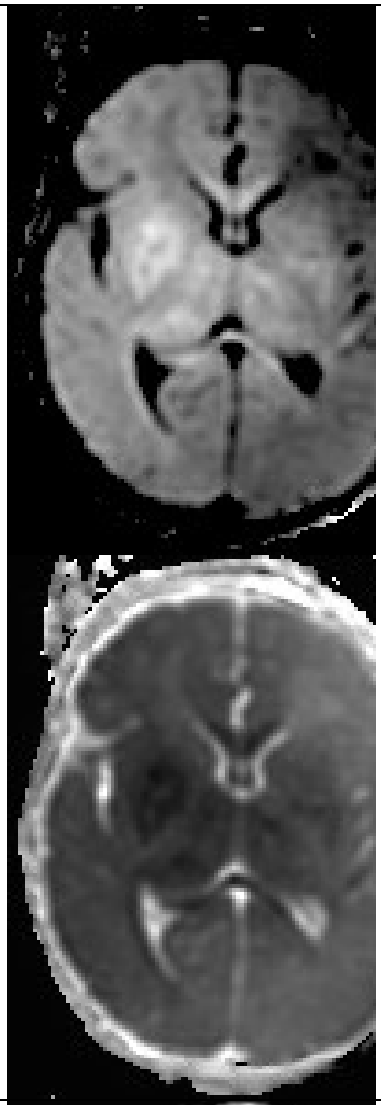
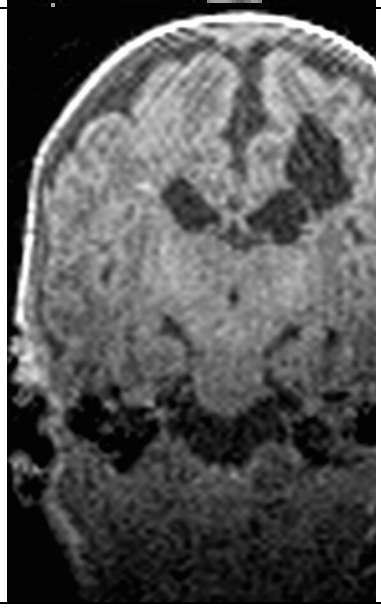
This is a quiz to test your knowledge. Don't worry, we don't ask for your answers or marks! It's just useful for you to know where you are now and what you have to learn in this section.

*Activity 10:*

Have a go at this quiz. ***Afterward*** the quiz read "The Basics of MRI" (Paper 5).

| Question | | Answer |
|---|---|---|
| 1 | What are the main advantages of cranial ultrasound over MRI? | |
| 2 | What are the advantages of MRI over cranial ultrasound? | |
| 3 | How much radiation is involved in MRI - a lot, a little, none? | |
| 4 | What are the greatest risk factors with MRI that could harm a baby being scanned? | |

| | | | |
|---|---|---|---|
| 5 | What does T1 and T2 weighted mean? | | |
| 6 | What plane is this – axial, coronal or sagittal? |   | |
| 7 | What sort of sequence is this?<br><br>• T1-weighted<br>• T2-weighted<br>• T2 FLAIR<br>• Diffusion weighted imaging<br>• MR proton spectroscopy |  | |

| | | | |
|---|---|---|---|
| 8 | What type of sequences are these and what is the pathology? |  | |
| 9 | What type of sequence is this? What is the pathology on this scan?<br>What artefact is present on this scan? |  | |

| | | |
|---|---|---|
| 10 | Which neonates should have an MRI scan? | |

***BEFORE MARKING YOUR ANSWERS, PLEASE READ THE ARTICLE:***

*Paper 5: "The Basics of MRI" before marking it*

## *Commentary 10 – the answers*

1. Cranial ultrasound (cUSS) is quick and cheap. Assuming you are trained properly, many people can perform cUSS – radiologist, radiographers, neonatologists etc. They can be brought to the baby at any time of the day, which is important for cardiovascularly unstable or extremely preterm neonates. cUSS visualises important neonatal abnormalities like intraventricular haemorrhage or cystic periventricular white matter damage.

2. MRI visualises some pathologies better than cranial ultrasound. Examples include subtle damage to the white matter, posterior fossa abnormalities, and perinatal stroke. Neonatal MRI is difficult to interpret. Your scan report is only as good as the person reporting it, the clinical information shared with the team, and the quality of the scan.

3. None.

4. The magnetic field: magnetic objects can fly across the room towards the scanner and potentially injure someone in it. Implantable devices or buttons on clothes may warm up and cause burns. They may move within the body. If implants are electronic, their settings may be changed or implantable pumps may stall. The scanner is noisy and ear protection is required.

5. These are two of the sequences used in MRI. They measure the relaxation of hydrogen molecules (protons) during MRI. How fast the recovery occurs in the z plane is T1 relaxation. Scans focussing on this are T1 weighted. How fast the relaxation occurs and signal is lost in the x-y plane is T2 weighted relaxation. Sequences focussing on this are T2 weighted.

6. Sagittal image. This is a T1 weighted image.

7. T2 weighted image in the axial plane.

8. Top – diffusion weighted imaging (b700) in the axial plane; bottom ADC map in the same patient. There is high signal in the putamen on the right hand side in the top image and possibly in the thalamus too. The same areas are dark on the ADC map. Both sequences should be viewed together. This is an acute profound hypoxic brain injury in a neonate with HIE clinically.

9. T1 weighted image in the coronal plane showing a large cyst in the periventricular white matter on the left. There is also movement artefact (look at the lines parallel to the surface of the brain).

10. Trick question! Nobody agrees. Some units scan all preterm infants, some scan none. Since the TOBY study most children with HIE will get MRI. It is also useful if you suspect congenital brain abnormalities or perinatal stroke.

***Please review the quiz questions again to see how much you have learnt.***

# 5. Outcome after neonatal encephalopathy in term neonates

## 5.1 Introduction

Encephalopathy is a condition in which the cardinal feature is the alteration in the level of consciousness.

You may hear the term used in other ways – for example, Volpe uses it for preterm brain injury (the "encephalopathy of prematurity") even though these infants may not be encephalopathic. We advise the term is best reserved for conditions affecting the level of consciousness.

Not all neonatal encephalopathy is hypoxic ischaemic encephalopathy. That is a very important point, and we make no apologies if you get bored of hearing us say it!

This section touches briefly on the causes of neonatal encephalopathy – we will discuss this in more detail on the course. In this reading we also focus on outcome following newborn encephalopathy and prognostication. This information will be useful for the workshops on the course.

## 5.2 Learning objectives

By the end of this session, you should be able to:

- Think about the causes of neonatal encephalopathy
- Know the most important factor to consider when prognosticating neurodevelopmental outcome
- Understand which children are likely to have severe / profound cognitive impairment and / or cerebral palsy after HIE
- Understand more about the outcome of mild and moderate HIE
- Understand that cognitive and behavioural difficulties without cerebral palsy can occur following neonatal encephalopathy

### 5.3 The causes of neonatal encephalopathy

*Activity 11:*

| List as many causes of neonatal encephalopathy as you can think of. |
| --- |
| |
| What do you think is the most important factor when thinking about prognosis in neonatal encephalopathy? |
| |

*Commentary 11:*

There are many causes of encephalopathy. HIE is one of the most common of course. Sources vary on what proportion of neonatal encephalopathy is HIE, but somewhere between 20-50% seems right. This will obviously depend on the population being studied, the quality of obstetric care, and the diagnostic approach towards aetiology.

Here are some of the causes in a term infant:

- Drugs – sedation, pain relief, anti-epileptics etc
- Intracranial haemorrhage
- Perinatal stroke (usually not encephalopathic)
- Septicaemia
- Meningo-encephalitis
- Trauma during delivery, accidental trauma and NAI
- Thyroid abnormalities
- Electrolyte imbalance
- Inborn errors of metabolism
- Epilepsy
- Raised intracranial pressure

As for the most important factor relating to prognosis – it's certainly tempting to put something like severity of encephalopathy down, or the frequency of seizures or the MRI appearances of the brain. This is clearly all useful information, but it's not the most important factor…

***Cause of encephalopathy***

The cause of the neonatal encephalopathy is much more important than severity. A child with a perinatal stroke can recover quickly with little, if any, long-term sequelae. However, non-ketotic hyperglycinaemia is not going to have a favourable outcome.

Once you start looking at HIE alone, then severity of encephalopathy and other investigations become important. We will study this a little bit next.

**5.4 Outcome following neonatal encephalopathy – the crystal ball! ***
*(Please read prior to the course)*

## *Activity 12:*

| | |
|---|---|
| | Please read Paper 6: Professor Linda de Vries' paper called "Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. We will look at outcome data before moving on to prognostic tests.<br><br>Answer these questions based on what you read. |
| 1. | From the article, what do you determine about the outcome (and at what ages) following:<br><br>**Severe HIE?** |
| | **Moderate HIE?** |
| | **Mild HIE?** |
| 2) | The American College of Obstetricians and Gynecologists (and some neurologists in medicolegal settings) say that an acute intrapartum event could only result in four limb CP of the spastic or dyskinetic type and could not result in isolated cognitive deficits.<br><br>What do you think about this statement? |

*We will now look at the patterns of brain injury on MRI after neonatal hypoxic ischaemic encephalopathy.*

3) Look again at Paper 6, page F221, at the section entitled "Patterns of brain abnormalities on MRI predict outcome in early childhood".

Complete the table below on pattern of injury and outcome.

| Pattern of brain injury | Duration of hypoxic ischaemic brain injury | Outcome |
|---|---|---|
| | | |
| | | |

4) And finally (a silly question, but there is a serious point behind it) – if we assessed the percentage of normal children aged 6 years who had passed their driving test and owned a car and compared this figure to the rate in children who had experienced severe HIE, had a BGT pattern on MRI and developed severe CP…

What would we find?

Why?

*Commentary 12:*

The range of potential outcome following HIE is broad – from "no difficulties" to "profound disabilities requiring care for all aspects of life, severe cerebral palsy and epilepsy".

The severity of the encephalopathy is important in HIE. Pin et al found that almost 100% of neonates with severe encephalopathy had poor outcome. We will discuss the severity / grades of encephalopathy on the course.

Moderate HIE has a more varied outcome. Neonates with moderate HIE can have cognitive and / or behavioural difficulties later in life. Some develop CP, but this is not exclusive. The suggested dogma that cognitive difficulties cannot be seen without CP in the context of HIE is, frankly, rubbish!

For example, Marlow et al showed survivors of moderate HIE can have normal overall cognitive abilities (ie what is commonly measured as IQ), whilst specific cognitive abilities (such as measured with language, memory, sentence repetition, verbal and visual recall testing along with sensorimotor scores) were lower. Children who had experienced moderate HIE were also more likely to require educational support at school. Unless assessments consist of comprehensive assessment of various cognitive functions and domains, they won't be appreciated and properly addressed.

Neonates with mild neonatal encephalopathy also fare less well than normal controls. Pin et al showed that the rate of adverse outcome at 3 years was 0% but this "long-term" outcome is really "short-term outcome" in the big picture of child development. The last question in the quiz was silly, but illustrates this point. The rate of normal children who have passed their driving test and own a car at six years of age is 0%. The rate of children with severe neonatal HIE and CP is the same at 0%. We can only measure something that is expected at that developmental age: six-year olds don't drive or own cars. There are many things that a 3-year old is not required to do but an 18-year old is. For example, it is only in childhood and adolescence that the more subtle difficulties with cognitive and social / behavioural functions become apparent. This highlights just how woeful the scientific evidence is on long-term outcome following mild and moderate neonatal encephalopathy.

In Lindstrom et al's study, children with mild HIE had lower scores than controls on the Movement ABC in adolescence. They also had more behavioural problems - but no ADHD or CP. These features can have significant adverse effects on a child both in the home and school environment, with a knock-on effect on self-esteem and confidence. So, this does beg the question – are we following these problems up appropriately? A normal outcome at 2-years in a neonatal or community follow-up clinic does not mean the child has escaped HIE unscathed.

Finally, the pattern of brain injury is discussed in this paper. The basal ganglia / thalami pattern of injury can also be associated with injury to other areas of the brain. This form of injury is highly likely to lead to cerebral palsy (with a gross motor function classification in the severe range), profound or severe learning difficulties and possible epilepsy.

In the watershed type of injury (prolonged partial asphyxia) a severe motor impairment is uncommon. Early developmental outcome may be “normal” but cognitive and behavioural problems may arise later in life.

Do we warn the families about these risks appropriately? Do we answer the questions the family want to ask? Families tend to look longer term and want tangible predictions. These may include: will the child walk? Talk? Feed themselves? Play sports? Go to normal or special school? Generic terms like “learning difficulties” and “cerebral palsy” mean something to professionals, but what do they mean to a family?

Some clinicians also feel uncomfortable breaking bad news or being certain about poor outcome. What a family may hear is a “wishy-washy” prognosis about “having to wait and see” when it’s clear (often also to the family!) that the outcome will be poor. These issues do families a great disservice. It is not uncommon for families to say, many years down the line, “Why did no one tell me that?”

**5.5 Prognostic tests in HIE ***
(Please read prior to the course)

*Activity 13:*

| | |
|---|---|
| | Read the abstract and conclusion of van Laerhoven et al's paper titled "prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systemic review" *(Paper 7).*<br><br>This paper discusses very early tests in the first week following HIE and their ability to predict early outcome. Remember the driving test analogy from Commentary 12 when you read it.<br><br>You're welcome to read the whole paper, if you are interested, but we will get the key points from these briefer sections. |
| 1) | What tests do they study to look at prognosis following HIE? Circle the ones that you have routine access to in your unit. |
| 2) | In the conclusion to the review, what do the authors suggest about these prognostic tests? |

## Commentary 13:

The review looks at many different prognostic tests, including:

- Conventional T1 and T2 w MRI
- Diffusion-weighted MRI
- MR proton spectroscopy
- aEEG
- EEG
- VEP
- SEP

What you have in your department depends on where you work. For example, conventional structural MRI has become a routine part of the clinical work-up in neonatal HIE, but not every unit has access to MR spectroscopy. Many units will not perform VEP and SEPs in routine clinical practice.

The conclusion reached is that no single prognostic test is perfect. Whilst there undoubtedly will be correlation between tests, a combination of different assessments is likely to give the best information to clinicians.

# Clinical and neurophysiologic correlates of neonatal seizures

ELI M. MIZRAHI, MD

SEIZURES pose a number of problems in the care of newborn infants. Seizure hazard is greater in the neonatal period than at any other time. In addition, clinical seizures are the most frequent sign—and indeed may be the only sign—of central nervous system (CNS) disorder in the neonate. Clinical seizures, however, may be difficult to recognize, and if untreated, may further compromise an already injured developing brain. Conventional anticonvulsant therapy, on the other hand, may not be completely effective in eliminating seizures, and overtreatment with large doses of anticonvulsants may also have adverse effects on the immature brain.

To address these problems of diagnosis and management effectively, it is essential that clinical seizures be recognized and distinguished from other behaviors that are not seizures. In clinical practice, however, most abnormal, stereotypic behaviors of the neonate are considered to be seizures and presumed to be epileptic in origin. Utilizing cribside electroencephalographic (EEG)/polygraphic/video monitoring, we have recently evaluated this concept and the assumption that all neonatal seizures are initiated and mediated by the same pathophysiological mechanism.[1]

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## CLINICAL MANIFESTATIONS OF NEONATAL SEIZURES

The clinical features of neonatal seizures have been characterized by others over the past several years. Most notable are several French investigators[2–6] who, beginning in the 1950s, described almost all the clinical manifestations currently considered to be seizures. Motor phenomena were characterized as either generalized tonic or focal or multifocal clonic. Clonic seizures could be bilateral but occur asynchronously on two sides of the body. It was appreciated that generalized tonic-clonic seizures do not occur in neonates.

Clinical behaviors that have since become known as "subtle" seizures were also described in this early period of investigation. Eye opening, paroxysmal blinking, nystagmus, chewing, rowing, and pedaling movements were described by Minkowski and Sainte-Anne-Dargassies.[3] Dreyfus-Brisac and Monod[7] remarked on the "atypical and anarchic" character of neonatal seizures and their propensity for only slight "peripheral phenomena." The autonomic features of some types of seizures were also described, including vasomotor changes, changes in respiration and skin color, and salivation.

Later, beginning in 1973, Volpe[8,9] classified neonatal seizures according to clinical manifestations: focal clonic, multifocal clonic, tonic, myoclonic, and subtle seizures. The last term comprised seizures with ocular movements; oral-buccal-lingual movements; swimming, pedaling, or rowing movements; or autonomic signs. This is currently the most widely accepted classification system.

## EEG AND NEONATAL SEIZURES

The interpretation of the neonatal EEG in relation to clinical diagnosis and management may be difficult. The interictal EEG provides few, if any, reliable signs of potential epileptogenesis. In the neonate, interictal sharp waves may be normal, of questionable significance, or clearly abnormal.[10] If abnormal, however, they are most often nonspecific and are usually not indicative of an epileptic process. Epileptogenesis in the neonate, as expresssed by the EEG, has been described as an "all-or-nothing" process; a single epileptiform discharge will initiate an electrographic seizure.[11]

The electrographic patterns of seizures are highly variable. They may be localized in a circumscribed region of the brain or may spread rapidly. They may be brief but have the potential to be quite prolonged. The seizure discharges themselves may also be highly variable in morphology, amplitude, and duration.[10,12]

### EEG/polygraphic/video monitoring

The early characterizations of neonatal seizures and their currently accepted classification formed the basis for our recent investigations.[1,13,14] We utilized cribside EEG/polygraphic/video monitoring techniques to study neonates suspected of having seizures.[1,13,15] We analyzed the video recordings for clinical events currently considered to be seizures and determined their relationship to simultaneously recorded EEG seizure activity. We also observed the way the seizures responded when tactile stimulation and restraint were used, and identified the etiologic factors and short-term outcome of the seizures. The methodology and specific results of these studies have been described elsewhere.[1,13,14]

During our monitoring studies of neonates, we were able to record all the clinical behaviors currently considered to be seizures. Although all clinical events were abnormal, not all were closely associated with EEG seizure activity. Some of the behaviors, in fact, occurred in the absence of any such activity. Based on the clinical characteristics of the seizures and their relationship to EEG seizure activity, an electroclinical classification of neonatal seizures was devised (see *Tables 1* and *2*).

**TABLE 1**
ELECTROCLINICAL CLASSIFICATION OF NEONATAL SEIZURES (n = 100)

| Type of seizure | Number and % of infants |
|---|---|
| Clinical seizures with a consistent electrocortical signature | 33 |
| Clinical seizures without a consistent electrocortical signature | 60 |
| Electrical seizures without clinical seizures | 5 |
| Infantile spasms | 2 |

From Kellaway and Mizrahi.[14]

**TABLE 2**
CLASSIFICATION OF CLINICAL SEIZURES (n = 95)

| Type | Number | % |
|---|---|---|
| Clinical seizures with a consistent electrocortical signature | 33 | 34.7 |
| Focal clonic: unifocal, multifocal, hemiconvulsive, axial | 23 | 24.2 |
| Focal tonic: asymmetric truncal, eye deviation | 5 | 5.2 |
| Myoclonic: generalized, focal | 4 | 4.2 |
| Apnea* | 1 | 1.1 |
| Clinical seizures without a consistent electrocortical signature | 60 | 63.2 |
| Myoclonic: generalized, focal, fragmentary | 17 | 17.9 |
| Generalized tonic: extensor, flexor, mixed extensor/flexor | 14 | 14.7 |
| Motor automatisms: oral-buccal-lingual, ocular signs, progression movements, complex purposeless movements | 29 | 30.5 |
| Infantile spasms | 2 | 2.1 |

* Apnea occurred in one infant treated with phenobarbital prior to monitoring
From Kellaway and Mizrahi.[14]

## CHARACTERIZATION AND CLASSIFICATION OF NEONATAL SEIZURES

### Clinical seizures with a consistent electrocortical signature

These clinical seizures always occur in a time-synchronized relationship to EEG seizure activity and include focal clonic, focal tonic, and some myoclonic seizures. Focal clonic seizures consist of rhythmic twitching of facial, limb, or axial muscles. They may be unifocal, multifocal, hemiconvulsive, or axial. Focal tonic seizures are a sustained asymmetric posturing of the limbs or trunk or a sustained deviation of the eyes. Myoclonic seizures with a consistent electrical signature may occur as either generalized or focal jerks of distal or proximal (axial) muscle groups.

In our studies, neonates with focal clonic seizures were usually awake and alert between seizures, and

their interictal background EEG activity was usually normal. Focal clonic seizures were most often associated with focal structural lesions, subarachnoid hemorrhage, infection, or (more rarely) metabolic disorders. The neonates with focal clonic seizures usually had a good short-term prognosis.

### Clinical seizures without a consistent electrocortical signature

Clinical seizures may also occur either without any accompanying EEG seizure activity or with an inconsistent relationship to such activity if it is present. This category includes some myoclonic seizures, all generalized tonic seizures, and motor automatisms.

Myoclonic seizures unassociated with EEG seizure activity may be either generalized or focal. Bilaterally symmetric tonic seizures are extensor, flexor, or mixed extensor/flexor. Motor automatisms (classified as subtle seizures by Volpe[9]) include oral-buccal-lingual movements (puckering, sucking, grimacing, or tongue protrusion), ocular signs (eye opening, blinking, oscillatory or roving eye movements), progression movements (swimming or rotary arm movements, stepping or pedaling of the legs), and complex purposeless movements.

Neonates who had generalized tonic seizures, motor automatisms, or myoclonic seizures unassociated with EEG seizure activity were characteristically obtunded or comatose, and their background EEG activity was abnormal (either depressed and undifferentiated or not of cerebral origin). These types of seizures were most often associated with hypoxic-ischemic encephalopathy and a poor short-term outcome.

In infants with generalized tonic posturing or motor automatisms, tactile stimulation provoked behaviors identical to those observed spontaneously. Both provoked and spontaneous behaviors could be suppressed with restraint or repositioning of the trunk or extremities.

### Electrical seizures without accompanying clinical seizures

Electrical seizures without clinical signs may occur in two circumstances. First, they may occur in infants not treated with anticonvulsants who are obtunded or comatose and who have depressed and undifferentiated background EEG activity. The electrical seizures are usually of the "depressed-brain type"[10] and the discharges are low in amplitude, remain confined to circumscribed regions, and show little augmentation.

Second, electrical seizures may occur in the absence of clinical seizures when the two become "decoupled" by anticonvulsant therapy. Infants who have focal clonic or focal tonic seizures accompanied by electrical seizure activity before anticonvulsant treatment may show persisting electrical seizures when the clinical seizures have stopped after administration of anticonvulsants. This control of the clinical seizures with persisting electrical seizure activity has been termed "decoupling."[1]

### Mixed seizures

Although most infants have only one type of seizure, some may have more than one. The usual combinations are motor automatisms, tonic posturing, and some myoclonic seizures, but some infants may have focal clonic seizures and tonic posturing and/or automatisms.

## NEUROANATOMIC AND NEUROPHYSIOLOGIC DETERMINANTS OF NEONATAL SEIZURES

On the basis of our monitoring studies, we have proposed that at least two pathophysiologic mechanisms may be responsible for initiation and mediation of the different types of neonatal seizures.[1,11,13] An epileptic process is responsible for focal clonic and focal tonic seizures. In addition, we hypothesize that a nonepileptic process may be responsible for tonic posturing and motor automatisms.

### Epileptic pathophysiology

The well-localized and, at times, fragmentary or anarchic character of some neonatal seizures is thought to be dependent on the relative epileptogenicity of brain structures and the properties of the brain that determine the propagation of electrical seizure activity in the developing brain.

Animal investigations indicate that the hippocampus, compared with the neocortex, has a greater structural complexity and exhibits increased excitability.[16] There is, however, a prominence of inhibitory synaptic activity in the immature neural network,[17] and the degree of development of the cytoarchitecture and myelinated pathways may prevent or delay the cortical spread of seizure activity.[6,18–20] These properties of the immature brain, which tend to confine rather than spread electrical activity, may restrict the epileptic discharges to the specific brain regions from which they originate.

Features that tend to confine epileptic electrical

activity may account for the clinical manifestations of some types of neonatal seizures. Focal clonic and focal tonic seizures may involve well-circumscribed regions of the body, just as epileptic discharges arise and remain localized within a specific, well-localized brain region.

The relative excitability of the hippocampus compared with neocortical inhibition may account for features of other types of seizures (not well characterized in our current studies) that have a predominance of signs mediated by the autonomic nervous system. These include changes in heart rate and blood pressure, pallor, flushing, pupillary dilatation or constriction, and salivation. These clinical signs may be mediated by activation of limbic system structures and may be initiated by epileptic activity within the hippocampus. The neurophysiologic characteristics of the immature brain suggest that there is a relative vulnerability of the hippocampus and that abnormal electrical activity tends to be confined to hippocampal structures, which may result in clinical seizures with a predominance of autonomic features.

### Nonepileptic pathophysiology

Tonic posturing and motor automatisms do not require electrocortical seizure activity for their elaboration. The seizures may be epileptic in character but are generated in the brain stem without manifestation of paroxysmal epileptic activity at the scalp. An alternative explanation may be that the seizures are generated at a brain stem level by a nonepileptic mechanism. This explanation is based on clinical and electrographic findings as well as on response to stimulation and restraint.

Infants with generalized tonic seizures and motor automatisms have clinical and electrographic evidence of forebrain depression; they are obtunded or comatose and their background EEG activity is depressed and undifferentiated. Clinical events, identical to those occurring spontaneously, may be provoked by tactile or proprioceptive stimulation. Increasing the intensity of the stimulation at a single site, or constant stimulation at an increasing number of sites, results in an increase in the intensity of the behavior (*temporal* and *spatial summation*). There may also be spread of the response (*irradiation*) to other muscle groups. In addition, both spontaneous and provoked responses may be suppressed by restraint or repositioning of the affected limb or trunk. All of these features are characteristic of reflex behavior, as demonstrated by animal studies,[21–25] and not of epileptic mechanisms.

On the basis of these observations, we have proposed that tonic posturing and motor automatisms occur as a consequence of depression or absence of cortical tonic inhibitory influences on brain stem facilitory centers.[1,11,13] This results in a facilitation, or "release," of primitive brain stem and spinal motor mechanisms. It has been proposed that these behaviors be classified as "brain stem release phenomena" rather than as epileptic seizures.[11]

## THERAPY

A detailed discussion of the use of anticonvulsants in neonates is provided by Painter (see article in this volume). Therefore, only two specific issues concerning therapy will be considered here. First, if some neonatal seizures are not epileptic in origin, anticonvulsant therapy may not be appropriate for all types of seizures. Clinical seizures with a consistent electrocortical signature are most clearly of epileptic origin; they include focal clonic and focal tonic seizures. Identification of these seizure types by EEG/polygraphic/video monitoring should suggest institution of anticonvulsant therapy. On the other hand, seizures that occur without accompanying EEG seizure activity and presumably are of nonepileptic origin may not require anticonvulsants.

It may be difficult to determine the effectiveness of anticonvulsant treatment of epileptic seizures. As noted above, when a drug such as phenobarbital, for example, is given to infants whose clinical seizures are closely associated with EEG seizure activity, the clinical seizures may stop while the electrical seizures persist virtually unchanged. Thus, the clinical seizures are decoupled from the electrical seizures.[1] The electrical seizures may be difficult to control, even when high dosages of anticonvulsants are used. However, the goal of anticonvulsant therapy for neonatal seizures has not been established: is it cessation of electrical seizures or of clinical seizures?

## HETEROGENEITY OF NEONATAL SEIZURES

In the past, neonatal seizures have been characterized and classified according to clinical manifestations, but their clinical significance, pathophysiology, and therapy have been determined by considering all types of seizures as a single group.

Our monitoring studies suggest that various seizure types are associated with varying degrees of cerebral

injury and differing etiologic factors and short-term outcomes. In addition, it may be that not all neonatal seizures are initiated and mediated by an epileptic process; some may be the manifestation of primitive reflexes mediated by the brain stem in the presence of forebrain depression. Anticonvulsant therapy may not be appropriate for all types of neonatal seizures. Thus, exact characterization and classification of each type of seizure form the basis for accurate diagnosis, management, and prognosis of neonates with seizures.

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# Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures

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## ABSTRACT

**Background:** Neonatal seizures are often subclinical, making accurate diagnosis difficult.

**Objective:** To describe the clinical manifestations of electrographic seizures recorded on continuous video-EEG, and to compare this description with the recognition of clinical seizures by experienced neonatal staff.

**Methods:** Term infants, at risk of seizures, were monitored by continuous 12-channel video-EEG from <6 hours of birth for up to 72 hours. All clinical seizures were recorded by experienced neonatal staff on individual seizure charts. Video-EEG recordings were subsequently analysed. The number, duration and clinical expression of electrographic seizures were calculated (in seconds), and compared with the seizures clinically suspected by the neonatal staff.

**Results:** Of 51 infants enrolled, nine had electrographic seizures. A further three had clinically suspected seizures, without associated electrographic abnormality. Of the total 526 electrographic seizures, 179 (34%) had clinical manifestations evident on the simultaneous video recording. The clinical seizure activity corresponded to 18.8% of the total electrographic seizure burden. Overdiagnosis also occurred frequently. Of the 177 clinically suspected seizure episodes documented by staff, 48 (27%) had corresponding electrographic evidence of seizure activity Thus, only 9% (48/526) of electrographic seizures were accompanied by clinical manifestations, which were identified and documented by neonatal staff.

**Conclusion:** Only one-third of neonatal EEG seizures displays clinical signs on simultaneous video recordings. Moreover, two-thirds of these clinical manifestations are unrecognised, or misinterpreted by experienced neonatal staff. In the recognition and management of neonatal seizures clinical diagnosis alone is not enough.

Neonatal seizures are associated with a significant incidence of brain injury and long-term neurodevelopmental delay.[1 2] Prompt therapeutic intervention may be important but recognition of seizures is hampered by a highly variable clinical expression and the frequent use of paralytic agents.[3–5] In addition, anticonvulsant treatment often leads to electroclinical dissociation—that is, the number of clinical seizures decreases while the number of electroencephalographic (EEG) seizures continues unabated or increases.[6 7] Certain neurological events previously considered to be seizures have also been thought to be either brainstem release phenomena or movement abnormalities.[8] EEG confirmation is essential for the evaluation of neonatal seizures. The combination of both EEG and clinical criteria most accurately diagnose and classify all seizures in neonates.[9] Because of the difficulty in deciding clinically whether a baby is seizing, clinical seizures may be overestimated, resulting in unnecessary treatment. Neonatal seizures may also be either underdiagnosed resulting in undertreatment, or incorrectly categorised resulting in potentially harmful treatment.[10 11]

Clinical observation of seizure semiology, unaccompanied by EEG confirmation, has severe limitations. Accordingly, the EEG plays an important part in understanding the nature of paroxysmal movements in neonates and in differentiating epileptic seizures from non-epileptic events.[9] The aims of this study were to quantify the clinical manifestations of electrographic seizures in neonates precisely and to compare that with the clinical recognition of neonatal seizures by experienced neonatal personnel. We wished to determine the gap between electrographic seizure burden, video-recorded clinical manifestations of seizures, and clinical documentation of seizures in a population of term infants.

## METHODS

This study took place in the neonatal intensive care units of the Unified Maternity and Neonatal Services in Cork between January 2003 and June 2005. The neonatal units (400 admissions a year) serve as tertiary regional referral centres for a population of 0.5 million (8500 births a year). Neonates were recruited into this study at birth if they fulfilled two or more of the following criteria: initial capillary or arterial pH <7.1, Apgar score <5 at 5 minutes, initial capillary or arterial lactate >7 mmol/l (normal newborn values <4 mmol/l) or abnormal neurology/clinical seizures. Infants' neurological status was assessed by a standardised neurological method.[12] In addition, neonates who did not fulfil these criteria at birth, but later developed clinical seizures, were recruited immediately after their first clinical seizure. Infants with either major congenital abnormalities or metabolic disorders were excluded from the study. The study was approved by the ethical committee of Cork University Hospital. Written informed parental consent was obtained for each participant. Clinical staff were not trained in EEG analysis and were unaware of the EEG findings. The digital EEG screen was set to non-display mode. Although staff were aware that studies on high-risk neonates were in progress, they did not know the specific study hypothesis. Anticonvulsant agents were administered for clinically suspected seizures only. Infants

receiving neuromuscular blockade were excluded from the group. In addition to the initial neurological assessment, a clinical Sarnat score was assigned at 24 hours of age.

A bedside 16 channel Viasys NicOne Video-EEG system was used to record multichannel EEG using the 10–20 system of electrodes placement designed for neonates (F4, C4, T4, O2, Cz, F3, C3, T3, O1). The digital video-EEG recording was started as soon as possible after recruitment, usually at 3–6 hours after delivery, and recorded for 24–72 hours. Thoracic respiratory movements, heart rate, continuous invasive blood pressure (from radial or umbilical arterial catheter if available) and oxygen saturation, were also measured simultaneously. Only those neonates with either clinical or EEG seizures were included in the analysis.

### EEG analysis

Each EEG recording was later analysed and electrographic seizures were distinguished from the continuing background activity by an experienced neonatal electrophysiologist (GBB). All seizures in each recording were counted and the duration of each seizure measured. An EEG seizure discharge was defined as a sudden repetitive stereotyped discharge lasting for at least 10 seconds on two or more EEG channels. In those infants with EEG seizures, the EEG seizure burden was calculated. This was defined as the number of electrographic seizure seconds in the total EEG recording. The time and duration of each electrographic seizure was also recorded. EEG epochs without clear simultaneous video recordings (for example if the infant was transiently obscured from view by staff, or equipment) were excluded from the analysis.

### Video analysis

Clinical manifestations of seizures were determined by observation of the continuous video recordings. This was carried out at a later stage by a research paediatrician (DMM), not involved in the clinical care of the infants. The movements of the infants observed before, during and after each electrographic seizure episode were analysed. Clinical manifestations of the EEG seizures were classified as previously described by Volpe: subtle, clonic, tonic or myoclonic.[13] Clinical seizure manifestations were defined as movements consistently associated with simultaneous abnormal electrographic discharges. The number and duration (in seconds) of clinical seizures were calculated for each infant.

### Staff recognition of seizures

In the neonatal intensive care unit setting, experienced nursing and medical staff generally identify, and record, what they believe to be seizure activity. Nurses document the number and duration of each clinical seizure event on a seizure chart in the bedside medical notes. They are trained to use certain clinical strategies to differentiate clinically between epileptic and non-epileptic movements. These include stimulus response, response to soothing and response to gentle restraint. In addition, they are careful to recognise subtle movements as possible seizures. In our unit, specific seizure nursing sheets are maintained as a standard of care at the bedside of all infants. All recognised clinical seizure events and their time, type and duration are recorded on these seizure sheets.

## RESULTS

Fifty-one infants were recruited to the study and had continuous EEG monitoring. Of these, 11 had clinically suspected seizures documented in the nursing/medical notes. One further infant had electrographic evidence of seizures which were unrecognised clinically. Our study focused on these 12 infants; table 1 gives their details.

In this study, the nursing seizure sheet, nursing notes and medical notes of each infant were examined retrospectively by a neonatologist (IA) following discharge of the infant from the neonatal unit. The number, time and description of the clinically suspected seizure events were noted. These were then compared with the video and EEG manifestations of seizures by a research paediatrician (DMM). A clinically suspected seizure was confirmed electrographically if there were electrographic seizure discharges at the time (within 5 minutes before or after the recorded time) of the clinically suspected seizure. This gap of 5 minutes before or after the documented time of onset was necessary to allow for minor discrepancies between staff recognition and documentation. Clinical seizures recognised by staff were recorded in minutes of seizure activity.

Electrographic seizures occurred in nine of the 12 infants. Clinically suspected seizures without electrographic evidence occurred in three of the 12 infants. The total number of EEG seizures recorded with simultaneous video-EEG was 526, with a

**Table 1** Details of the 12 infants with clinically suspected or electrographically identified seizures, or both

| Study No | Birth weight (g) | Gestation | Diagnosis† | Sex | Fetal heart rate monitoring | Mode of delivery | pH‡ | Apgar 5 min |
|---|---|---|---|---|---|---|---|---|
| 1 | 3030 | 39 | HIE grade II | M | Tachy/decals | Vacuum | 6.9 | 5 |
| 2 | 3670 | 40 | HIE grade II | M | Tachycardia | Vacuum | 7.2 | 6 |
| 3 | 3300 | 42 | HIE grade II | M | Variable decals | Vacuum | 7.04 | 7 |
| 4* | 3760 | 42 | HIE grade III | M | Home birth | NVD | 7.15 | – |
| 5* | 3625 | 42 | HIE grade III | F | Home birth | NVD | 7.18 | – |
| 6 | 3140 | 41 | HIE grade II | F | Tachycardia | Vacuum/forceps | 7.16 | 8 |
| 7 | 3750 | 41 | MCA infarct | M | Tachy/decals | Emer CS | 7.17 | 9 |
| 8 | 3250 | 41 | HIE grade III | M | Bradycardia | Forceps | 7.06 | 7 |
| 9 | 1830 | 40 | HIE grade III | F | Late decals | NVD | 7.18 | 6 |
| 10 | 4020 | 40 | HIE grade III | F | Bradyacardia | NVD | 7.04 | 2 |
| 11 | 2950 | 40 | HIE grade III | M | Variable decals | Forceps | 6.5 | 5 |
| 12 | 4050 | 41 | HIE grade II | F | Bradycardia | NVD | 6.8 | 3 |

*Patients 4 and 5 were planned home births and so Apgar scores and antenatal monitoring were not available.
†Grade of encephalopathy is Sarnat grade I–III.
‡pH, pH on initial blood gas within 1 hour after delivery.
decals, decelerations; Emer CS, emergency Caesarean section; HIE, hypoxic–ischaemic encephalopathy; MCA, middle cerebral artery infarct; NVD, normal vaginal delivery; Tachy, tachycardia.

**Table 2** Seizure details of 12 infants with clinically suspected or electrographically recorded seizure activity

| Study No | Time of EEG recording (hours from birth) | EEG seizure (n) | EEG seizure (s) | Mean EEG seizure duration (s) | Video recorded clinical seizure (n) | Video recorded clinical seizure (s) | Mean video seizure duration (s) | Description |
|---|---|---|---|---|---|---|---|---|
| 1 | 20–49.3 | 17 | 1380 | 86 | 2 | 133 | 66 | Staring, eye deviation |
| 2 | 14–58* | 56 | 4668 | 41 | 45 | 662 | 14.7 | Yawning, blinking, multifocal clonic |
| 3 | 18–69 | 64 | 19 492 | 291 | 16 | 2935 | 183 | Mouthing, multifocal clonic |
| 4 | 3.5–23 | 42 | 3115 | 69 | 20 | 946 | 47.3 | Apnoea, irregular resps, clonic jerks LUL |
| 5 | 4–59† | 34 | 3213 | 95 | 9 | 713 | 79.2 | LLL clonic, occasionally RLL and LUL |
| 6 | 22–88 | 56 | 6223 | 118 | 11 | 1315 | 119.5 | Mouthing, yawning, multifocal clonic |
| 7 | 26–74 | 14 | 4636 | 346 | 5 | 210 | 42 | LUL clonic jerks, rhythmic head jerking |
| 8 | 20–87 | 205 | 61 122 | 311 | 60 | 13 921 | 232 | Tonic ULs, staring, multifocal clonic |
| 9 | 12–78‡ | 38 | 9138 | 317 | 11 | 368 | 33.4 | Multifocal clonic |
| 10 | 3–67 | 0 | 0 | 0 | 0 | 0 | 0 | Clonus, tremors, staring, apnoea |
| 11 | 4.5–36.5 | 0 | 0 | 0 | 0 | 0 | 0 | Clonus, generalised jerking all four limbs |
| 12 | 5.5–36 | 0 | 0 | 0 | 0 | 0 | 0 | Clonus, jerking all four limbs on handling, apnoea |
| Total | | 526 | 112 987 | 215 | 179 | 21 203 | 118 | |

Cases 10–12 were infants with clinically suspected seizures, but no electrographic seizures.
*Video obscured by blanket for additional 18 electrographic seizures.
†Portions of video lost through technical difficulties; unable to view an additional 139 electrographic seizures.
‡Video obscured for two additional electrographic seizures.
LLL, left lower limb; LUL, left upper limb; RLL, right lower limb; ULs, upper limbs.

total seizure burden of 112 987 seconds. Of these 526 seizures, only 179 (34%) had clinically recognisable seizure activity in the simultaneous video recording. The types of clinical seizures seen were clonic (125, 70%), subtle (42, 23%) and tonic (12, 7%). No myoclonic seizures were noted. All of the nine infants with electrographic seizures had clinical signs at some stage during their video-EEG seizures. Eight of the nine infants were recognised as having clinical seizures by nursing/medical staff (table 2).

The mean duration of the clinical seizure manifestations, when they did occur, was shorter than that of the electrographic components (118 seconds and 215 seconds, respectively). In total only 18.8% (21 203/112 943 seconds) of the total electrographic seizure burden had obvious clinical signs on video-EEG (fig 1). An individual example from case 8 is shown in fig 2.

Clinically suspected seizure activity was recorded in the medical notes of 11/12 infants. In these 11 infants, the number of suspected seizure episodes was 177. Forty-eight of these events were confirmed to be electroclinical seizures on simultaneous video-EEG. In all only 48/526 (9%) electrographic seizures had clinical signs which were recognised and documented by nursing/medical staff. Table 3 gives the findings for each individual infant.

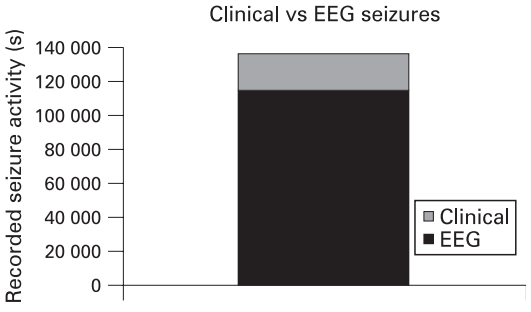


**Figure 1** Total recorded electrographic seizure activity measured in seconds, versus total clinical seizure manifestations in nine patients with electrographic seizures recorded on continuous video-EEG during the first 72 hours of life.

Only 48/179 (27%) of the seizures which had clinical features were recognised and recorded by medical and nursing staff. One patient (case 2) had 45 brief focal and multifocal clonic seizures recorded on video-EEG, none of which were documented by medical staff. The infant did not receive anticonvulsant medication despite having an electrographic seizure burden of 4668 seconds over 44 hours.

Overdiagnosis of seizures also occurred frequently, with 73% (129/177) of seizures documented in medical/nursing notes having no correlating electrographic seizure activity. Misinterpreted abnormal movements consisted of generalised muscle clonus/jitteriness, as well as subtle movements such as mouthing, and fisting. These movements occurred during periods of EEG with suppressed amplitude and no seizure activity.

Ten of the 12 infants had received anticonvulsant medication (phenobarbitone) before the initiation of video-EEG. Cases 2 and 9 did not receive anticonvulsants before, or during, the video-EEG recordings.

## DISCUSSION

Our data confirm the extent of the unrecognised burden of subclinical seizures in neonates. Even with detailed review of continuous video-EEG monitoring, only 34% of electrographic seizures had overt clinical signs. This implies that even at its best, clinical detection of seizures will miss over 65% of neonatal seizures.

Previous video-EEG studies, recorded during attempts to treat electrographic seizures, have reported that only 15–20% of all neonatal seizures have clinical manifestations.[14 15] We have shown that the number of correctly identified and documented seizures is even lower (9%). This reflects the brief and focal nature of neonatal seizures. Although the majority (70%) of the clinical manifestations were clonic in nature, they often involved brief jerking of a single hand or foot. As the seizures progressed, the movements shifted from limb to limb. These signs were essentially the "tip of the iceberg" against a

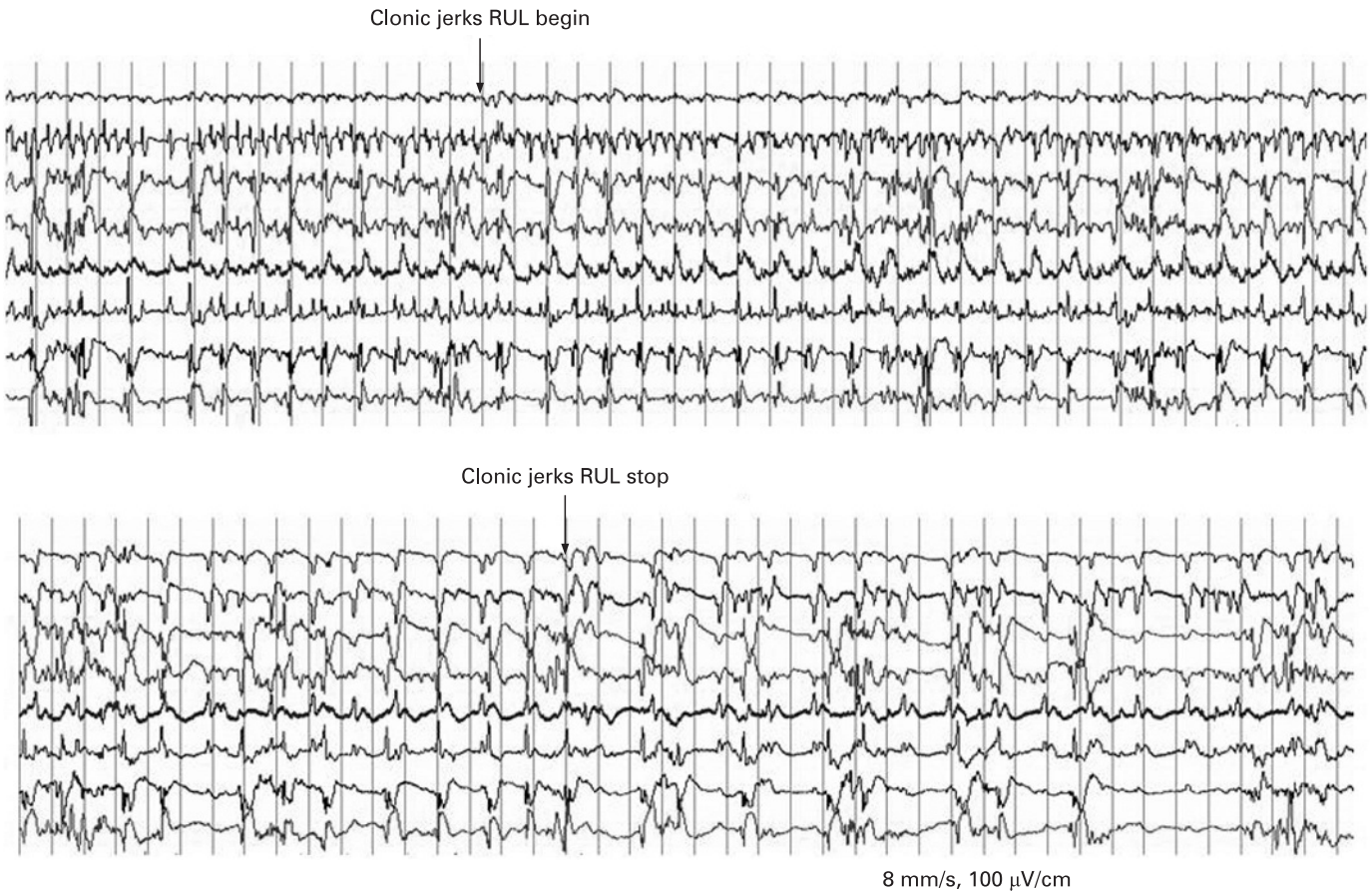


**Figure 2** Example of an individual seizure from case 8. Electrographic seizure discharges began at 22.09.20. On simultaneous video recording, clonic jerks of right upper limb (RUL) began at 22.13.35, and stopped at 22.16.07. Electrographic seizure discharges continued until 22.17.31.

background of more prolonged electrographic seizures (fig 1). We found that only 23% of the clinical seizure manifestations were subtle in nature. This is similar to the results reported in previous detailed descriptions of seizures in term infants.[3 9]

**Table 3** Seizure details of 12 infants with clinically suspected or electrographic seizure activity

| Case No | EEG seizure (n) | Video recorded clinical seizure (n) | Documented seizures in medical/nursing notes (n) | Correctly identified electroclinical seizures (n) |
|---|---|---|---|---|
| 1 | 17 | 2 | 21 | 1 |
| 2 | 56 | 45 | 0 | 0 |
| 3 | 64 | 16 | 9 | 3 |
| 4 | 42 | 20 | 25 | 12 |
| 5 | 34 | 9 | 8 | 3 |
| 6 | 56 | 11 | 4 | 3 |
| 7 | 14 | 5 | 2 | 1 |
| 8 | 205 | 60 | 32 | 25 |
| 9 | 38 | 11 | 9 | 0 |
| 10 | 0 | 0 | 26 | 0 |
| 11 | 0 | 0 | 31 | 0 |
| 12 | 0 | 0 | 10 | 0 |
| Total | 526 | 179 | 177 | 48 |

Do subclinical seizures matter? Animal studies suggest that seizures cause neuronal apoptosis and impaired neurogenesis in the immature brain.[16 17] Infants with hypoxic–ischaemic encephalopathy may be particularly susceptible to seizure-associated brain damage. Since 20–50% of infants with neonatal seizures experience later epilepsy,[18] diagnostic accuracy is essential, particularly for the newborn who has prolonged electrographic seizures. Past studies have linked neonatal seizures with worse developmental outcome, but these studies were based on clinical diagnosis alone, with its inherent limitations.[2 19] Despite the amount of electroclinical dissociation which we have demonstrated, 8/9 infants did, at some stage, have clinical seizures correctly identified by their carers, and received anticonvulsants. It is the extent of their subclinical seizure burden that remains unrecognised. Does it matter if we are unaware of the majority of their seizures burden? Only with detailed continuous video-EEG studies of electrographic seizures, and long-term neurological outcome, will we be able to answer these important questions.

We have also shown that overdiagnosis of seizures occurs frequently, with only 27% of clinically suspected seizures confirmed electrographically. Many of the movements identified correctly by staff as being abnormal (eg, fisting, mouthing, clonus) were not accompanied by electrographic discharges. These movements have been described by Mizrahi and Kellaway as "motor automatisms", of uncertain origin.[3] They may reflect brainstem release phenomena, or may be electrical seizures in deep cerebral structures, which are not transmitted

### What is already known about this topic

- The greatest risk of seizures is in the neonatal period.
- Neonatal seizures are associated with a high risk of long-term neurological deficit.
- Neonatal seizures are difficult to diagnose accurately and may be subclinical.

### What this study adds

- Only one-third of neonatal seizures have clinical expression on simultaneous video-EEG.
- Only one-third of that clinical expression is correctly recognised by experienced neonatal staff.
- Neonatal seizures are frequently overdiagnosed with inappropriate administration of anticonvulsants.

to surface EEG electrodes. Although their aetiology remains unclear, their presence usually reflects a severe underlying encephalopathy, with an increased risk of concurrent electrographic seizures, adding to the confusion.

These factors led to three infants in our group receiving large doses of anticonvulsants unnecessarily. The possible adverse effects of unnecessary anticonvulsant treatment in critically ill neonates are important. Hypotension, hypoventilation resulting in the need for mechanical ventilation, and fatal cardiac arrhythmias have all been attributed to anticonvulsant treatment in the newborn period.[10 11]

We used a reduced electrode montage for EEG recording (12 channels) in this study. The reason for this was simply that it was easier and more practical to maintain the reduced number of electrodes over long recording periods (>24 hours). However, our EEG montage did comprehensively cover the head and included wide-spaced derivations to maximise seizure detection. In a study by Tekgul *et al*,[20] a full electrode montage was compared with a reduced electrode montage (nine electrodes) for the ability to detect and characterise neonatal seizures and background electroencephalography (EEG). The sensitivity and specificity of the reduced montage for detecting electrographic seizures was 96.8% and 100%, respectively. For grading background abnormalities, the sensitivity and specificity of the reduced montage was 87% and 80%.

Most of the seizures which we recorded occurred after administration of phenobarbitone, which is known to increase electroclinical dissociation, and may partially explain the number of subclinical seizures seen in this study. However, our findings give an accurate reflection of the management of neonatal seizures in the neonatal intensive care unit. In most units, anticonvulsants are administered based on the clinical judgment of the staff. Clinical signs of seizures may stop, to the relief of all, with the electrographic seizure activity continuing unabated. Clinical signs, when they did occur were, on average, only half the duration of the underlying electrographic seizures. Our current armamentarium of anticonvulsants is limited to ineffective drugs with significant side effects.[21 22] There is an urgent need for randomised controlled trials of a new generation of anticonvulsants in the management of neonatal seizures, involving continuous video-EEG monitoring, and more importantly, long-term developmental follow-up.

In conclusion, neonatal seizures are difficult to detect, diagnose and manage. Clinical diagnosis alone is not enough. Accurate, reliable and easily accessible EEG monitoring in neonates is an urgent need.

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**Competing interests:** None.

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# Outcome following neonatal seizures

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Outcome
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Term

SUMMARY

Neonatal seizures are the most common manifestation of neurological disorders in the newborn period and an important determinant of outcome. Overall, for babies born at full term, mortality following seizures has improved in the last decade, typical current mortality rates being 10% (range: 7–16%), down from 33% in reports from the 1990s. By contrast, the prevalence of adverse neurodevelopmental sequelae remains relatively stable, typically 46% (range: 27–55%). The strongest predictors of outcome are the underlying cause, together with the background electroencephalographic activity. In preterm babies, for whom the outlook tends to be worse as background mortality and disability are high, seizures are frequently associated with serious underlying brain injury and therefore subsequent impairments. When attempting to define the prognosis for a baby with neonatal seizures, we propose a pathway involving history, examination, and careful consideration of all available results (ideally including brain magnetic resonance imaging) and the response to treatment before synthesizing the best estimate of risk to be conveyed to the family.



## 1. Introduction

Seizures are the most frequent manifestation of neurological disorders in the newborn period. The reported prevalence varies widely, depending on the baseline population and the diagnostic criteria used. Most outcome data come from case series in which the diagnosis was purely clinical. Clinical diagnosis of seizures generally underestimates the electrical seizure frequency, and the first reported clinical seizure is also an unreliable time point.[1] There are no large studies of outcome following prospective electroencephalographic (EEG) monitoring.

The estimated prevalence of babies with clinical seizures is around 1–3 per 1000 live births. In the preterm population this is even higher and seizures are more prevalent at lower gestational ages and lower birthweight. Reports describe rates of 2–3 per 1000 live births in general population and term babies; 4.4 per 1000 live births between 1500 and 2500 g; 55–130 per 1000 live births <1500 g and up to 64 per 1000 live births in infants <1000 g birthweight.[2–10] Most of the studies reporting the prevalence of seizures in preterm babies are from an era when intraventricular haemorrhage (IVH) was far more common than currently. Recently, West et al.[11] used amplitude-integrated (a)EEG monitoring prospectively in a cohort of 84 babies born before 29 weeks of gestation and admitted to their unit in Auckland in 2002–2004, none of whom was considered to have clinical seizures: five had definite electrographic seizures (four of whom died and the other survived with multiple disabilities).

Although the prognosis for term and particularly preterm babies has generally improved in the last decades, seizures still identify those babies at increased risk of dying or surviving with neurological impairment, developmental delay or later epilepsy. The rate of unfavourable outcome is higher when there is EEG confirmation.[11–14] The main predictor of adverse outcome remains the underlying cause, particularly global hypoxic–ischaemic injury. The debate as to whether the seizures themselves – or non-treatment of seizures – can cause additional brain injury and contribute to later impairment is still unclear. Certainly the presence of continuous or very frequent seizures (status epilepticus) may lead to neuronal damage in the experimental model.[2,15,16] One human neonatal trial of treatment to electrical quiescence using aEEG monitoring showed an association between the seizure burden and severity of brain injury measured with magnetic resonance imaging (MRI), but these results await confirmation.[14]

In our opinion the clinician should only attempt to give a prognosis to the parents of a baby with seizures after consideration of all the available information. Current standards of investigation should enable the cause to be determined in the vast majority of

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cases. With routine ultrasound imaging only 5 of 61 (8%) babies in Leeds were considered to have seizures of unknown cause, and a similar percentage of 'unknown' cases was reported in 2002–2007.[17,18] The prognosis can then be refined according to the underlying cause, the duration of seizures and the response to treatment, and may include information from serial examination of the baby and the results of investigations including neuroimaging and the background EEG (Fig. 1).

## 2. Mortality

In term babies, mortality following seizures has fallen from 40% before 1969 to around 7–16% in more recent reports (Table 1), but overall rates of impairment remain at around 30% (Table 2).[19] Mortality is higher in preterm babies with seizures, ranging from 22% to 58% (Table 3). In term babies, those with inborn errors of metabolism or severe hypoxic–ischaemic encephalopathy (HIE) have the highest mortality, although therapeutic hypothermia has altered the pattern of outcome following HIE, reducing the risk of death. Twenty-three of 77 admissions (29%) to the Connecticut neonatal intensive care unit (NICU) between 1992 and 1998 died during their stay on the unit.[20] In our own experience, during the 42 months between 2009 and 2012, 63 babies were admitted with EEG confirmation of seizure, of whom 13 (20.6%) died; 9/50 were term and 4/13 were preterm. Our institution is a referral centre for therapeutic hypothermia: 67% of deaths in the term group were due to severe HIE, and all babies died after withdrawal of care because of a poor prognosis, which may explain our relatively high mortality.

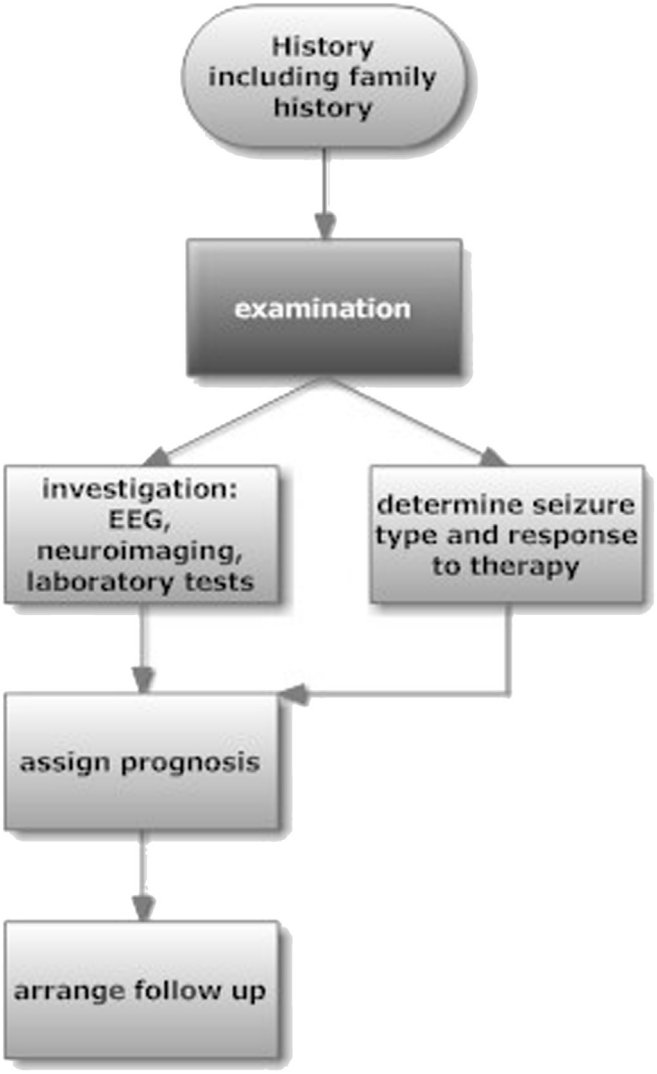


**Fig. 1.** Pathway for estimating the risk of adverse outcome in neonatal seizures.

## 3. Adverse neurodevelopmental outcomes

### 3.1. Experimental evidence

There is a considerable body of evidence from experimental data showing that neonatal seizures can adversely affect the developing brain.[15] Brain development may be altered even after brief seizures. Brain injury following repetitive seizures may occur via several mechanisms, such as hypercapnia, hypoxia, alteration in cerebral blood flow (producing ischaemia or haemorrhage), decrease in energy substrate (brain glucose), increase in lactate, or through release of excitatory amino acids.[3,15] Recurrent seizures, individually not necessarily prolonged, are associated experimentally with long-term functional, morphological and physiological deficits in animal models.[15] The main abnormalities observed are in synaptogenesis (rather than neuronal loss), and the hippocampus appears to be most sensitive in terms of neurogenesis and synaptic reorganisation.[21] Synaptic reorganisation, manifest as mossy fibre sprouting, is seen in the dentate granule cells of the hippocampus of immature rats who have seizures induced with flurothyl.[21]

For a more detailed review on the mechanisms of neonatal seizures, see Y. Ben-Ari, 'Mechanisms and effect of seizure in the immature brain' of this issue.

### 3.2. Clinical evidence

Glass et al. evaluated 143 infants with HIE, 32% of whom had clinically identified seizures.[22] The presence of seizures was associated with adverse long-term outcomes at 4 years of age, the prevalence of which was higher with increasing severity of seizures. This association was independent of the severity of HIE or brain injury. Using multivariate regression analysis to examine the effect of seizures on outcomes, and controlling for the severity of HIE using an MRI score to document brain injury, infants who had severe neonatal seizures had global intelligence quotients which were substantially lower than those with fewer seizures. Children with mild–moderate seizures had intermediate outcomes. Thus it seems likely that the presence and frequency of seizures indicates either a more serious injury or may cause independent neurological damage that leads to later impairment.

Babies that present with very frequent recurrent seizures or neonatal status epilepticus generally have a very poor outcome – in one study of 56 neonates with status epilepticus this was as high as 75%.[16] In another study of neonatal seizures, status epilepticus persisting for more than 30 min was associated with death or impairment in 90%.[12]

### 3.3. EEG evidence and the influence of background EEG on prognosis

Certain electrographic seizure characteristics correlate with an unfavourable prognosis.[2,12,13,23,24] For example, some studies have associated poor neurological outcome with higher seizure frequency (>5/h) and babies with HIE who have a high seizure burden have a worse outcome.[13,25] These findings are consistent with previous reports that a longer duration of electrical seizures is

**Table 1**
Reported outcomes from individual studies following neonatal seizures by aetiology.

| Clinical category and publication *Aetiology (% of total)* | Year of study | No. of children | Deaths *n* (%) | No. of children followed up | Outcome for survivors | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Normal *n* (%) | Any disability *n* (%) | No or mild impairment only | Moderate or severe impairment |
| Overall | | | | | | | | |
| Legido et al.[12] | 1982–85 | 40 (T + P) | 13 (33) | 27/27 | 9 (33) | 18 (67) | 12 (40) | 15 (60) |
| Scher et al.[5] | 1983–87 | 30 (T) | 10 (33) | 20/20 | 12 (60) | 8 (40) | 13 (65) | 7 (35) |
| Bye et al.[50] | n/a | 32 (T + P) | 11 (34) | 19/21 | 12 (63) | 7 (37) | 12 (63) | 7 (37) |
| McBride et al.[13] | 1994–97 | 40 (T + P) | 10 (25) | 30/30 | – | 14 (47) | – | – |
| Tekgul et al.[19] | 1997–2000 | 100 (T) | 7 (7) | 89/93 | 42 (47) | – | 64 (72) | 25 (28) |
| Ronen et al.[4] | 1990–94 | 62 (T) | 10 (16) | 52/52 | 28 (54) | 24 (46) | | |
| Garfinkle and Shevell[31] | 1991–2007 | 120 (T) | 11 (9) | 109/109 | 43 (39) | 66 (61) | – | – |
| Global HI (40–50) | | | | | | | | |
| Bergman et al.[51] | 1976–79 | 35 | – | 35/35 | – | – | 19 (54)[a] | 15 (43)[a] |
| Lombroso[52] | ? | 51 | 11 (22) | 40/40 | 11 (28) | 29 (73) | – | – |
| Mizrahi and Kellaway[53] | ? | 16 | 4 (25) | 12/12 | 5 (42) | 7 (58) | – | – |
| Andre et al.[54] | 1980–81 | 34 | 4 (12) | 30/30 | 21 (70) | 9 (30) | – | – |
| Legido et al.[12] | 1982–85 | 14 | 4 (29) | 10/10 | 3 (30) | 7 (70) | 3 (30) | 7 (70) |
| | | 2 (CHD) | 0 | 2/2 | 1 (50) | 1 (50) | 2 (100) | 0 |
| Ortibus et al.[24] | 1989–93 | 30 | 10 (33) | 20/20 | 2 (10) | 18 (90) | – | – |
| Bye et al.[50] | n/a | 11 | 5 (45) | 6/6 | 5 (83) | 1 (17) | – | – |
| McBride et al.[13] | 1994–97 | 23 | 7 (30) | 16/16 | 7 (44) | 9 (56) | 10 (63) | 6 (37) |
| Tekgul et al.[19] | 1997–2000 | 36 | – | 36/36 | – | – | 18 (50) | 18 (50) |
| Ronen et al.[4] | 1990–94 | 38 | 13 (34) | 25/25 | 10 (40) | 15 (60) | – | – |
| Glass et al.[22] | 1996–2003 | 41 | 16 (39) | 23/25 | – | 14 (61) | – | – |
| Kwon et al.[35] | 2000–03 | 127 | 78 (62)[b] | – | – | – | – | – |
| Garfinkle and Shevell[32] | 1991–2007 | 62 | 5 (8) | 57/57 | 23 (40) | 34 (60) | – | – |
| Focal HI (7.5–20) | | | | | | | | |
| Levy et al.[55] | 1980–83 | 7 | 0 | 7/7 | 1 (14) | 6 (86) | – | – |
| Mizrahi and Kellaway[53] | ? | 3 | 0 | 3/3 | 2 (67) | 1 (33) | – | – |
| Legido et al.[25] | 1982–85 | 3 | 0 | 3/3 | 2 (67) | 1 (33) | 3 (100) | 0 |
| Perlman et al.[56] | 1991–93 | 8 | – | 8/8 | 2 (25) | 6 (75) | 4 (50) | 4 (50) |
| Mercuri et al.[57] | 1991–94 | 7 | – | 7/7 | 4 (57) | 3 (43) | 6 (86) | 1 (14) |
| Ortibus et al.[24] | 1989–93 | 20[b] | 3 (15) | 17/17 | 9 (53) | 8 (47) | – | – |
| Estan and Hope[58] | 1987–93 | 12 | 0 | 12/12 | 11 (92) | 1 (8) | – | – |
| Bye et al.[50] | n/a | 2 | 0 | 2/2 | 2 (100) | 0 | 2 (100) | 0 |
| McBride et al.[13] | 1994–97 | 7 | 0 | 7/7 | 3 (43) | 4 (57) | 5 (71) | 2 (29) |
| Tekgul et al.[19] | 1997–2000 | 16 | – | 16/16 | – | – | 16 (100) | 0 |
| Intracranial haemorrhage (7–17) | | | | | | | | |
| Lombroso[52] | ? | 30 | 6 (20) | 24/24 | 9 (38) | 15 (62) | – | – |
| Mizrahi and Kellaway[53] | ? | 6 | 0 | 6/6 | 5 (83) | 1 (17) | – | – |
| Andre et al.[54] | 1980–81 | 6 | 3 (50) | 3/3 | 1 (33) | 2 (66) | – | – |
| Ortibus et al.[24] | 1989–93 | 20[c] | 3 (15) | 10/17 | – | – | 9 (90) | 1 (10) |
| Legido et al.[12] | 1982–85 | 1 | 1 (100) | 0/0 | 0 | 0 | 0 | 0 |
| Tekgul et al.[19] | 1997–2000 | 15 | – | 15/15 | – | – | 13 (87) | 2 (13) |
| Cerebral dysgenesis (4–12) | | | | | | | | |
| Bergman et al.[51] | 1976–79 | 5 | – | 5/5 | – | – | 0 | 5 (100) |
| Lombroso[52] | ? | 19 | 6 (32) | 13/13 | 1 (8) | 12 (92) | – | – |
| Mizrahi and Kellaway[53] | ? | 1 | 0 | 1/1 | 0 | 1 (100) | – | – |
| Ortibus et al.[24] | 1989–93 | 5 | 3 (60) | 2/2 | 0 | 2 (100) | – | – |
| Legido et al.[12] | 1982–85 | 5 | 3 (60) | 2/2 | 1 (50) | 1 (50) | 1 (50) | 1 (50) |
| Bye et al.[50] | n/a | 3 | 1 (33) | 2/2 | 1 (50) | 1 (50) | – | – |
| Tekgul et al.[19] | 1997–00 | 4 | – | 4/4 | – | – | 0 | 4 (100) |
| Ronen et al.[4] | 1990–94 | 9 | 4 (44) | 5/5 | 0 | 5 (100) | – | – |
| Hypoglycaemia (3–5) | | | | | | | | |
| Bergman et al.[51] | 1976–79 | 7 | – | 7/7 | – | – | 5 (71) | 2 (29) |
| Lombroso[52] | ? | 19 | 1 (5) | 18/18 | 14 (78) | 4 (22) | – | – |
| Mizrahi and Kellaway[53] | ? | 1 | 0 | 1/1 | 1 (100) | 0 | 1 (100) | 0 |
| Ortibus et al.[24] | 1989–93 | 4 | 0 | 4/4 | 2 (50)[c] | 2 (50)[c] | – | – |
| Legido et al.[12] | 1982–85 | 2 | 0 | 2/2 | 0 | 2 (100) | 1 (50) | 1 (50) |
| Bye et al.[50] | n/a | 1 | 1 (100) | 0/0 | 0 | 0 | – | – |
| Tekgul et al.[19] | 1997–2000 | 3 | – | 3/3 | – | – | 2 (67) | 1 (33) |
| Infection (5–17) | | | | | | | | |
| Bergman et al.[51] | 1976–79 | 16 | – | 16/16 | – | – | 9 (56) | 7 (44) |
| Lombroso[52] | ? | 20 | 5 (25) | 15/15 | 7 (47) | 8 (53) | – | – |
| Mizrahi and Kellaway [53] | ? | 5 | 0 | 5/5 | 2 (40) | 3 (60) | – | – |
| Andre et al.[54] | 1980–81 | 13 | 5 (38) | 8/8 | 7 (88) | 1 (12) | – | – |
| Ortibus et al.[24] | 1989–93 | 11 | 5 (45) | 6/6 | 0 | 6 (100) | – | – |
| Legido et al.[12] | 1982–85 | 5 (meningitis) | 2 (40) | 3/3 | 1 (33) | 2 (67) | 1 (33) | 2 (67) |
| | | 2 (sepsis) | 2 (100) | 0/0 | 0 | 0 | 0 | 0 |
| McBride et al.[13] | 1994–97 | 2 | 1 (50) | 0/1 | – | – | – | – |
| Bye et al.[50] | n/a | 3 | 0 | 3/3 | 0 | 3 (100) | 0 | 3 (100) |
| Tekgul et al.[19] | 1997–2000 | 3 | – | 3/3 | – | – | 2 (67) | 1 (33) |
| Ronen et al.[4] | 1990–94 | 17 | 3 (18) | 14/14 | 7 (50) | 7 (50) | – | – |
| | | 7 term | 0 | 7/7 | 7 (100) | 0 | – | – |
| Ter Horst et al.[59] | 2000–2006 | 12 | 3 (25) | 9/9 | 5 (56) | 4 (44) | 7 (78) | 2 (22) |

**Table 1** (*continued*)

| Clinical category and publication *Aetiology (% of total)* | Year of study | No. of children | Deaths *n* (%) | No. of children followed up | Outcome for survivors | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Normal *n* (%) | Any disability *n* (%) | No or mild impairment only | Moderate or severe impairment |
| Inborn error of metabolism (1–2) | | | | | | | | |
| Legido et al.[12] | 1982–85 | 1 | 1 (100) | 0 | 0 | 0 | – | – |
| Bye et al.[50] | n/a | 1 | 1 (100) | 0 | 0 | 0 | – | – |
| Tekgul et al.[19] | 1997–2000 | 1 | 0 | 1/1 | 1 (100) | 0 | – | – |
| Unknown aetiology (7–15) | | | | | | | | |
| Bergman et al.[51] | 1976–79 | 16 | – | 16/16 | – | – | 12 (75) | 4 (25) |
| Lombroso[52] | ? | 54 | 3 (6) | 51/51 | 37 (73) | 14 (27) | – | – |
| Legido et al.[12] | 1982–85 | 3 | 0 | 3/3 | 1 (33) | 2 (67) | 1 (33) | 2 (67) |
| Bye et al.[50] | n/a | 4 | 1 (25) | 3/3 | 2 (67) | 1 (33) | – | – |
| Tekgul et al.[19] | 1997–2000 | 11 | 0 | 11/11 | 9 (82) | – | 11 (100) | 0 |
| Ronen et al.[4] | 1990–94 | 5 | 0 | 5/5 | 2 (40) | 3 (60) | – | – |

T, term; P, preterm; HI, hypoxia–ischaemia; CHD, coronary heart disease; n/a, not available.
[a] Hypoxic–ischaemic encephalopathy and intracranial haemorrhage grouped together.
[b] Haemorrhage and infarction grouped together.
[c] Metabolic aetiologies grouped together.

associated with increased risk of mortality and morbidity, which does suggest that allowing electrical seizures to go untreated may either induce neuronal injury or exacerbate existing brain injuries.[13]

Only one trial has attempted to address short-term outcomes for this issue. Van Rooij et al. report an 11-centre randomised trial in which 42 term babies with HIE and seizures were assigned to treating only clinical seizures ($N = 19$) or all clinical and electrographic seizures ($N = 23$) spanning the period of introduction of therapeutic hypothermia. In the 'clinical only' group aEEG was recorded but the attending staff were blinded to the recording. No baby presented with subclinical status epilepticus and none received muscle relaxants. Electrographic seizure duration tended to be longer in infants in whom only clinical seizures were observed and clinical seizures were not consistently correlated with aEEG patterns, although only single-channel recordings were made. Median seizure duration was 196 min in the clinical-plus-aEEG group and 503 min in the clinical-only group. Seizure duration was correlated with severity of MRI injury in the clinical-only group and in the whole population. Although not statistically significant, the differences appear clinically important.

However, Kurul et al.[26] in a small study of a mixed population of newborn babies with seizures found no psychomotor problems in seven infants with EEG-only seizures at 12 months of age, by contrast with 54% of 13 infants with clinical seizures confirmed on EEG.

**Table 2**
Summary of typical outcomes in reports of babies born at term by aetiology.

| | No impairment (%) | Death (%) | Disability (%) | Disability among surviving children (%) |
|---|---|---|---|---|
| Overall | 40% (36–45) | 12% (7–33) | 46% (27–55) | 54% (40–61) |
| Global HIE | 31% (7–62) | 35% (8–62) | 46% (26–60) | 61% (30–90) |
| Stroke | 38% (14–92) | 0 | 46% (8–86) | 46% (8–86) |
| Cerebral dysgenesis | 5% (0–5) | 38% (0–60) | 59% (40–100) | 95% (63–100) |
| Infection | 44% (0–100) | 28% (0–45) | 34% (0–60) | 44% (0–100) |

HIE, hypoxic–ischaemic encephalopathy.
Values are mean (range).

The inter-ictal pattern of background EEG activity has repeatedly been shown to correlate well with outcome, both in full term and preterm infants and generally independent of the underlying aetiology.[27] Prediction, as would be anticipated, is best at extremes, significant adverse neurodevelopmental sequelae being rare when background activity is normal. A persistently abnormal background activity (burst–suppression pattern, prolonged inter-burst intervals of >20 s, marked voltage suppression or electro-cerebral silence) increases the likelihood of a poor outcome. The rate of improvement of the background EEG is a useful prognostic tool, with most experience being reported in HIE, but it is critical that background EEG be interpreted in full knowledge of medication (sedatives, anticonvulsants and other medication) and gestational age. Typically, background activity is suppressed following recent hypoxic ischaemic insult, and the return of sleep–wake cycling within 36 h can be seen as a good prognostic indicator.[28] With the advent of therapeutic hypothermia, it can take longer for normal background patterns to return, and a good prognosis can still be hoped for even if the return is delayed until 48 h.[29]

When attempting to predict outcome in a term baby with HIE, there is a wealth of experience based on background EEG, seizure burden, clinical examination and results of neuroimaging, which should all be considered before talking to parents (Fig. 1).

## 4. Neurological and developmental outcomes in term infants with neonatal seizures related to specific aetiology

Determining the cause of seizures is essential before attempting to give a prognosis, and modern standards of investigation allow a cause to be assigned in around 95% of cases (Fig. 1). Tables 1 and 2 summarise the reported prevalence of aetiologies and outcomes. Post-asphyxial encephalopathy, cerebral dysgenesis and meningitis/encephalitis are most consistently associated with adverse neurodevelopmental outcome. By contrast, focal cerebral ischaemia (stroke), subarachnoid haemorrhage, transient metabolic disturbances and idiopathic seizures have almost universally favourable outcome, including the familial cases and seizures presenting around the fifth day of age ('fifth-day fits'). Fifth-day fits now seem very rare: no cases have been reported in the literature since 1989.[2,30]

Tekgul et al.[19] described 100 term babies with clinically diagnosed neonatal seizures over a 38-month period. Seven died and four were lost to follow-up, 89 were followed up at 12–18 months. The authors report outcome by clinical neurological examination,

**Table 3**
Individual reports of outcome following neonatal seizures in preterm babies.

| Publication | Year of study | Population | Age | Seizures | *n* | All with neonatal seizures | | | Domain of impairment (% survivors assessed) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Death *n* (%) | Normal *n* (%) | Impaired *n* (%) | Development *n* (%) | Ongoing seizures *n* (%) | Cerebral palsy *n* (%) | Hearing (H) Vision (V) *n* (%) |
| Ronen et al.[4] | 1990–95 | <37 weeks | >7 years | Clinical | 26 | 11 (42%) | 3 (12%) | 12 (46%) | 6/15 (40%) | 6/15 (40%) | 8/15 (53%) | – |
| Scher et al.[5] | 1983–87 | Preterm (</>30 weeks) | 6.5 years | EEG-confirmed | 62 | 36 (58%) | 9 (14%) | – | 15/36 (42%) | 6/36 (17%) | 21/36 (59%) | – |
| Watkins et al.[8] | 1977–81 | <1000 g | 5 years | Clinical | 65 | 35 (54%) | 10 (15%) | 19 (29%)[a] | 12/30 (40%) | n/a | 12/30 (40%) | H: none V: 7/30 (23%) |
| Van Zeben-van der Aa et al.[9] | 1983 | <32 weeks and <1500 g | 2 years | Clinical | 72 | 44 (61%) | 16 (22%) | 12 (17%)[b] | – | – | – | – |
| Davis et al.[7] | 2000–05 | <1000 g | 18–22 months | Clinical | 383 | 86 (22%) | 37 (10%) | 260 (68%) | 154 (55%)[c] 177 (64%)[d] | 47/297 (16%)[e] | 94 (32%) | H: 32 (11%) V: 119 (43%) |

EEG, electroencephalography.
[a] 20% severe; 4.5% moderate; 4.5% mild.
[b] 16% 'major',1% 'minor'.
[c] Bayley Scales of Infant Development (BSID-2) Psychomotor Development Index <70.
[d] BSID-2 Mental Development Index <70.
[e] Treated seizures: 23/297 (8%).

type of seizure, EEG findings, neuroimaging, and extensive aetiological investigation on neurological and developmental outcome. Overall, 28% (25/89) of the survivors in this cohort of term infants with neonatal seizures had a poor outcome (defined as moderate or severe motor or neurosensory impairment, low developmental scores (Bayley Scales of Infant Development 2E, Mental Development Index (MDI) score <70), or post-neonatal seizures), but outcome varied between different aetiologies.

Garfinkle and Shevell[31,32] report outcomes for 120 of 124 term babies with seizures born between 1991 and 2007 treated in a single NICU in Montreal. Mean age at follow-up was 4.4 years for those with normal outcomes (minimum 12 months) and 6.0 years for those with abnormal outcomes (minimum 24 months). Eleven children (9%) died and 56 (47%) survived with impairment: 25% had cerebral palsy (which accounted for six of the deaths) and 38% had global developmental delay (eight of these children died). Most children had complex impairment in more than one field (only six children had isolated CP, 12 isolated developmental delay and five epilepsy) and 17 (14%) were impaired in all three domains.

### 4.1. Hypoxic ischaemic encephalopathy

This is the most frequent cause of seizures at term, and also the most researched with respect to predictors of outcome. The prognosis in HIE is determined from a range of clinical and investigative modalities which include neuroimaging and spectroscopy. The lactate:N-acetylaspartate (Lac:NAA) ratio determined by spectroscopy is not widely available but has been demonstrated to be a very accurate tool.[33]

In some studies, the duration of electrographic seizures in newborn babies is associated with worse MRI appearances[14] and poor neurodevelopmental outcome[13] (see previous section). Newborn babies with HIE as a cause of seizures tend to have more seizures which are longer (i.e. a higher seizure burden) than those with stroke.[13] These data suggest that controlling seizures after global hypoxic–ischaemic insults is prudent, and that success may enhance outcome. In general, reported outcomes are similar to those of Garfinkle and Shevell who described cerebral palsy in 28/62 (45%) who experienced neonatal seizures due to asphyxia.[32] Thirty-three (53%) had developmental delay and 31% epilepsy.

Therapeutic hypothermia not only improves the outcomes of babies with HIE by reducing the rate of death and disability at 18 months of age, but it also appears to reduce the seizure burden. In a cohort of 64 babies with moderate or severe encephalopathy who underwent prolonged continuous EEG monitoring, 37 babies had EEG seizures. In babies with moderate encephalopathy there was a significant reduction in seizure burden from a mean of 162 to 49 min, but the effect was not seen in children with severe encephalopathy (223 and 224 min respectively).[34] Therapeutic hypothermia appears either to act directly to reduce seizure burden or to augment the action of conventional anticonvulsants in this setting, which may be one route by which it is effective in improving long-term outcomes. These data are consistent with those from preclinical models.[34]

Kwon et al.[35] studied 127 babies who presented with clinical seizures among 208 with HIE entered into the National Institute of Child Health and Human Development (NICHD) trial of therapeutic hypothermia (61%). After adjustment for hypothermia and severity of encephalopathy, the presence of clinical seizures (no EEG confirmation available) was not associated with a worse outcome (death, moderate or severe disability or lower Bayley MDI scores at 18 months of age). They concluded that the mortality and morbidity in this group of infants with HIE can be better explained by the severity of encephalopathy. However, Glass et al.[22] observed that even after adjusting for cooling and the degree of encephalopathy, their group with seizures had a doubling of the risk of survival with a Bayley MDI <70, just failing to reach conventional statistical significance (95% confidence interval: 0.83–4.48). The NICHD trial secondary analysis does not exclude seizures as part of the causal pathway from encephalopathy to impaired outcomes, which it does seem to be in light of the findings of Low et al. mentioned above.

### 4.2. Focal infarction

Many children who sustain perinatal arterial stroke will survive with minimal or no disability, whether or not they present with seizures. Involvement of all three sites including the cerebral hemisphere, the basal ganglia and the posterior limb of the internal capsule generally predicts a later hemiplegia irrespective of the size of the infarct.[36,37]

Children with cerebral sinus venous thrombosis (CSVT) often present with seizures, and outcome in symptomatic cases is generally poor.[38] It is important to have a high index of suspicion and to perform magnetic resonance venography, as early treatment with low molecular weight heparin may improve long-term outcome

although international practice remains variable.[38,39] CSVT is diagnosed more often now that MRI is used, and this has a variable prognosis depending on the severity, although 30–50% of babies with symptomatic CSVT have a neurodevelopmental deficit (Kersbergen et al.[39]). None of the 33 cases diagnosed in Utrecht between 2002 and 2010 developed cerebral palsy, but 19% developed epilepsy and three of the 12 survivors assessed at 2 years had a Developmental Quotient (Griffiths Mental Developmental Scale) (DQ) more than 1 SD below the mean.

### 4.3. Haemorrhage

Primary subarachnoid haemorrhage as a cause of seizures has a universally good prognosis.

Intraventricular haemorrhage is rare in term infants but in those that present with seizures there is frequently an associated CSVT, or the bleeding arises from the choroid plexus. Many term babies who sustain IVH have significant medical complications such as congenital heart disease, or a requirement for extracorporeal membrane oxygenation, and these conditions tend to dominate the prognosis.[40] IVH remains largely a disease of preterm babies, and when IVH is accompanied by seizures the prognosis is generally poor.[11]

### 4.4. Metabolic disorders

Metabolic disorders such as hypoglycaemia and hypocalcaemia are an uncommon cause of seizures in modern practice. When seizures are seen in association with hypoglycaemia, they do not necessarily occur at the same time as the low glucose levels.[41] If neuroglycopenia is profound enough to result in seizures, around 50% of the children are likely to be impaired at follow-up.[42]

Severe, prolonged symptomatic hypoglycaemia is associated with damage in the parieto-occipital lobes on MRI resulting in cognitive and visual disability. The outcome of symptomatic hypoglycaemia appears to be worse in babies who have a poor ketogenic response, particularly those with hyperinsulinaemia.[43] Early hypoglycaemia is often seen in babies who were asphyxiated, and although the effect is difficult to disentangle from the primary problem, these babies tend to have a worse outcome.[44]

Inborn errors of metabolism presenting with seizures are rare, but tend to have a poor prognosis because neonatal presentation is usually a sign of more severe type. The outcomes for those children depend on the outcome and severity of each disorder, and the time taken to achieve control of symptoms.

Many children with pyridoxine dependency have severe cognitive disabilities despite early diagnosis and treatment, although recently there have been suggestions that higher doses may improve the outcome.[45]

### 4.5. Meningitis

Bacterial meningitis may present with seizures, in which case there is a high risk of later impairment (around 50%). This prognosis may be refined using the pattern of background EEG activity, neurological examination and neuroimaging. Most babies who have viral meningitis presenting with seizures have some impairment at follow-up.

### 4.6. Congenital malformations of the brain

Disorders of neuronal migration such as lissencephaly or schizencephaly can present with neonatal seizures. The prognosis is driven by the underlying diagnosis.

### 4.7. Familial epileptic syndromes

Benign familial neonatal convulsions (BFNC) are an example of a 'channelopathy'. This rare condition has an autosomal dominant inheritance with 85% penetrance, and mutations have been found in the genes situated on chromosomes 20q and 8q which code for a family of voltage-gated potassium channels [M (for muscarine) channels]. There is usually a family history of neonatal seizures but they are associated with normal psychomotor development, a normal inter-ictal EEG and a favourable outcome.

### 4.8. Epileptic encephalopathies

In Ohtahara syndrome (early infantile epileptic encephalopathy) seizures usually develop within the first 10 days of life and may occur as early as the first hour after delivery. The prognosis is very poor; psychomotor development is arrested and severe neurological abnormalities such as spastic diplegia, hemiplegia, tetraplegia, ataxia, or dystonia develop.

## 5. Risk of later epilepsy

One question often raised by parents is the likely risk of seizures recurring during childhood. It is appropriate to stress that this is highly dependent on the underlying condition and the risk of epilepsy posed by that. However, there are estimates of later risk for children following seizures complicating common neonatal conditions: between 10% and 20% babies with neonatal seizures will go on to have further seizures in childhood.[19]

Legido et al.[25] evaluated a cohort of 40 patients with EEG-confirmed seizures of varying aetiologies (28 term and 12 preterm infants). Significant predictors of later epilepsy were severely abnormal neurological evaluation, >10 seizures per hour and moderately–severely abnormal EEG background. Other clinical or neurophysiological variables (in particular, seizure duration, variously defined) did not contribute to the prediction. Of the subgroup of 20 patients with a diagnosis of 'asphyxia' a severely abnormal neurological evaluation was the sole predictor, but all inter-ictal EEG backgrounds were moderately–severely abnormal in this group.

In children surviving HIE, the frequency of epilepsy is probably higher than in any other group. In one retrospective analysis of 62 term infants with HIE and clinical seizures, 26% had post-neonatal seizures, but for most children this was in combination with other impairments (such as developmental delay or cerebral palsy).[32]

Toet et al.[46] in The Netherlands reported on 165 babies with perinatal asphyxia, in whom 9 out of 91 (10%) survivors developed epilepsy, mostly between 3 months and 4 years later. The authors observed that this was a lower incidence than previously reported and state that in their unit babies receive treatment for both clinical and 'subclinical' seizures because routine aEEG monitoring is in place. This group also reported a high incidence (18%) of later epilepsy in children who had perinatal arterial stroke. There was a strong relationship between abnormal neurological outcome and post-neonatal epilepsy.

Neonatal seizure burden seems to be reduced among children with HIE who are treated with therapeutic hypothermia[34] but in the trials this effect was minimal (typical relative risk: 0.96; 95% confidence interval: 0.85–1.10).[47] Table 4 shows the prevalence of seizures at follow-up in the major trials for all children. Among the control arms of the three early major trials, seizures were present in 14–16% at 18 months and in 16% of the NICHD cohort at 6–8 years. A small and non-significant reduction in seizures was seen following neonatal hypothermia to 10–15% (and 10% at 6–8 years in

**Table 4**
Prevalence of seizures at 18–24 months in trial populations from major therapeutic hypothermia studies.

| Trial | Reference | Reported to have seizures at 18–24 months | | |
|---|---|---|---|---|
| | | Cooling | Control | OR/RR (95% CI) |
| CoolCap | 60 | 11/72 (15%) | 11/67 (16%) | OR: 0.92 (0.38–2.24) |
| TOBY | 61 | 12/116 (10%) | 16/116 (14%) | RR: 0.75 (0.37–1.51) |
| NICHD | 62 | 13/77 (12.8%) | 14/65 (13.6%) | |
| Moderate HIE | | 9/60 (15%) | 10/49 (21%) | RR: 0.69 (0.27–1.76) |
| Severe HIE | | 4/17 (24%) | 4/16 (29%) | RR: 0.79 (0.22–2.90) |
| ICE | 47 | 6/79 (7.6%) | 2/58 (3.4%) | RR: 2.2 (0.46–10.52) |
| Neo.nEURO.network | 63 | n/a | n/a | |

OR, odds ratio; RR, risk ratio; CI, confidence interval; TOBY, Whole Body Hypothermia for the Treatment of Perinatal Asphyxial Encephalopathy; NICHD, National Institute of Child Health and Human Development; HIE, hypoxic–ischaemic encephalopathy; ICE, Infant Cooling Evaluation; n/a, not applicable.

the NICHD cohort). The Infant Cooling Evaluation trial reported very different and lower rates of epilepsy with a greater proportion in their cooled group at follow-up. Thus although increasingly therapeutic hypothermia is believed to reduce neonatal seizure burden there is as yet little evidence that this translates to a significant reduction in later epilepsy.

The prevalence of later epilepsy is high following status epilepticus[48] although the background EEG pattern before the onset seizures may correlate better with outcome than the duration.[16] It is likely that the severe seizure disorder represents extensive underlying pathology, reflected in the poor outcome. There is no association between the ability to control status epilepticus and subsequent neurodevelopmental outcome.[16]

In preterm children this has been rarely studied systematically, but the persistence rate may be significantly higher. In a cohort of 88 babies, comprising 62 term and 26 preterm, followed to a median age of 10 years, the prevalence of epilepsy was 40% in preterm, compared to 18% in term infants, and the presence of seizures was independently predictive of poor outcome.[4]

## 6. Outcomes in preterm infants following neonatal seizures

Compared with term babies, the population prevalence of clinical seizures is higher in preterm infants and outcomes in this group are worse. Despite this, there are fewer reports of outcomes in this group as seizures are still relatively infrequent and most outcome studies concentrate on whole populations, in whom co-morbidities may determine outcome more closely; this renders it difficult to study outcomes following seizures per se.[7]

Table 3 summarises the data for outcome following neonatal seizures in preterm children from a range of different studies.

In a cohort of 88 infants described by Ronen et al.,[4] 62 term and 26 premature infants were followed to a median age of 10 years. Rates of death and impairment in the preterm group were significantly higher than in terms (death 42% vs 16%, disability 46% vs 39%, cerebral palsy 53% vs 17%, epilepsy 40% vs 18%, mental retardation 40% vs 14%).

Davis et al.[7] report long-term outcomes for surviving babies of <1000 g birthweight who had seizures in the NICHD cohort. Clinical seizures occurred in 416 of 6499 babies (6.4%), a large proportion of whom died after 36 weeks of postmenstrual age (22%). Seizures were significantly associated with late death or neurodevelopmental impairment (odds ratio: 3.15; 95% confidence interval: 2.37–4.19).

Overall, in reports including 'preterm' babies, around 40% of seizures result from hypoxia–ischaemia in near-term babies, with similar prognosis to HIE in term babies. Among more immature infants, germinal matrix haemorrhage and its associated complications (haemorrhagic parenchymal infarction, progressive ventriculomegaly) more frequently provoke neonatal seizures than in the term population, and underlie up to 30–45% of seizures occurring preterm.[2,3,5,10] The prevalence of germinal matrix haemorrhage, particularly severe intraventricular haemorrhage, has fallen, which should translate into reduced seizure prevalence.

Tonic seizures are relatively more common among preterm babies, compared with term, and indicate a poorer prognosis.[20]

Evidence is also emerging that subclinical seizures appear to be more frequent in preterm babies when EEG monitoring is systematically performed in high-risk infants, hence many babies may have untreated seizures but the risk of failing to diagnose and treat them is unknown. In the study from Scher et al.[5] 45% of 62 preterm children had electroclinical seizures (37% of those <30 weeks of gestational age), compared with 53% of 30 term babies.[5,12] In two cohorts of preterm babies with EEG-confirmed seizures, only two of 11 and none of the 11 infants were found to have clinical seizures.[11,49] Because of this, the prevalence of neonatal seizures in preterm infants is reported to be much higher when using EEG recording compared with a reliance on clinical diagnosis (15–21%).[11,49] Babies with subclinical seizures are more likely to have lower gestational age, lower birthweight and to be sicker.

In our view, routine EEG monitoring is not indicated in low-risk term or moderately preterm babies, who seem to be unlikely to experience subclinical seizures, but it should be remembered that the use of EEG recording is an important tool to detect seizures in high-risk infants (for example, following encephalopathy, severe IVH, congenital cerebral anomalies, confirmed meningitis/encephalitis),[13] especially if the baby is receiving muscle relaxants as part of care. Increased availability and use of cotside EEG monitoring in high-risk preterm babies is likely to yield dividends in the future.

## 7. Conclusions

Clinical and electrographic seizures are important risk factors for poor outcomes in term and preterm children. Seizures are the manifestation of significant disturbance of neuronal function, which is usually associated with underlying neurological disorder, which in turn is the major determinant of outcome. In many scenarios complicated by seizures, the extent to which they are part of the causative pathway to later impaired outcome is unclear, but untreated seizures may amplify brain-injuring processes and worsen outcome. There is some debate as to whether seizures themselves are damaging, but, given the current state of knowledge, it is our view that every effort should be made to control seizures, with a reasonable expectation of minimizing any further damage. It is now clear that many babies have subclinical seizures which are unrecognised even in neurologically focused intensive care, and it remains to be seen whether or not the increased use of cotside EEG and aEEG monitoring with treatment to electrical quiescence can improve outcome.

**Practice points**

Factors determining high risk of poor outcome in neonatal seizures:

- prematurity;
- HIE;
- cerebral dysgenesis;
- central nervous system infection;
- severe IVH;
- severely abnormal EEG inter-ictal activity (isoelectric pattern, paroxysmal, burst–suppression and low-voltage background).
- Less strongly associated (variable reports):
  - severely abnormal neurological examination (less specific).
  - severely abnormal neuroimaging.
  - early onset of seizures (within 24 h; related to HIE in term babies).
  - severity of seizures/presence of status epilepticus.

Associated with favourable outcome:

- focal infarct ('stroke') on MRI;
- transient metabolic disturbance, e.g. hypocalcaemia;
- normal inter-ictal EEG activity;
- normal early neurological examination;
- diagnosis of benign familial seizures;
- neonatal sleep myoclonus;
- clinical seizures with no EEG correlate;
- less strongly associated:
  - normal/mild abnormality on neuroimaging.
  - late onset (>5 days; related with benign neonatal seizures)
  - focal clonic seizures, likely related to focal structural lesion in the brain.

## Conflict of interest statement

None declared.

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# Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial

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# Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial

**WHAT'S KNOWN ON THIS SUBJECT:** Seizures are common in full-term infants with HIE. A substantial portion of neonatal seizures are subclinical. There is concern about possible adverse effects of neonatal seizures on the immature brain.

**WHAT THIS STUDY ADDS:** Immediate treatment of both clinical and subclinical seizures reduced the total duration of seizure patterns, which suggests a possible reduction of brain injury.

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## abstract

**OBJECTIVES:** The goals were to investigate how many subclinical seizures in full-term neonates with hypoxic-ischemic encephalopathy (HIE) would be missed without continuous amplitude-integrated electroencephalography (aEEG) and whether immediate treatment of both clinical and subclinical seizures would result in a reduction in the total duration of seizures and a decrease in brain injury, as seen on MRI scans.

**METHODS:** In this multicenter, randomized, controlled trial, term infants with moderate to severe HIE and subclinical seizures were assigned randomly to either treatment of both clinical seizures and subclinical seizure patterns (group A) or blinding of the aEEG registration and treatment of clinical seizures only (group B). All recordings were reviewed with respect to the duration of seizure patterns and the use of antiepileptic drugs (AEDs). MRI scans were scored for the severity of brain injury.

**RESULTS:** Nineteen infants in group A and 14 infants in group B were available for comparison. The median duration of seizure patterns in group A was 196 minutes, compared with 503 minutes in group B (not statistically significant). No significant differences in the number of AEDs were seen. Five infants in group B received AEDs when no seizure discharges were seen on aEEG traces. Six of 19 infants in group A and 7 of 14 infants in group B died during the neonatal period. A significant correlation between the duration of seizure patterns and the severity of brain injury in the blinded group, as well as in the whole group, was found.

**CONCLUSIONS:** In this small group of infants with neonatal HIE and seizures, there was a trend for a reduction in seizure duration when clinical and subclinical seizures were treated. The severity of brain injury seen on MRI scans was associated with a longer duration of seizure patterns. *Pediatrics* 2010;125:e358–e366

**KEY WORDS**
neonatal seizures, subclinical seizures, amplitude-integrated electroencephalography, antiepileptic drugs

**ABBREVIATIONS**
AED—antiepileptic drug
aEEG—amplitude-integrated electroencephalography
cEEG—conventional electroencephalography
HIE—hypoxic-ischemic encephalopathy
EEG—electroencephalography

This trial has been registered at the International Standard Randomized Controlled Trial Number Registry (identifier ISRCTN61541169).

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Neonatal seizures are common in full-term infants with hypoxic-ischemic encephalopathy (HIE) and pose a high risk for death or neurologic disability.[1–4] Clinical recognition of neonatal seizures may be difficult, because manifestations may be subtle.[4] Conventional electroencephalography (cEEG) is the standard method to confirm neonatal seizures. Unfortunately, this tool has its limitations; in most units, equipment, technicians, and experienced clinical neurophysiologists are not available 24 hours per day. In the past decade, amplitude-integrated electroencephalography (aEEG) has become a bedside tool that is now used routinely in many NICUs. Prolonged monitoring with aEEG as well as continuous video electroencephalography (EEG) has shown that a substantial proportion of neonatal seizures are subclinical, especially after administration of antiepileptic drugs (AEDs).[5–9] Because clinical recognition of neonatal seizures is difficult, the presence of clinical seizures may be overestimated, resulting in unnecessary use of AEDs. Conversely, subclinical neonatal seizures may not be recognized without continuous monitoring, resulting in inadequate treatment.[9,10] Although human data are scarce, studies suggest an adverse effect of both clinical and subclinical seizures on neurodevelopmental outcomes. Neonatal seizures have been reported to predispose patients to later problems with regard to cognition, behavior, and development of postneonatal epilepsy.[1,2,11] Although there is potential harm of seizures in the immature brain, there also is concern about possible adverse effects of anticonvulsant medications on the developing brain.[12–14] Previous studies showed that infants treated for clinical and subclinical seizures had a lower incidence of postneonatal epilepsy, compared with those treated only for clinical seizures.[15–18] This was one of the reasons we performed this randomized, controlled trial to investigate whether immediate treatment of both clinical and subclinical seizures detected with continuous aEEG resulted in reduction of the total duration of seizures and less-severe brain injury seen on MRI scans.

## METHODS

### Study Design

We conducted a randomized, prospective, multicenter trial (Subclinical Seizure Question [Suseque] Study). Eleven perinatal centers in the Netherlands and Belgium participated between November 2003 and April 2008. All participating centers were trained in the application and interpretation of aEEG and followed a standardized study protocol. The institutional review board of every center approved the protocol. Written informed consent was obtained from parents before randomization.

### Entry Criteria

Infants were eligible for the study on the basis of gestational age of $\geq$37 weeks, admission to 1 of the NICUs $<$24 hours after birth, and diagnosis of HIE and neonatal seizures. HIE was defined on the basis of meeting $\geq$3 of the following criteria: (1) signs of intrauterine asphyxia (ie, late decelerations on fetal electrocardiograms or meconium-stained liquor), (2) arterial cord blood pH of $<$7.10, (3) delayed onset of spontaneous respiration, (4) Apgar score of $\leq$5 at 5 minutes, or (5) multiorgan failure (elevated liver enzyme levels, reduced diuresis, and cardiovascular problems).

Exclusion criteria included the presence of congenital or chromosomal abnormalities, maternal use of narcotics or sedatives, treatment with phenytoin before referral, and administration of muscle-relaxing drugs. Infants who demonstrated subclinical status epilepticus at the beginning of the aEEG registration also were excluded, because immediate treatment with AEDs was considered indicated.

### Randomization

For infants who met the entry criteria, aEEG was started immediately after admission. If infants demonstrated clinical seizures, then they were treated with AEDs. When infants showed their first subclinical seizure, as confirmed with aEEG, they were assigned randomly to either group A (treatment of both clinical and subclinical seizure patterns) or group B (blinding of the aEEG registration and treatment of only clinical seizures). We stratified randomization according to center with a randomized block design with a block size of 6. Randomization codes for every center were supplied in numbered sealed envelopes.

### aEEG Monitoring

aEEG was performed with an Olympic 6000 cerebral function monitor (Natus, Seattle, WA). Single-channel aEEG signals were recorded from 2 parietal needle electrodes (corresponding to P3 and P4 in the International 10–20 System). The EEG signal was filtered, rectified, and smoothed before it was printed out at slow speed (6 cm/hour). A second tracing recorded the electrode impedance continuously. The Olympic 6000 monitor gave access to the raw EEG data in the review mode and, with the latest software version, the raw EEG signal ran continuously during recording. For blinding of the screen, we used special software (Olympic Medical, Seattle, WA). During blinding, the impedance recording was visible and events such as care procedures, medications, and clinical seizures could be marked.

### Treatment Protocol

Table 1 shows the treatment protocol. In the first years (November 2003 to

**TABLE 1** Treatment Protocol for Neonatal Seizures

| Step | Treatment |
|---|---|
| 1 | Phenobarbitone: 20 mg/kg, eventually another 10 mg/kg |
| 2[a] | Midazolam: loading dose of 0.05 mg/kg, followed by continuous infusion of 0.15 mg/kg per h, to maximum of 0.2 mg/kg per h (when seizures have been stopped for 24 h, tapered to 0.1 mg/kg per h and stopped after 48 h) |
| 3[a] | Lidocaine: loading dose of 2 mg/kg, followed by continuous infusion of 6 mg/kg per h for 6 h, then 4 mg/kg per h for 12 h, and then 2 mg/kg per h for 12 h (always stopped after 36 h) |
| 4[a] | Clonazepam: loading dose of 0.1 mg/kg, followed by continuous infusion of 0.1–0.5 mg/kg per d |
| 5[a] | Pyridoxine: 50 mg/kg |
| 6[a] | Further treatment on basis of clinician's decisions |

[a] Every next step is taken when no effect is seen within 1 to 2 hours after administration of the AED or when recurrence of seizures is noted.

June 2005), lidocaine was given as a second-line drug. Because of concerns about potential cardiovascular side effects and the fact that midazolam was sometimes used around the time of intubation, we changed our treatment protocol,[19] with midazolam being given as the second AED. Twenty-six infants received midazolam as a second drug.

## Grading of HIE

HIE was classified as moderate (grade II) or severe (grade III) according to the criteria described by Sarnat and Sarnat.[20] Evaluation of HIE took place 24 and 48 hours after birth.

## aEEG Analysis

Seizure patterns (characteristic pattern, with a sudden increase of both minimal and maximal amplitudes of the recorded signal and a decrease in amplitude in the postictal period) were classified[21] as a single seizure pattern, repetitive seizures (≥3 seizure patterns during a 30-minute period), or status epilepticus (continuous seizure pattern for ≥30 minutes, presenting as a "sawtooth pattern" or as continuous increases of the lower and upper margins). All aEEG recordings were analyzed off-line after the completion of enrollment. Analysis was performed independently by 2 aEEG experts (Drs de Vries and Toet), with respect to seizure patterns and background pattern. The readers had full access to all marked events, for differentiation between true ictal discharges and artifacts. When there was disagreement about seizure discharges or background patterns between the 2 raters, a third rater (Dr van Rooij) was involved and consensus was reached.

For each infant, the total duration of seizures was calculated (in minutes) by using the raw EEG data. When status epilepticus was seen, this was taken as 1 period. Only seizure patterns that could be confirmed with the raw EEG data were selected. When AEDs were given, we assessed whether treatment was appropriate, meaning that AEDs were given within 2 hours after the onset of clinical and/or subclinical seizures and another AED was administered if no effect was seen within 1 to 2 hours. For infants in group B, who received AEDs for clinical seizures, we analyzed the aEEG findings for the presence of EEG seizure patterns at the time when clinical seizures were observed.

## MRI Scoring

Depending on their clinical condition, infants underwent MRI 4 to 10 days after birth. MRI scans were reviewed retrospectively by 2 investigators (Drs Groenendaal and de Vries), who were blinded to aEEG results. The severity of brain injury was assessed by using conventional T1- and T2-weighted spin echo sequences, with diffusion-weighted imaging and apparent diffusion coefficient maps when available. Injury was scored for the basal ganglia and thalami in combination with cortical involvement, the watershed areas, and the posterior limb of the internal capsule, by using systems described previously as being predictive for neurodevelopmental outcomes after HIE[22–24] (Table 2).

## Statistical Analyses

Before the study was started, a power analysis was performed by using a power ($1 - \beta$) of .80 and a significance level ($\alpha$) of .05. This resulted in a sample size of 65 infants in both groups.

**TABLE 2** Scoring System for Brain Injury Seen on MRI Scans

| Score | Description |
|---|---|
| Basal ganglia and thalamus | |
| 0 | Normal |
| 1 | Abnormal signal in thalamus |
| 2 | Abnormal signal in thalamus and lentiform nucleus |
| 3 | Abnormal signal in thalamus, lentiform nucleus, and perirolandic cortex |
| 4 | More-extensive involvement |
| Watershed areas | |
| 0 | Normal |
| 1 | Single focal infarction |
| 2 | Abnormal signal in anterior or posterior watershed white matter |
| 3 | Abnormal signal in anterior or posterior watershed cortex and white matter |
| 4 | Abnormal signal in both anterior and posterior watershed zones |
| 5 | More-extensive cortical involvement |
| Posterior limb of internal capsule | |
| 0 | Myelination present |
| 1 | Myelination present but impaired |
| 2 | Myelination absent |

Statistical analysis was performed by using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). Comparisons of baseline and aEEG characteristics between groups were made with Fisher's exact test or $\chi^2$ tests for categorical variables and with *t* tests for logarithmically transformed continuous variables. Univariate linear regression models were used to test differences in the duration of seizure patterns between groups and to evaluate the association between seizure duration and MRI scores. The level of significance was set at .05.

## RESULTS

### Baseline Characteristics

During the study period, a total of 138 infants met the inclusion criteria (Fig 1). Neonatal baseline characteristics are summarized in Table 3. There were no substantial differences between groups regarding clinical characteristics. One infant also had a right-sided middle cerebral artery infarction and a left-sided anterior cerebral artery infarction. None of the infants received hypothermia as treatment for HIE.

### aEEG Characteristics

aEEG characteristics are summarized in Table 4. These characteristics were not statistically different between treatment arms.

### Duration of Seizure Patterns

For the 33 infants, we calculated a total duration of seizure patterns of 19 378 minutes (10.8% of total registration time). For 12 of the 33 infants, there was ≥1 episode of disagreement between the 2 reviewers regarding seizure discharges, but consensus was reached in all cases.

In both groups, there was a wide distribution of seizure discharges (Fig 2). The duration (median ± SD) of seizure patterns was 196 ± 340 minutes in group A, compared with 503 ± 1084 minutes in group B (Fig 3). No significant difference in duration was found between the groups by using linear regression. In both groups, a longer duration of seizure activity was noted for infants with grade III HIE, compared with infants with grade II HIE, although this difference was not significant ($P = .8$) (Fig 4).

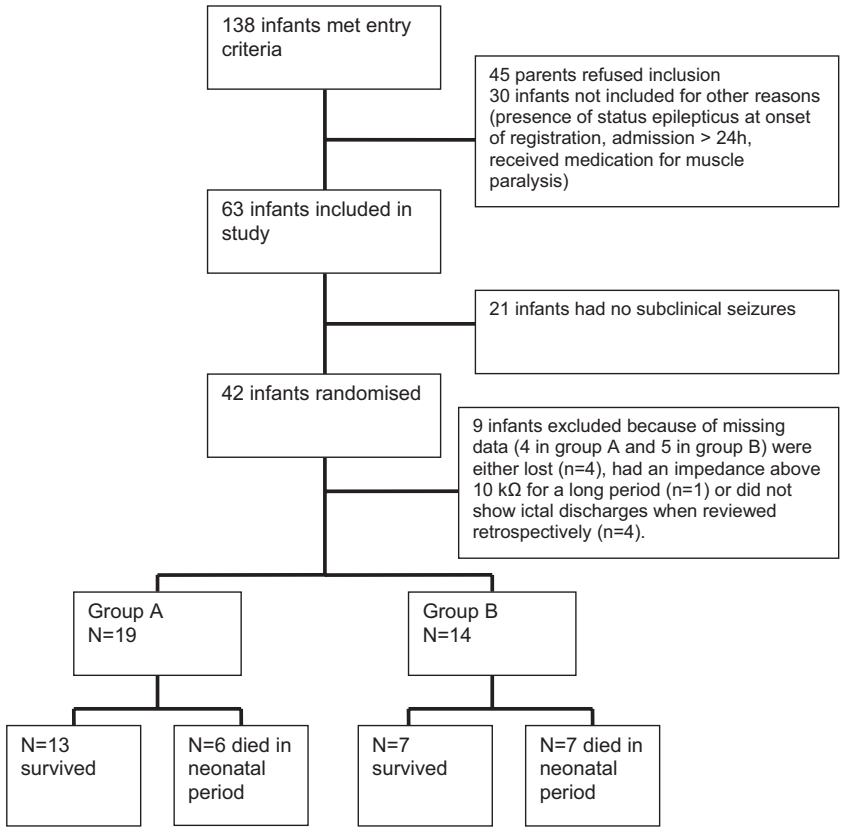


**FIGURE 1**
Flow diagram of inclusion.

**TABLE 3** Baseline Characteristics

| | Group A ($N = 19$) | Group B ($N = 14$) | Total ($N = 33$) |
|---|---|---|---|
| Gestational age, mean ± SD, wk | 39.5 ± 1.8 | 39.9 ± 1.3 | 39.7 ± 1.6 |
| Birth weight, mean ± SD, g | 3254 ± 701 | 3416 ± 487 | 3320 ± 620 |
| Gender, *n* (%) | | | |
| Male | 8 (42) | 7 (50) | 15 (46) |
| Female | 11 (58) | 7 (50) | 18 (54) |
| Outborn, *n* (%) | 17 (90) | 12 (86) | 29 (88) |
| Apgar score at 5 min of ≤5, *n* (%) | 12 (67) | 11 (79) | 23 (72) |
| Cord pH, mean (range) (group A, $N = 12$; group B, $N = 11$) | 6.87 (6.67–7.00) | 6.88 (6.64–7.30) | 6.87 (6.64–7.30) |
| Lacatate level, mean (range), mmol/L (group A, $N = 15$; group B, $N = 13$) | 14.1 (2.2–26) | 9.3 (3.1–29.0) | 11.9 (2.2–29.0) |
| HIE, *n* (%) | | | |
| Grade II | 11 (58) | 7 (50) | 18 (55) |
| Grade III | 8 (42) | 7 (50) | 15 (45) |
| Mode of delivery, *n* (%) | | | |
| Vaginal | 3 (16) | 4 (29) | 7 (21) |
| Ventouse extraction | 2 (10) | 3 (21) | 5 (15) |
| Cesarean section, emergency | 14 (74) | 7 (50) | 21 (64) |
| Meconium-stained liquor, *n* (%) | 9 (47) | 7 (50) | 16 (49) |
| Mechanical ventilation, *n* (%) | 15 (79) | 13 (93) | 28 (85) |

**TABLE 4** aEEG Characteristics

| | Group A ($N = 19$) | Group B ($N = 14$) | Total ($N = 33$) |
|---|---|---|---|
| Start of aEEG registration, median (range), h after birth | 4.5 (2–23) | 6.5 (0.5–24) | 5 (0.5–24) |
| Start of clinical seizures, median (range), h after birth | 6.5 (1–22) | 3 (1–16) | 4.5 (1–22) |
| Start of randomization, median (range), h after birth | 15.25 (4–35) | 17.5 (5–31) | 16.75 (4–35) |
| Total monitoring time, median (range), h | 86.25 (10–170) | 87.75 (22–202.75) | 87 (10–202.75) |
| Background pattern before randomization, *n* (%) | | | |
| Continuous/discontinuous normal voltage | 9 (48) | 3 (21) | 12 (36) |
| Burst suppression | 5 (26) | 4 (29) | 9 (28) |
| Continuous low voltage/flat trace | 5 (26) | 7 (50) | 12 (36) |
| EEG status epilepticus, *n* (%) | 12 (63) | 10 (71) | 22 (67) |
| Given AED before monitoring, *n* (%) | 12 (63) | 9 (64) | 21 (64) |
| Total no. of AEDs administered, *n* (%) | | | |
| <3 | 5 (26) | 7 (50) | 12 (36) |
| ≥3 | 14 (74) | 7 (50) | 21 (64) |

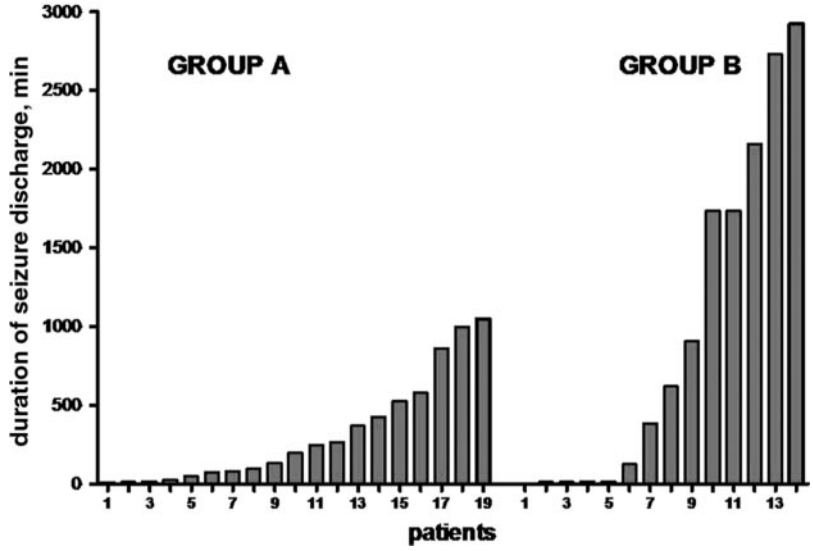


**FIGURE 2**
Difference in distributions of total duration of seizure patterns in the treatment group (A) and the nontreatment group (B).

## AED Treatment

Twelve infants (63%) in group A and 9 infants (64%) in group B received phenobarbitone in the referral hospital (given for treatment of suspected clinical seizures and not as prophylaxis). Fourteen (74%) of the 19 infants in group A received ≥3 AEDs, compared with 7 infants (50%) in group B. These differences were not statistically significant.

## aEEG Analysis and AED Treatment in Group A

In a review of data for the 19 infants in group A, treatment was appropriate for only 8 infants. For the other 11 infants, seizures existed for ≥2 hours before treatment was started or a second- or third-line AED was given or treatment was not effective but no other AED was given. In a comparison of the duration of seizure patterns for the infants who were treated appropriately ($n = 8$) and those who were not ($n = 11$), we found a significant difference in duration (37 vs 248 minutes; $P = .02$).

## aEEG Analysis and AED Treatment in Group B

In a review of aEEG registration for the infants in group B, clinically suspected seizures (treated with 1 or 2 AEDs) could not be confirmed with aEEG for 6 of the 14 infants. All infants showed EEG seizure patterns several hours before ($n = 3$) or after ($n = 3$) treatment of clinically suspected seizures. For 7 infants, clinical manifestations were confirmed with aEEG. For 4 of those infants, seizure patterns existed for a longer time before clinical signs were seen; for 5 of them, clinical symptoms resolved after AED administration but EEG seizure patterns persisted. One infant, who was assigned randomly after a subclinical seizure pattern was observed, received no AEDs. No clinical signs were noted after blinding of the registration, and no new EEG seizures were seen in a review of the recording.

## MRI Scores

MRI was performed for 26 (79%) of the 33 infants (15 in group A and 11 in group B). Infants in both groups underwent MRI at a mean age of 5.5 days (range: 3–9 days). We excluded 1 infant with bilateral perinatal arterial stroke from the analysis. In both groups, the median MRI score was 4. Five infants in group A and 4 in group B had MRI scores of <4. When data for the whole group of 25 infants were assessed, there was a significant relationship between the duration of seizure patterns and MRI scores in linear regression analyses (Fig 5). When analyses were performed for both groups, a significant relationship was found only in the blinded group (Fig 5).

## Neonatal Death

Thirteen infants died during the neonatal period, including 6 in group A and 7 in group B. All except 1 infant had grade III HIE; for most of the infants, intensive care treatment was withdrawn because of an expected poor prognosis. This decision was based on multiple examinations, including clinical assessment, EEG background patterns and persistence of seizure patterns, and neuroimaging data (cranial

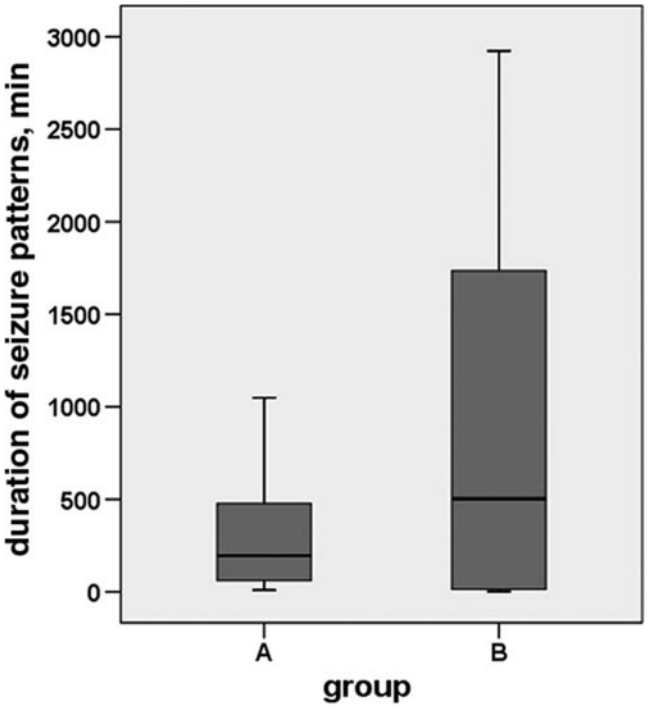


**FIGURE 3**
Box plot of duration of seizure patterns for the clinical and subclinical seizure treatment group (A) and the clinical seizure treatment group (B). The horizontal lines indicate the median; box, 25th and 75th percentiles. The vertical lines indicate the limit lines; the ranges.

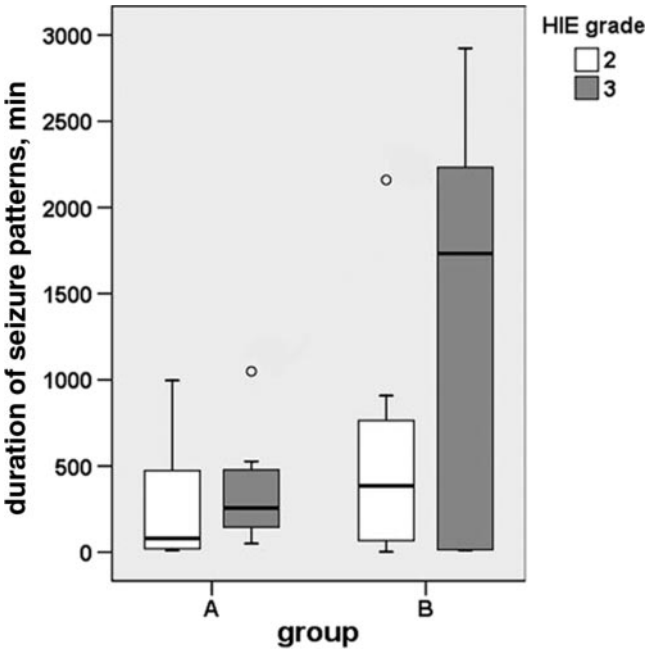


**FIGURE 4**
Box plot of duration of seizure patterns with respect to grade of HIE in group A and group B. The horizontal lines indicate the median; box, 25th and 75th percentiles. The vertical lines indicate the limit lines; the ranges.

ultrasound and/or MRI data). Infants who died during the neonatal period had a longer duration of seizure patterns than did survivors (428 vs 164 minutes). Infants who died had shorter recording times because of withdrawal of intensive care, which probably restricted the total duration of seizure patterns. In the group of survivors, no significant differences between the groups with respect to time on a ventilator, time of stay in the NICU, and time to discharge were found.

## DISCUSSION

This is the first randomized, controlled trial studying the effect of treatment of subclinical seizures. In this small group of infants, we found a trend for reduction of seizure duration when clinical and subclinical seizure patterns detected with aEEG were treated, although this trend was not statistically significant.

There was no statistically significant difference between groups in the number of AEDs used, although 74% of the infants in the active treatment group received ≥3 drugs, compared with 50% in the other group (treatment of clinical seizures only). It was noted that infants who were treated appropriately for both clinical and subclinical seizure patterns received more AEDs within a relatively short period, which resulted in a significantly shorter duration of seizure patterns, compared with those who were not treated appropriately. This suggests that treatment is more likely to be effective when it is initiated without delay. It is possible that the differences between groups would have been stronger and perhaps even statistically significant if treatment of the infants in the active treatment group had been optimal for all infants.

The mortality rate was lower in group A (32%) than in group B (50%). Although the 2-year assessment of the infants is still awaited, MRI results now are often considered as markers for short-term outcomes. A significant association was found between seizure pattern duration and higher MRI scores (more-severe brain injury), es-

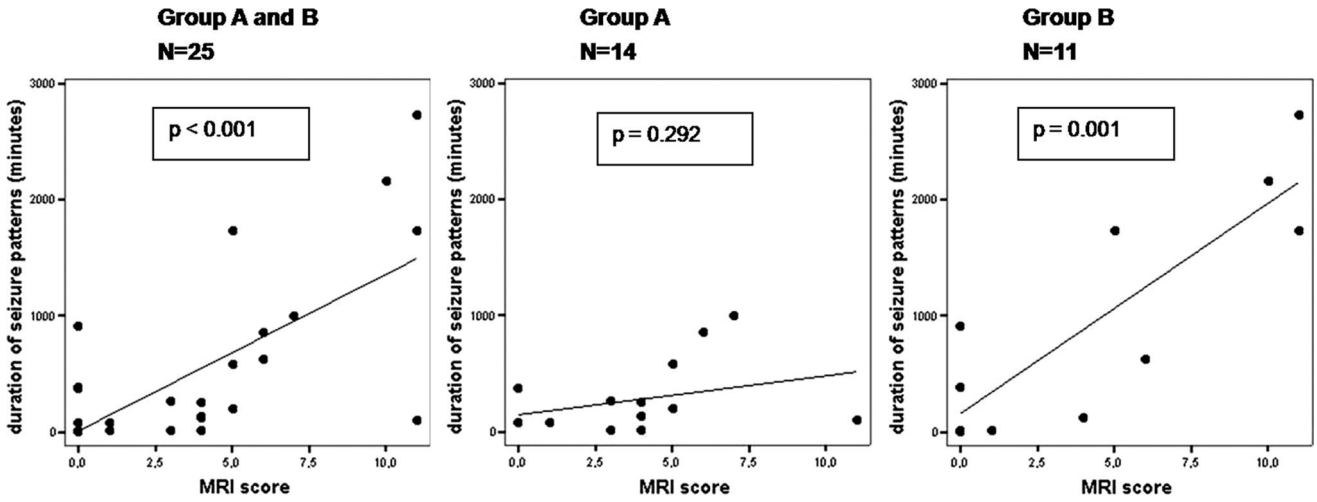


**FIGURE 5**
Relationship between duration of seizure patterns and MRI scores (linear regression).

pecially for infants in the blinded group who had a longer duration of seizure patterns. This finding supports the assumption that prolonged clinical and subclinical seizures induce or enhance already-existing brain injury.[1,2,25] Wirrell et al[25] reported that seizures superimposed on hypoxia-ischemia significantly exacerbated brain injury in rat pups. Translation of these findings into clinical practice is complicated. In human studies, it is difficult to measure the effect of seizures on neuronal injury and to distinguish this from the underlying pathogenesis of brain damage and possible effects of AED treatment. The few available studies in neonates do suggest that seizures are likely to increase neuronal injury.[1,2,26–28]

Only neonates with HIE were included in this study, to yield a homogeneous group. Only 1 infant also showed bilateral perinatal arterial stroke. The median duration of seizure patterns in this group of infants with HIE was longer than expected. One half of the patients had grade II HIE and, because most of the infants were undergoing mechanical ventilation and showed some signs of multiorgan failure, it is likely that we included more-severely affected infants within the moderate HIE spectrum. All infants developed their first seizure and were admitted within 24 hours after birth. Infants with mild grade II HIE would by definition show clinical seizures.[20] When their seizures were controlled with a loading dose of phenobarbitone and the infants were otherwise faring well, they usually would not be referred to a NICU and therefore would not be eligible for our study.

Four infants were excluded from analyses because they showed no EEG seizures retrospectively. Three of them were assigned randomly to group A. Only 2 of them received phenobarbitone in the referral hospital. In all cases, the suspected seizure discharge was restricted to a single short episode and the decision was made not to treat the infants. All 4 infants showed normal background patterns and survived the neonatal period.

Our study is an aEEG study, and it is well recognized that this technique has limitations. Previous studies showed that short and focal seizures may be missed.[29,30] Shellhaas et al[31] reported that aEEG alone has significant limitations in the diagnosis and quantification of neonatal seizures. In that study, however, the interpreters had no access to the raw EEG data when evaluating aEEG recordings. New digital aEEG devices do have access to a simultaneous display of the original raw EEG signal, and a novel seizure-detection algorithm has been developed to improve seizure detection with aEEG.[23,32–34] This probably will help to increase expertise in the recognition of seizures. For our study, we included only seizures that were confirmed by the raw 1-channel EEG tracing. In a recent study by Shah et al,[33] 76% of seizures seen on full cEEG recordings were identified by using 2-channel aEEG with access to the raw 2-channel EEG tracings. The long duration of the aEEG registration seems to outweigh the limitations of obtaining detailed information during a much shorter, 30-minute cEEG registration. aEEG does not replace cEEG, and ≥1 cEEG study should be performed for every child presenting with moderate or severe encephalopathy.

A limitation of our study is the study population. Before the study was started, a sample size of 130 infants was calculated with power analysis. Obtaining informed parental consent was more difficult than anticipated, because the parents were reluctant to allow blinding of the monitoring de-

vice. Also, parents were asked to give permission shortly after an unexpected complicated delivery of a critically ill infant who required acute neonatal transfer to a level 3 NICU. Another limitation is that we did not use video registration; therefore, we cannot exclude the possibility that some subclinical seizures had some subtle clinical symptoms.[4,10] However, Murray et al[10] showed that only 27% of clinically suspected seizures were subsequently confirmed to be ictal discharges with cEEG. This was also seen in our study, because infants in group B were sometimes treated for clinical seizures that could not be confirmed with aEEG or EEG. These movements have been described as "motor automatism" of uncertain origin.[8] One could imagine that these movements were indeed seizures but, being focal, were not identified with single-channel aEEG or EEG recording.

Furthermore, there was a discrepancy in the level of expertise at the participating centers, with 2 centers having >10 years of experience and other centers having started using the technique only recently. This lack of experience probably led to a delay in seizure treatment of 11 infants in group A.

## CONCLUSIONS

We report the results of the first randomized, controlled trial of treatment of subclinical seizures. In this small group of infants with HIE, a trend was found for a reduction in the duration of seizure patterns when clinical seizures and subclinical seizure patterns were treated. This trend, as well as the significant association of seizure duration and severity of brain injury found on MRI scans, which was seen for infants who received treatment for clinical seizures only, suggests that recognition and treatment of neonatal seizures in infants with HIE can reduce brain injury.

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# Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial

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# The Basics of MRI

BPNA NeoNATE Course

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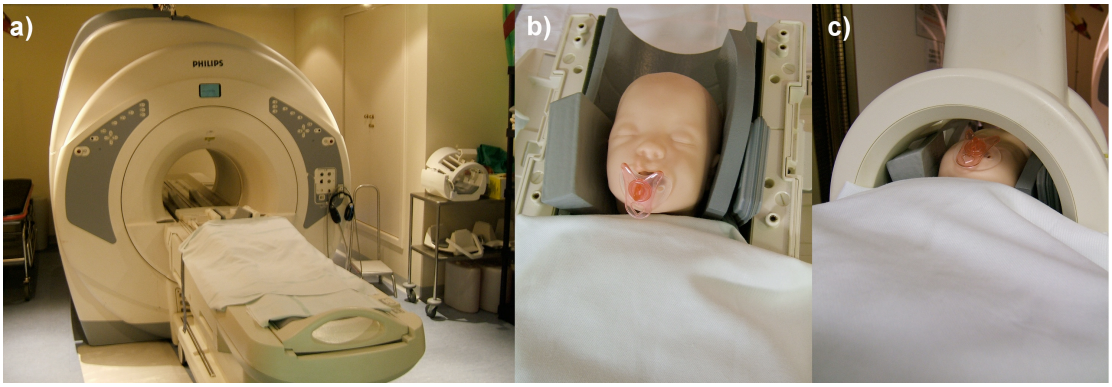
Sheffield Children's Hospital, Sheffield, May 2014

## Introduction

A Magnetic Resonance Imaging (MRI) scanner is a long tunnel with a small central bore. The patient lies on a table, which can move in and out of the central bore (figure 1a). In the case of neuroimaging, the head is placed in a "radiofrequency receiver coil" (figure 1b and c) before the patient is put into the central bore. This takes the measurements that build up the pictures.

**Figure one:** pictures of a 1.5T scanner (a) and a doll in the coil (b and c)




MRI is all about using magnets to change the hydrogen molecules in our tissues. Strong magnetic fields can alter the alignment / direction and movement of the molecules making up body tissues. As the magnetic field is turned off, the hydrogen molecules "relax" back to their ordinary states.

The scanner measures these changes. At different times the scanner will apply additional magnetic gradients across the tissue. For example, at one point the magnetic field might be stronger on the right of the brain and become gradually weaker towards the left. Or, it might be stronger at the front and gradually become weaker towards the back of the brain. In these situations, the hydrogen molecule movement and orientation will be different in the stronger compared to the weaker magnetic field. By applying many of these gradients in lots of different directions at different times, the scanner builds up a picture of what the brain looks like.

This paper explains a little more about MRI scanners, the different types of sequences used, terminology, and practicalities.

## Parts of the MRI scanner

The scanner contains several different parts. These include:

- *The magnet:* the majority of the scanner that you see, looking like a doughnut, is a very strong magnet. The magnet is an electromagnet, i.e. made up of wire, coiled many, many times. The wire is cooled to not far off absolute zero (under -250°C) by surrounding it in liquid helium. At this temperature, the resistance in the wire is virtually zero and the electricity conducts along the wire easily. This generates the magnetic field. The magnet is constantly cooled down and always on.

*The magnet is always kept cool.*

*So, it is always on.*

*This is important to remember for safety reasons (see later)*

- MRI magnets come in different strengths. The degree of magnetism is measured in Tesla (abbreviated to T). One Tesla is roughly equivalent to 20 000 times the earth's magnetic field strength. Most MRI scanners in hospitals are 1.5T, but stronger magnets are increasingly used – for example 3T scanners.

- *Shim coils:* There are extra electrical coils within the scanner. These can be varied by the radiographers (or automatically by the machine) to ensure that the magnetic field is exactly the same within the bore (called a homogenous magnetic field). This process is called shimming.

- *Gradient coils:* There are three "gradient coils" in the scanner that vary the magnetic field within the bore and create the magnetic gradients we have mentioned. The three coils are used to representing the x, y and z directions (figure 2). In the case of MRI, the Z axis (also called $B_0$) runs straight through the middle of the bore, from front to back.

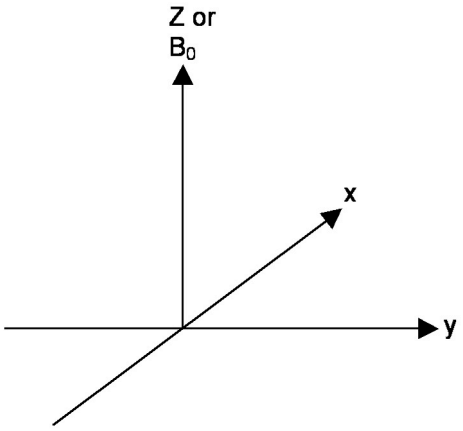



**Figure 2:**

The axes / planes that the gradient coils relate to

- *Transmitter coil:* The body of the scanner also contains an “integral transmitter radio frequency coil”. This part of the machine can send out a pulse of electromagnetic radiation. This gives a “nudge” to move the direction of the hydrogen molecules. This pulse of transmitted electromagnetic radiation means that the hydrogen atoms take up energy. The wavelength of the emitted radiofrequency (RF) pulses varies and depends on the magnetic field strength.

- *Receiver coil:* placed directly around the part of the body to be imaged is a “radiofrequency receiver coil”, which we have briefly mentioned before (figure 1b and c). This is essentially a very complex radio antenna. When the pulse of transmitted electromagnetic radiation is turned off, then the hydrogen atoms will relax and give out energy as electromagnetic radiation. The receiver coil receives the signals from the tissues and sends them back to the scanner and the computer. From there the computer analyses the data and makes the picture.

  If you are scanning a neonate’s head, you put this receiver coil around the head. Receiver coils vary in size and shape depending on the body part and size of patient being imaged. For example the coil to image the spine is flat. In some units the neonatal head coil is the same one used to scan an adult’s knee!

- *Farraday cage:* The MRI scanner room has copper shielding in the walls and doors. This is a Faraday shield or cage. It protects the MRI scanner, particularly the receiver coil, from radiofrequency interference trying to break in from the outside world! If the Farraday cage was not there, then there would be too much background ‘noise’ and the pictures would be rubbish.

## How images are produced

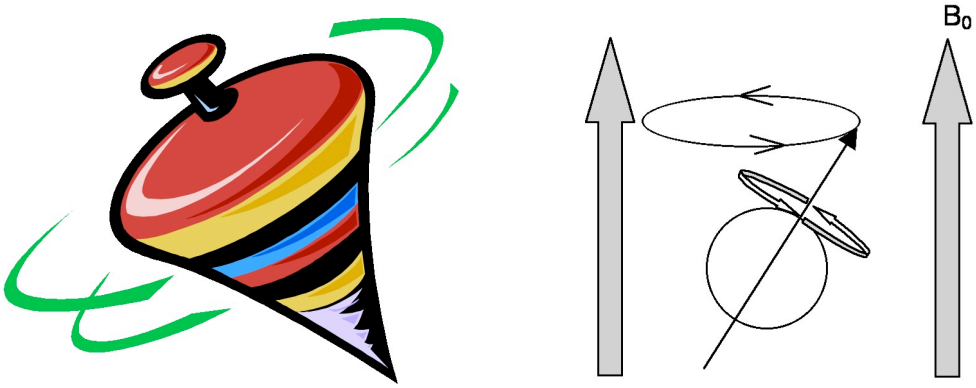
MRI images are all about hydrogen molecules. If you remember back to school physics, a hydrogen molecule is essentially just a proton.

As a proton spins, it generates it’s own magnetic (not magic!) moment. This means it becomes weakly magnetic. Like any magnet, the proton develops a north and a south pole, called a dipole. At any one time, all the magnetic dipoles of the protons in a tissue are arranged in random directions. Thus, when you add them up, they cancel each other out.

When someone enters the central bore of the scanner, the magnet is on. The majority of hydrogen molecules will line up parallel to the $B_0$. The majority of hydrogen molecules will have their magnetic pole in the same direction as the magnet’s.

In addition to spinning, the hydrogen molecules also “precess”. The easiest way to think about this is to imagine a spinning top. After it has spun a while, it begins to wobble, and you can see the handle in the top moves in a bigger and bigger circle (as well as spinning) until it falls over (figure 3).

**Figure 3:** *Left* – the spinning top not only spins, but wobbles (green lines). This is precession. *Right* – the hydrogen molecule spins (circular block arrow) giving it a magnetic dipole (line arrow through centre of proton). It also precesses (line circular arrow). As it enters the magnetic field the dipole lines up with $B_0$.




How fast hydrogen molecules / protons precess depends on the strength of the magnetic field.

Compared to the massive magnetic field in the scanner, the strength of all of the magnetic dipoles lined up in $B_0$ is weak. So, the scanner cannot measure this effect. But when we flip them into a different direction, such as along x or the y axis (see figure 2), then the scanner can detect them.

The MRI scanner uses the transmitted RF pulses we have mentioned to flip the direction / axis of the precessing protons / hydrogen atoms. Think of RF pulses as being like a strong gust of wind making trees move and bend in the same direction. The protons also end up precessing in time with each other so that they are each at the same point in their precessing spin. This is called being “in phase” – like soldiers marching in time with each other or a number of spinning tops spinning in time.

When the RF pulse is turned off, the protons gradually lose their energy and change their direction back to where they were before - along $B_0$. Taking the example of the wind the trees flex back to their normal posture. At the same time, they stop precessing in phase and wobble in their own individual way – like soldiers breaking out of step to cross a bridge or spinning tops wobbling I many different ways. This process is called relaxation.

During relaxation, the protons give off a small amount of energy / signal. This will be strong at first, but then fades. This signal can be recorded in the RECEIVER coils (figure 1b and 1c).

If you measure the recovery of the signal in the z axis, this is called T1 relaxation. It’s very confusing because the T is different from the T used for Tesla. Just forget what this T stands for. If you measure how much the signal is lost in the x-y plane, then this is T2 relaxation.

**Table 1** Approximate T1 and T2 relaxation times for a selection of tissue types in the human body

| Tissue type | Approximate T1 relaxation time in 1.0T field strength MR scanner (ms) | Approximate T2 relaxation time in 1.0T field strength MR scanner (ms) |
|---|---|---|
| **Fat** | 180 | 90 |
| **Liver** | 270 | 50 |
| **Adult white matter** | 390 | 75 |
| **Adult grey matter** | 520 | 90 |
| **Muscle** | 600 | 40 |
| **Blood** | 800 | 180 |
| **Cerebrospinal fluid** | 2000 | 200 |
| **Water** | 2500 | 2500 |

(from Bushong, 2003)

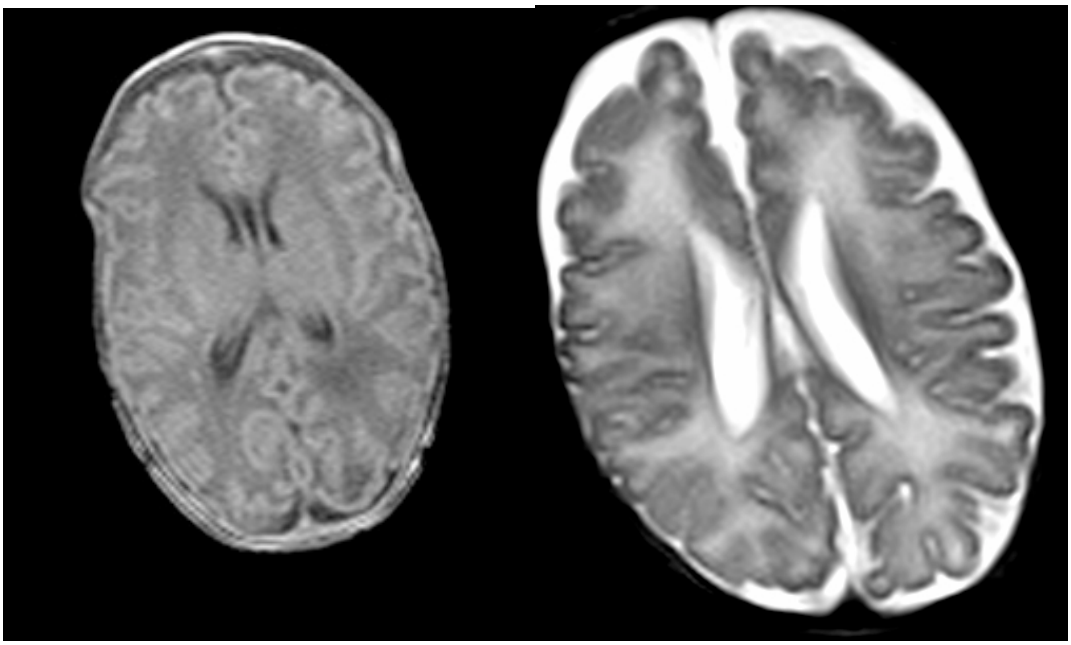
Table one shows that different parts of the body have different T1 and T2 relaxation times. CSF has long T1 and T2 relaxation times compared to fat. The relaxation time depends on how many free protons the tissues have within them. For instance, the brain's grey and white matter have slightly varying fat and water constituents. The make-up of the intracellular and extracellular environment may also exert varying effects upon a proton's capacity to move / diffuse.

The difference in how quickly various tissues relax makes up the pictures you see. By applying lots of magnetic gradients across the tissue in many different directions, the scanner divides the brain up into tiny little cubes / volumes (also known as voxels). It then pin-points the amount of T1 and T2 relaxation in each one. The scanner then shades each cube (from white to black, with many shades of grey in between) according to how quickly the relaxation in the cube occurs. When all the cubes are put together, a big jigsaw puzzle is assembled. Suddenly the picture becomes clear!

The grunting and banging you hear from an MRI scanner is the coils and other parts of the machine turning on and off to generate hundreds and hundreds of gradients.

You can get different pictures in MRI by getting the scanner to adjust how quickly or often it sends RF pulses. Similarly, you can vary soon you measure the signal back from the tissue. This helps to generate different types of pictures or "sequences". For example, you can get T1 weighted images that look at – you've guessed it! – T1 relaxation. Or, you can get T2 weighted imaging looking at (duh!) T2 relaxation (see figure 4).

**Figure 4:** *Left* – a T1 weighted axial image of the neonatal brain; *Right* - an ultrafast T2 weighted axial image of the neonatal brain



## MRI safety

Radiographers and radiologists are trained in MRI safety. Listen to them.

Never go in the scanner room without checking it is OK.

Never take anything in the scanner room (including resuscitation kit or patient beds,) without checking it is safe.

Do what they say - even in an emergency – or you could make a sick patient a dead patient.

Most of the risks associated with MRI are due to one of two mechanisms.

*The strength of the magnetic field.* The magnetic field is exceptionally strong. The magnet is ALWAYS TURNED ON! It is only the additional gradients that are turned on and off.

The strong magnetic can cause things that are made out of magnetic metal to fly across the room at great force and speed. They can end in the central bore where the patient is. This includes beds, chairs, oxygen cylinders, pens, keys, mobile phones, stethoscopes, coins, watches etc (figure five).

**Figure five:** *Left* – a cleaner's floor buffer in the middle of the central bore of a MRI scanner. *Right* – an oxygen cylinder in the scanner. Imagine if you ran in with a cylinder to given oxygen to a baby who was desaturating. The cylinder would fly, like a torpedo, straight into the scanner and would probably kill the baby.

*Gilk (2006) found at http://www.psqh.com/sepoct06/mrisuites.html*

All patients, staff and family members wanting to enter the MRI room must complete a safety questionnaire. This is because metallic foreign bodies in patients, staff and family can also move. This includes surgical clips for abdominal surgery, cerebral aneurysm surgery and metal foreign objects in the eye.

*The heating effect of the RF pulses.* The patient will heat up (by absorbing electromagnetic energy) whilst being subjected to the transmitted RF pulses in the MRI scanner. There is a maximum amount of heating which a patient can safely endure.

All metallic foreign bodies may heat up and then they can cause burns.

The RF pulses and the strong magnetic field may affect implanted devices like cardiac pacemakers, cardiac defibrillators, cochlear implants and programmable VP shunts.

*Pregnant women* The effects of MRI on a fetus are unknown. Therefore, pregnant women are asked to avoid entering MRI scanner rooms.

*Noise:* The MR scanner is very loud when working. Ear protectors (ear plugs and head phones) should be worn by staff and the neonate in the scan room.

*Effects of contrast* Intravenous gadolinium based contrast agents are generally well tolerated. Anaphylaxis after intravenous gadolinium administration has an estimated incidence of 0.02%.

## Specific issues in neonatology

- MR compatible monitoring equipment is required in the MR scan room
- Keeping the neonate still for MR image acquisition is not normally a problem after a feed and this is especially so in premature neonates.
- The temperature of the neonate requires close monitoring and maintenance.
- Transferring the neonate to the MR scanner if they are unwell will require the use of a transport incubator or the use of a specially designed MR compatible incubator.

## What are different sequences used for and what do they look like?

There are lots of different sequences and confusing terms. We've tried to decode some of the language and explain why these sequences are useful. This list is not exhaustive of all types of MR sequences – we've just chosen the most useful ones.

*The planes of MRI pictures*
The pictures can be taken from different angles. The main ones are described in table 2 and figure 6.

**Figure 6:** the planes used in MRI *(from S Clare, PhD Thesis, 1997)*

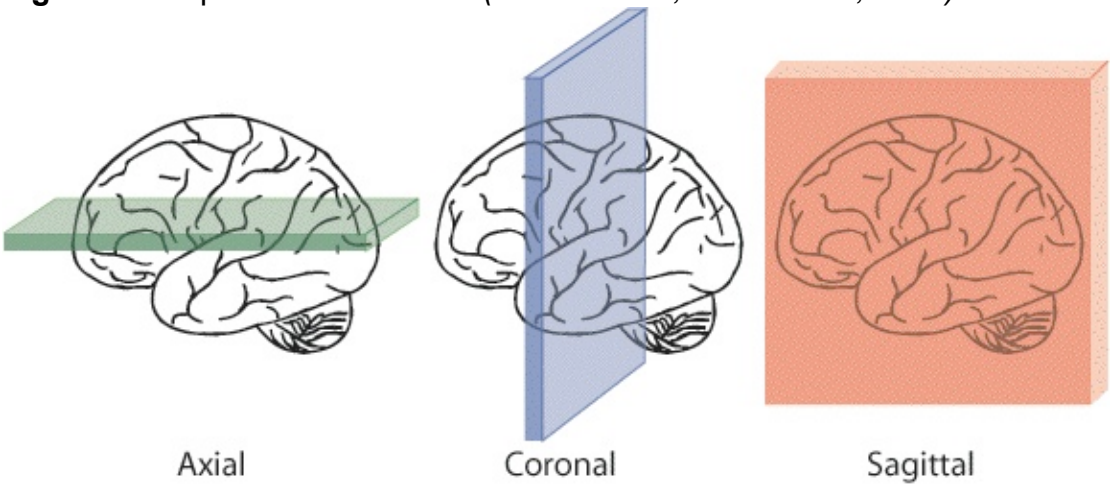
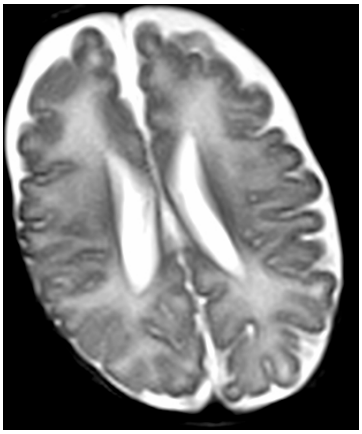
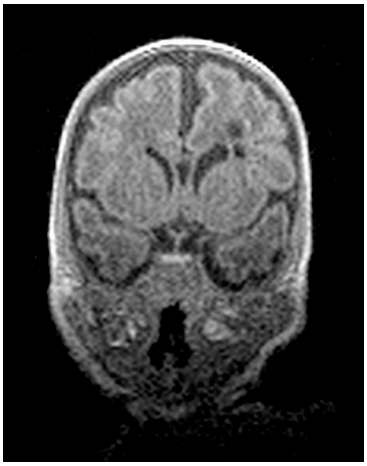
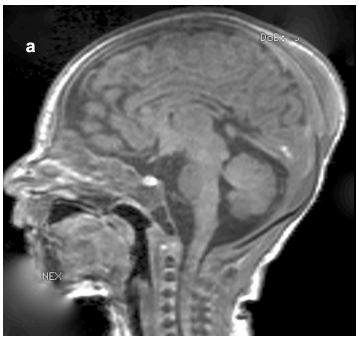


**Table two:** The common planes used in MRI

| *Name of plane* | *Description of plane* | *Pictoral example* |
|---|---|---|
| **Axial** | A slice that is taken from the feet looking up towards the head.<br><br>It looks like it's taken from above (Axial – Above: the two A's go together) but it's really from the feet upwards |  |
| **Coronal** | This is a picture taken from the front e.g. towards the face – like a selfie!<br><br>Coronal – crown. This doesn't help me remember it, but it's what is in the books! |  |
| **Sagittal** | A picture taken from the side of the head, as if you're taking a picture of your ear. (Sagittal –Side) |  |

If you see something that looks odd on an MRI scan - see if it is visible on other planes and other sequences. You might be confusing it for artefact or "volume averaging" if it is just on one.

What is volume averaging? Each slice contains information on the relaxation of many little cubes. These are averaged together to make your picture. How many cubes are averaged depends, amongst other things, on how thick the slice is: a 10mm slice will have more than a 1mm slice. The thicker the slice, the more information is averaged and the less detail you see. Sometimes lumping so much information together causes odd findings – such as if you have white and grey matter and CSF in the same area that is averaged together.

*Different MRI sequences used in neonatal care*

- **T1 weighted imaging (figure 4 left)**. In the neonate, the white matter is normally darker (lower T1 signal) than the grey matter. The CSF looks dark. So if you look from the grey matter to white matter to CSF it goes: light, dark, darker. T1 scans are good at showing whether the structure of the brain or anatomy is OK – i.e. is everything there that should be there?

  If oedema is present, the tissue looks darker than normal. If the grey matter is injured and cell death is occurring, the grey matter will look even more bright than normal a few days (at least 5) after the event has occurred.

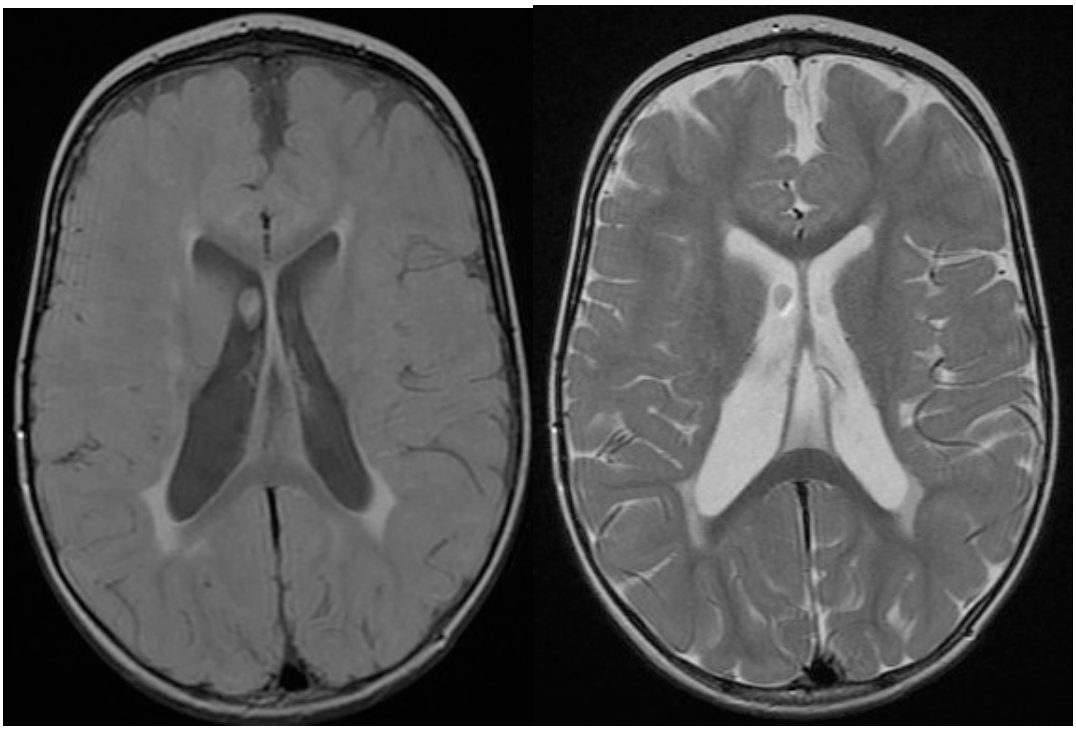
- **T2 weighted imaging (figure 4 right)**. In the neonate the cortex and deep grey nuclei are normally darker (lower T2 signal) than the white matter. T2 weighted imaging is good at demonstrating acute pathology as pathology often has lots of fluid in it – swelling / oedema. So, it shows up bright (high T2 signal). For example, loss of the normal difference in signal between grey and white matter suggests higher free water (oedema) in the grey matter.

  White matter brain injury of prematurity is often present in the white matter next to the ventricles. It can be difficult to see this pathology on T2 imaging because it is bright lying right next to the CSF, which also looks white. There's a clever way you can get around this. This is by...

- **Flair imaging.** This is a T2 weighted sequence but the bright signal from the CSF is suppressed. Hence, the CSF looks black. You could easily mistake this for a T1 weighted image if you didn't know what you were doing! But, the shades of the grey matter and white matter show you that

this is not T1 imaging. Flair is rarely used in neonates because of the high water content of the whole neonatal brain. But Flair imaging is useful in older children, for example ex-preterm infants with spastic diplegia, because you can look for evidence of injury in the periventricular white matter. In Figure 7, which is from an older child and not a neonate, you can see that with the CSF signal suppressed, the gliosis (scarring) next to irregular shaped ventricles is present. This is white matter injury of prematurity (periventricular leukomalacia).

**Figure 7:** *Left* - T2 weighted FLAIR imaging in the axial plane. This is an older child born preterm. You can see dilatation of the posterior bodies of the lateral ventricles. This is caused by brain injury and loss of volume of the periventricular white matter or coalescence of cysts into the ventricles. This is periventricular leukomalacia (PVL). There is scarring of the white matter adjacent to the ventricles that appears white.
*Right* – standard T2 weighted imaging in the same child. Note how the CSF signal is not suppressed and the pathology is harder to see.



- **Diffusion weighted imaging**. In the neonate, there is normally free diffusion of water in the ventricles (CSF). In the brain parenchyma the amount of diffusion is in the middle of the spectrum. Pathology can alter how much water molecules diffuse within tissues.

  These changes can be detected with diffusion-weighted imaging. Often, on first glance, these images look rubbish! They are totally out of focus and don't show the anatomy at all well. But that's what they are supposed to look like. These images give you an idea of water molecule diffusion not anatomy.

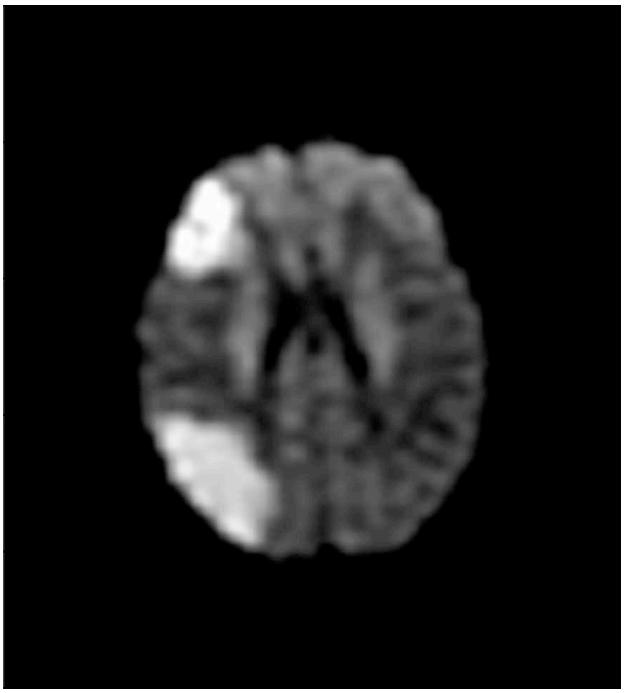
There are many different images which the MRI scanner can produce from DWI imaging. There are the b zero, b100, b700, b1000, and DWI values in the x, y and z coordinates. You must be sure which images you are looking at before attempting to interpret the images.

Alongside the DWI images is a set of pictures called an ADC (apparent diffusion coefficient) map. The ADC maps often look almost the opposite of the DWI images. Both the DWI b1000 or b700 together with the ADC map must be studied together to see what is going on.

With 5-7 days after an injury causing acute cell death, or infection, or stroke or haemorrhage the ability of the water molecules to diffuse in tissues is reduced. This is called restricted diffusion. The areas affected look bright on DWI and dark on ADC map. These images can show injury very prominently, sometimes before it is visible on T1 or T2 weighted sequences (or the changes on these sequences is subtle). See figure 8.

After day 5-7 and certainly by day 10 or the ADC images can look normal, as they move past “normal” to very abnormal high signal. This is called pseudo-normalisation. This is the reason some radiologists and neonatologists like to scan neonates with HIE early (before day five) – because the DWI data is most useful at this time. Others prefer to scan later because they want to wait until the T1 weighted images are more likely to show abnormality, and sacrifice the DWI data. When you scan depends on your radiologist’s preference and how easy / quick it is to get a scan in your unit.

**Figure 8:** Diffusion weighted imaging in the axial plane of a neonate. It’s easy to see the areas of abnormality on the right, which represent areas of stroke.



You can draw circles in different areas of the brain on the ADC maps made by DWI. These circles can give you a number indicating how much water diffusion is present. This number is called the apparent diffusion coefficient. Our experience is that ADC values from any region of the brain don't really help you with prognostication.

Diffusion weighted imaging typically measures water molecule diffusion from three angles. You can do this from many, many more – 32, 64, over a hundred! In this situation you can get an idea of how much the water molecules diffuse AND the direction in which most of the water diffuses. This is diffusion tensor imaging (DTI).

The direction of water molecule diffusion is important because water molecules will prefer to diffuse along a nerve rather than try to hurdle over or wriggle around it. Think of a pan with some spaghetti stuck in it, waiting to go soft. Now pour olive oil on the spaghetti – the oil tends to run along the spaghetti strands rather than finding it's way between the individual strands. So it is within the brain!

If you give a colour to each particular direction, you can generate colour DTI pictures. These pictures give you a flavour of the directions of the axons (figure 9 and 10).

**Figure 9** A diffusion tensor imaging map from an adult to give an idea of how you can gain pictures of where you assume the nerve bundles are.

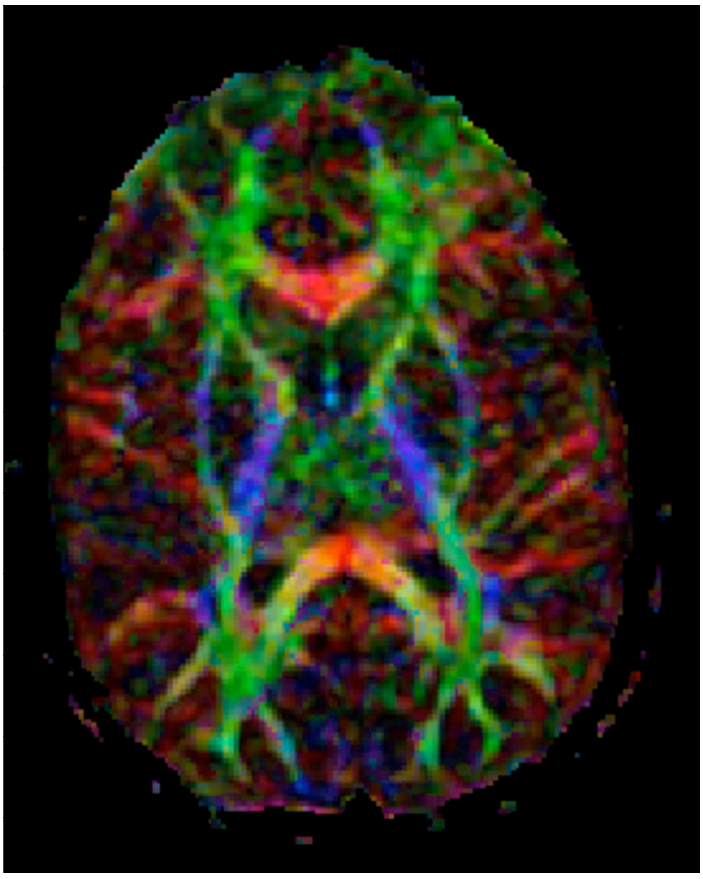
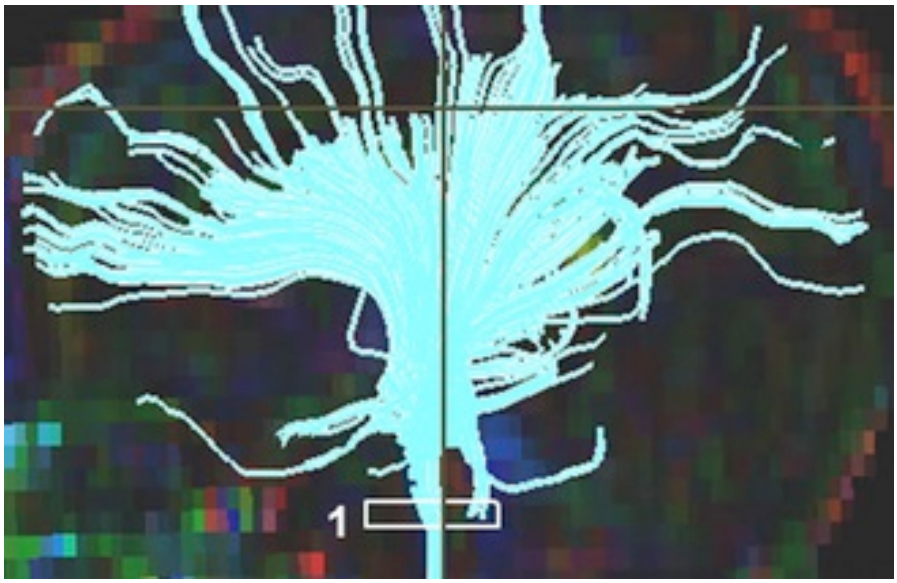


**Figure 10:** DTI tractography at term in a preterm infant (from Kaur et al 2014)



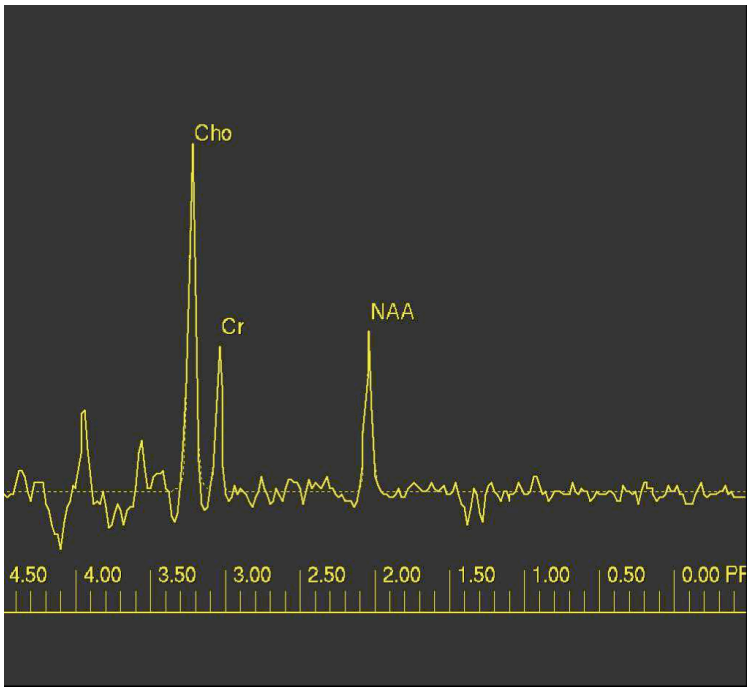

As with DWI, you can get a number from DTI images showing how much direction there is to water diffusion from any part of the brain. The higher the number, the more the water flows in one direction. These values are called anisotropy values. (There are various different types - fractional, relative etc – but don't get hung up on this or what the differences are. It's essential to do with mathematical equation you use to come up with the number.)

Anisotropy is important in neonatology because, as the nerve axons grow, get fatter and get wrapped in myelin, they form more of a barrier preventing water from diffusing across the axons. Instead water increasingly diffuses along them – anisotropy values increase. There is a lot of work going on with DTI that has shown that anisotropy values do change a lot in the preterm brain as it matures and myelinates, but that these changes are not the same as in a fetus. There are differences in anisotropy values between preterm infants at term corrected age and term controls. Whether they can be used to provide prognostic information in the clinical setting is not yet clear.

- **Gradient echo T2 and susceptibility weighted imaging (SWI).** These sequences are used to demonstrate evidence of intracranial haemorrhage or calcification, both of which appear dark on these image sequences. These sequences may be particularly useful in premature neonates to see if there is any evidence of intra-parenchymal or intra-ventricular haemorrhage.

- **MR spectroscopy.** This sequence allows assessment of the relative concentration of different brain metabolites; N-acetyl aspartate (**NAA**) a marker of normal glial cells integrity, **creatine** a marker for all cells and possibly relate to energy requirements, **choline** a marker of cell membrane turnover, **lipid and lactate** (figure 11). Rarely other metabolites may be demonstrated on the spectrospcopy.

**Figure 11** A MR spectroscopy result from a neonate. Cho = choline, Cr = creatine, NAA = N acetyl aspartate. If you look at the numbers, just over where it says 1.50 (it is really over about 1.33) is a W shape. This is a small amount of lactate.

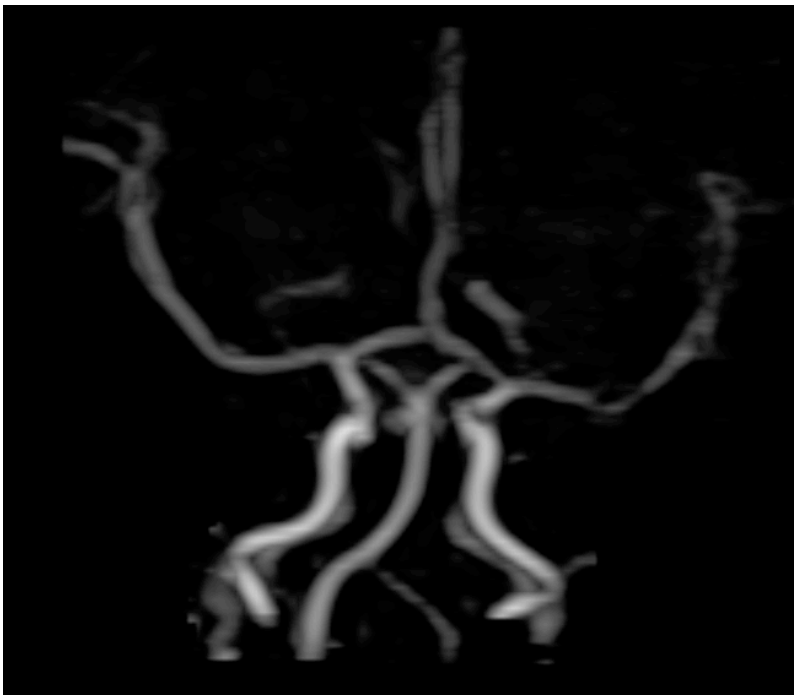



The scientific evidence on the use of MRS in neonatology is limited. There is some suggestion that it may be useful in prognostication following HIE, and our work has suggested it may be of use in preterm infants, but it needs verification in bigger studies with long-term follow-up. MRS is particularly useful in some metabolic conditions. For example, large amounts of lactate may point you towards a metabolic condition. There are conditions in which the creatine peak is absent or NAA is very high. These can help make a diagnosis in children, particularly when they are out of the neonatal age group.

- **Other sequences. Perfusion imaging** looks at how well fluid moves from the blood or lymphatic system into tissues. **BOLD functional MRI** looks at changes in blood flow when the brain does something (e.g. a neonate' hand is moved in the scanner). These may be employed for research purposes but don't yet have any role in clinical care.

- **MR angiography (MRA) and MR venography (MRV)** utilise the flow of blood at different rates and in different inflow directions to produce images of the intracranial arterial (figure 12) and venous systems.

**Figure 12:** MRA of a neonate with incontinentia pigmenti who had haemorrhagic destruction of the brain. The MRA shows in the vessels on the right of the image (as you look at it) are narrow compared to the left.



- **Intravenous contrast. Gadolinium** shortens both T1 and T2 values in tissues where it accumulates (where there is no blood-brain barrier). This accumulation of gadolinium causes in increase in T1 signal and a decrease in T2 signal. The decrease in T2 signal is difficult to appreciate and therefore gadolinium is normally used with T1 images.

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EDITOR'S CHOICE

# Long-term outcome after neonatal hypoxic-ischaemic encephalopathy

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## ABSTRACT

Outcome of full-term infants with neonatal encephalopathy of hypoxic-ischemic origin is often assessed in infancy or early childhood and data on outcome in childhood and adolescence is limited. MRI performed in the neonatal period has made a huge contribution to recognition of different patterns of injury. These different patterns of injury are related to the severity of later motor and cognitive disabilities.

Long-term follow-up shows that cognitive and memory difficulties may follow even in children without motor deficits. It is therefore recommended to perform follow-up assessment into childhood in children with and without adverse neurological outcome in early infancy.

Neonatal encephalopathy (NE) occurs in 1–6/1000 live full-term births and carries a high risk for subsequent neurodevelopmental disabilities.[1] Long-term outcome is known to depend on the severity of the neonatal condition.[2 3] The term NE is now more often used than perinatal asphyxia (PA). This is because PA is difficult to define and in order to be reliable, needs access to several markers which are not always available, such as fetal heart rate tracings, umbilical cord gases and reliable Apgar scores. Individually, these markers have been shown to not correlate very well with subsequent outcome.[4 5] NE is 'a clinically defined syndrome of disturbed neurological function in the earliest days of life in the full-term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures'. The widely used three-level grading system of mild, moderate and severe encephalopathy, based on clinical symptoms and EEG, was developed by Sarnat and Sarnat.[6] They based their encephalopathy score on an assessment in only 21 infants. The development of encephalopathy in full-term infants within hours to days after birth is now considered essential in order to be confident about an underlying perinatal insult, and NE is almost invariably associated with several of the markers mentioned above.[7] NE can develop for reasons other than hypoxic-ischaemia, for example, metabolic disorders, therefore a combination of markers suggestive of the presence of PA as well as the development of NE is obligatory.

Most studies reported so far have focused on early neurodevelopmental outcome at 18–24 months, looking mainly at development of cerebral palsy (CP) or severe cognitive deficits.[8] Outcome of infants with mild NE have been reported to be comparable to non-affected full-term infants,[2 9] while those with severe NE will either die or invariably develop CP and cognitive deficits. Pin *et al*[3] reviewed 13 empirical studies, meeting strict inclusion criteria and found adverse outcomes under 3 years in none of the infants with mild NE, 32% in those with moderate NE and almost 100% of those with severe NE. Very similar data were found in an earlier review by Dilenge, *et al*.[10] The infants with moderate NE tend to have a more variable outcome and other techniques, such as neuroimaging techniques, in particular MRI and neurophysiological tests, especially amplitude integrated EEG (aEEG) and evoked responses are required to more accurately predict neurodevelopmental outcome.[11 12]

Only a few studies provide detailed assessment of longer term outcome.[13–16] The American College of Obstetricians and Gynecologists task force on NE and CP made a statement that an acute intrapartum event (most often associated with a sentinel event) could only result in CP of the tetraplegic or dyskinetic type and could not result in isolated cognitive deficits.[17] A recent review by Gonzalez and Miller[18] provided sufficient data to illustrate that survivors of NE following PA are also at increased risk of cognitive deficits, even in the absence of motor deficits. Outcome studies performed so far, found cognitive functioning at school age to be normal in children with mild NE.[13 14] The first study looking at long-term outcome at 5.5 and 8 years following NE, was performed by Robertson *et al*[14] They found that non-disabled survivors of moderate NE were similar to controls with respect to receptive vocabulary and perceptual motor skills, but showed marked delays in reading, spelling and arithmetic. These children were more likely to be at least one grade behind controls or those with mild NE. A recent study by Marlow *et al*[16] assessed 65 children with NE at 7 years of age. They classified infants as having moderate NE when they presented in the first week after birth with either seizures alone or any two of the following: abnormal consciousness; difficulty maintaining respiration (of presumed central origin); difficulty feeding (of presumed central origin); abnormal tone and reflexes, with all lasting for more than 24 h. The children with severe NE had to fulfil one or more of the following criteria: ventilation for more than 24 h; two or more anticonvulsant treatments required; comatose or stuporous. One should be aware of these definitions of moderate and severe NE, as the presence of requiring ventilation and two or more anticonvulsant drugs would be considered to be moderate NE by most clinicians. Some of their severe NE cases could therefore represent more severely affected moderate NE children.

No neonatal neuroimaging or neurophysiological data, such as aEEG was available for these children. They reported that those with moderate NE were not different from controls with respect to general cognitive ability, but lower in language and sensorimotor domains, as well as narrative memory and sentence repetition. The children were more likely to require extra educational assessment, teaching provision and support, even though they did not have any overt neuromotor impairment. Among the more severely affected children, referred to as severe encephalopathy, memory for names, orientation and reported everyday memory function were also significantly poorer than for either comparison children or the moderate encephalopathy group.

Specific memory impairment has been the topic of recent studies, initially noting a specific and severe impairment of episodic memory (context-rich memory for events) with relative preservation of semantic memory (context-free memory for facts).[19] Since then, others have found problems in verbal learning and/or recall[14 20 21] and in visual recall[20] in school-aged children and adolescents with moderate NE. These findings stress the importance of detailed examination of the developmental impact of NE on memory function. The known associations between the hippocampal structures and memory function[22–25] suggest that children with NE could be at risk of developing problems in this specific domain of cognitive functioning.

## PATTERNS OF BRAIN ABNORMALITIES ON MRI PREDICT OUTCOME IN EARLY CHILDHOOD

The increased use of neuroimaging techniques and MRI in particular, has been a tremendous help in timing of brain injury and recognising the pattern of injury.[11 26] Performing MRI within the first 2 weeks after birth, Cowan *et al*[26] were able to show that more than 90% of affected newborns had evidence of perinatally acquired lesions on their MRI, with a very low rate of established antenatal brain injury. The use of diffusion-weighted imaging (DWI) has also greatly improved our ability to time the onset of brain lesions. A reduced apparent diffusion coefficient can be calculated, showing reduced values (restricted diffusion) during the first few days after the insult, with pseudonormalisation by the end of the first week.[27]

Comparable to studies in a primate model,[28] two main patterns of injury can be distinguished with MRI in the full-term neonate:

1. *A basal-ganglia-thalamus pattern* (BGT) predominantly affecting bilaterally the central grey nuclei and perirolandic cortex. Associated involvement of the hippocampus and brain stem is not uncommon (figure 1). This pattern of injury is most often seen following an acute sentinel event[29] and is also referred as a pattern following 'acute near total asphyxia'.[30] Using conventional MRI, it was shown by Rutherford *et al*[31] that absence of a normal-high signal intensity of the posterior limb of the internal capsule is highly predictive of severe adverse sequelae. More accurate information about timing of injury can sometimes be obtained when measuring the apparent diffusion coefficients, but due to evolution over time, this was mainly helpful in the most severely affected infants, who had an MRI performed within the first few days after birth.[32] The children with the BGT pattern of injury are often so severely disabled that they will not be included in long-term follow-up studies. Ability to sit by 2 years of age and walk by 5 years of age occurred in five of the seven children who showed involvement restricted to the nucleus lentiformis and ventro-lateral thalamus, while none of the 10 children with more extensive injury, including injury to the perirolandic cortex and hippocampus were able to reach these goals.[33] Himmelmann *et al*[34] studied 48 children at a mean age of 9 years (range 4–13 years) with dyskinetic CP mostly due to BGT injury and found that most children had Gross Motor Function Classification System levels of level IV, n=10 and level V, n=28. The rate of learning disability (n=35) and epilepsy (n=30) increased with the severity of the motor disability.
2. *The watershed predominant pattern of injury* (WS) is the other pattern of injury which is also referred to as a pattern seen following 'prolonged partial asphyxia'. The vascular WS zones (anterior-middle cerebral artery and posterior-middle cerebral artery) are involved, affecting white matter and in more severely affected infants also the overlying cortex (figure 2). The lesions can be unilateral or bilateral, posterior and/or anterior. Although loss of the cortical ribbon, and therefore the grey-white matter differentiation can be seen on conventional MRI, DWI highlights the abnormalities and is especially helpful in making an early diagnosis.[35] A repeat MRI may show cystic evolution, but more often atrophy and gliotic changes will be recognised.[36] It is also more common after hypotension, infection and hypoglycaemia, all of which may be associated with a more protracted course.[37] As (severe) motor impairment is uncommon in this group of infants, they are not uncommonly considered to have an early normal outcome, when seen at 12–18 months and are then discharged from further follow-up. However, suboptimal head growth, behavioural problems and delay in language are common.[38 39] Several studies have now, however, shown that these children 'grow into their deficits' and it is this group in particular that needs follow-up well into early childhood. Miller *et al*[40] were first able to recognise cognitive deficits associated with the WS pattern of injury at 30 months,

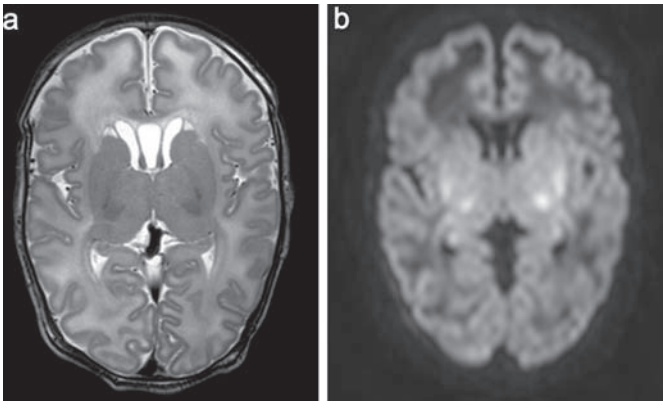


**Figure 1** MRI on day 5. (A) T2 weighted spin echo sequence showing a large cavum septum pellucidum and supendymal pseudocysts as incidental findings. The white matter has a high signal intensity, especially anteriorly and the basal ganglia are swollen and the thalami are of lower signal intensity. (B) Diffusion weighted imaging shows low SI in the anterior white matter and areas of restricted diffusion in the ventrolateral thalami and lentiform nuclei bilaterally. Restricted diffusion is also seen at the level of the hippocampi.

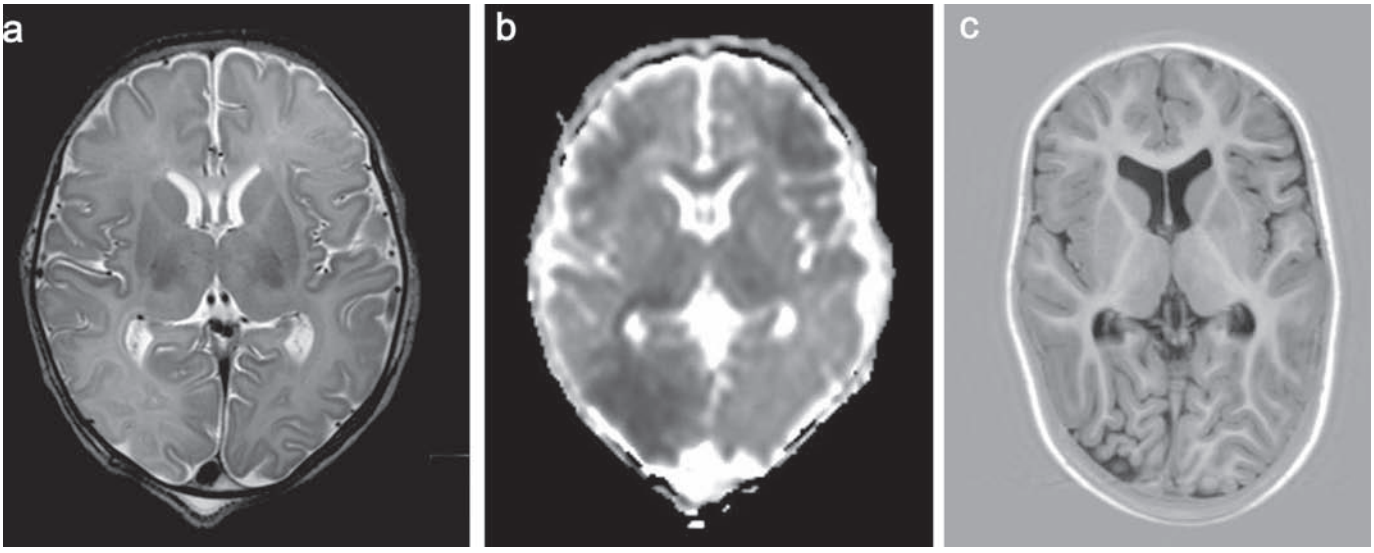


**Figure 2** MRI on day 3 (A,B) and at 22 months (C) in an infant with WS injury. (A) T2 weighted spin echo sequence image showing loss of the cortical ribbon mainly in the left frontal and right parieto-occipital region. (B) Apparent diffusion coefficient map also showing involvement of the right anterior watershed region as well as the right optic radiation. (C) Inversion recovery sequence showing sequelae in the right occipital region. Outcome at 3 years is within the normal range (DQ 90).

while the problems were largely overlooked, when seen at 12 months. More recently they also showed a correlation with verbal IQ at 4 years of age.[39]

In addition to the above described two main patterns of brain injury, *lesions restricted to the periventricular white matter*, not dissimilar from the so-called punctate white matter lesions in the preterm infant can also be distinguished as a separate pattern of injury, although less common (figure 3). Li *et al*[41] pointed out that infants with this type of injury are significantly less mature and they were noted to have milder encephalopathy and fewer clinical seizures relative to other newborns in the cohort with the two more common patterns of injury. Finally perinatal arterial ischemic stroke and perinatal haemorrhagic stroke can occur but these lesions are usually not related to PA[42 43] and are therefore outside the scope of this review.

Although not widely used at present, magnetic resonance spectroscopy is especially helpful when an MRI is performed on day 1, when changes on conventional MRI are often restricted to cerebral edema, and at a time when changes in the posterior limb of the internal capsule are not yet visible and DWI changes may still become more extensive.[44] There is no agreement about the best ratios to predict outcome. Roelants-Van Rijn *et al*[45] concluded that low N-acetylaspartate/choline and high lactate/N-acetylaspartate ratios best predicted a poor outcome in neonates with cerebral hypoxia-ischemia with echo times of 272 and 136 ms having a better predictive value than echo times of 31 ms. A recent meta-analysis including 32 studies and 860 babies, found the diagnostic odds ratio to be highest for lactate/N-acetylaspartate (82.1 (21.3, 316.9)), followed by Lac/creatine (25.4 (7.1, 91.8)) and N-acetylaspartate / creatine (4.31 (1.4, 13.8)).[46] Magnetic resonance spectroscopy can be a useful early magnetic resonance biomarker and is put forward as a surrogate end point in clinical trials.[46]

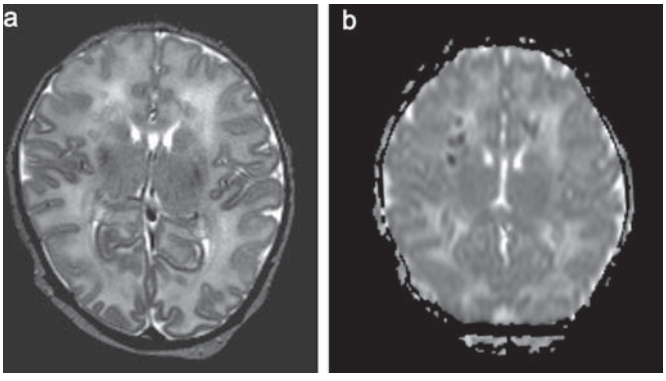


**Figure 3** MRI on day 7 in an infant with punctate white matter lesions. (A) T2 weighted spin echo sequence image showing multiple Punctate white matter lesions (PWML) predominantly on the right side. (B) Apparent diffusion coefficient map showing the PWML as areas of restricted diffusion. Outcome at 3 years was within the normal range (DQ 96).

Few studies have correlated neonatal MRI and outcome in early childhood. Belet *et al*[47] described that normal neonatal MRI findings were associated with a normal neurological outcome (negative predictive value: 100%) and abnormal MRI findings had the highest predictive value in predicting an abnormal outcome at the age of 4 months and 4 years (positive predictive value: 100%). Barnett *et al*[15] studied 68 full-term infants with NE at 5–6 years of age. Of the 53 surviving infants, 19 developed CP while the remaining 34 were considered normal at 2 years of age. When seen at school-age, eight children showed minor neurological dysfunction and/or perceptual motor difficulties, one had only cognitive impairment and 25 were considered normal. While 83% of those with a normal outcome had a normal neonatal MRI or an MRI with discrete white matter lesions, 80% of those with minor neurological dysfunction and/or perceptual-motor difficulties had mild or moderate basal ganglia lesions or more marked white matter lesions.

## LONG-TERM OUTCOME IN LATER CHILDHOOD AND ADOLESCENCE

Data on long-term outcome are scarce and often lack sophisticated neonatal neuroimaging data or other early biomarkers, such as neurophysiology (including aEEG and evoked

potentials). Data that are available tend to include children, where asphyxia was based on Apgar scores or often incomplete Sarnat criteria. In a recent study Lindström *et al*[48] looked at 15–19-year-old children with moderate encephalopathy in the neonatal period and found that the majority of children had cognitive deficits (81%). The children were considered to be eligible for the study, based on an Apgar score <7 at 5 min and meeting clinical criteria for moderate NE. Of 56 eligible children, 13 did not agree to participate. Of the 43 children who did participate, 13 (30%) had CP, 22 (51%) had cognitive dysfunctions without CP and only 8 (19%) had no obvious impairments. A previous study, using diffusion tensor imaging, showed long-term white matter disturbances which are not repaired by adolescence with moderate HIE in a small group of eight teenagers.[49]

A hospital-based cohort of 164 full-term infants with NE following PA, admitted to our level three Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital in Utrecht between 1993 and 1997, was studied in detail at 9–10 years of age. In the neonatal period 46 children (28.0%) died including all children with severe NE. All survivors were seen in the follow-up clinic up to 18 months of age and those with an abnormal neurological outcome were seen until 5 years of age. Of the 118 survivors, 80 were finally examined at 9–10 years of age. Of the children not examined, six were too severely affected to participate, seven (mild NE 5, moderate NE 2) could not be traced and the parents of 25 children (mild NE 13, moderate NE 11) refused to participate mainly due to MRI being part of the protocol.

The children (mild NE, n=34; moderate NE, n=46) included in this study were invited to the hospital for neurodevelopmental assessment, including general motor functioning (Movement Assesment Battery for Children (ABC) test), general intellectual functioning (Wechsler Intelligence Scale for Children III Dutch version), extensive behavioural and memory testing and an MRI scan. Thirty-three children had both a neonatal and childhood MRI and there was a good correlation for site and pattern of injury between the two scans.[50] Children with moderate/severe lesions on the neonatal or childhood MRI (BGT/WS or focal infarction) had significantly more often a total impairment score on the Movement ABC test ≤p15, and a score of ≤85 on the Wechsler Intelligence Scale for Children III. They more often developed CP and more often attended special education. In a subgroup (n=61) of the same cohort and in 47 controls the area of the corpus callosum (CC) was measured and related to the Movement ABC test score.[51] Children with moderate NE had significantly smaller middle and posterior parts and total areas of the CC. Children with mild NE and moderate NE scored significantly worse on the Movement ABC test than controls. The poorer motor skills in children with NE could be partly explained by a smaller size of the CC.

In the same cohort we were able to show that both mild and moderate NE have a negative effect on daily life behavioural functioning at the age of 9–10 years.[52] Behavioural problems were assessed using the Child Behaviour Checklist, Teacher's Report Form, Diagnostic Interview Schedule for Children IV and the Children's Social Behavior Questionnaire. At the level of daily life behavioral functioning, overall, both children with mild NE and moderate NE were judged by their teachers as showing more problematic behavior than comparison children, but the difference was significant only for children with moderate NE. There were no significant differences between the groups in the prevalence of attention deficit hyperactivity disorder classifications according to the Diagnostic Interview Schedule for Children IV criteria. In contrast, scores on the Teacher's Report Form F indicated higher levels of attention problems in children with moderate NE than in the comparison group. One other previous study reported an elevated rate of Autism Spectrum Disorders in children with moderate and severe NE with heterogeneous aetiology.[53]

We finally found, in addition to a global effect of NE on general intellectual functioning in both mild and moderate NE, specific negative effects on memory, associated with the degree of NE. Compromised maintenance and retrieval of information in verbal, visuospatial and verbal associative long-term memory, and speed of working memory processes were related to moderate NE, while mild NE was related to normal short term and working memory functions, and slightly weakened verbal learning capacity.[54]

## CONCLUSIONS

It has become increasingly clear that childhood survivors of NE, in the absence of CP, are at increased risk of cognitive, behavioural and memory problems. Although most children with mild NE studied so far were not found to significantly differ from controls, we found them to be performing in between the controls and those with moderate NE, suggesting a gradual effect. Longitudinal monitoring of educational and behavioural development is therefore recommended in both children with mild and moderate NE. This also applies to the infants who participated in the recent multicentre trials using hypothermia. The protective effect of hypothermia can only be fully appreciated when these children will be followed into childhood. We can only hope that in the future there will be more population based case–control studies of NE, starting in the neonatal period with sophisticated neuroimaging and neurophysiology and continuing into childhood and adolescence with detailed neurodevelopmental assessment.

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**Provenance and peer review** Commissioned; externally peer reviewed.

**Patient consent** Parental consent obtained.

**Ethics approval** This study was conducted with the approval of the University Medical Centre Utrecht.

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# Long-term outcome after neonatal hypoxic-ischaemic encephalopathy

Linda S de Vries and Marian J Jongmans

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# Prognostic Tests in Term Neonates With Hypoxic-Ischemic Encephalopathy: A Systematic Review

Henriette van Laerhoven, Timo R. de Haan, Martin Offringa, Bart Post and Johanna H. van der Lee

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# Prognostic Tests in Term Neonates With Hypoxic-Ischemic Encephalopathy: A Systematic Review


## abstract

**BACKGROUND AND OBJECTIVE:** Hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia in term neonates causes long-term neurologic sequelae or death. A reliable evidence-based prognosis is essential. The study goal was to investigate the prognostic value of currently used clinical tests in neonatal patients with perinatal asphyxia and HIE.

**METHODS:** Searches were made on MEDLINE, Embase, Central, and CINAHL for studies occurring between January 1980 and November 2011. Studies were included if they (1) evaluated outcome in term infants with perinatal asphyxia and HIE, (2) evaluated prognostic tests, and (3) reported outcome at a minimal follow-up age of 18 months. Study selection, assessment of methodologic quality, and data extraction were performed by 3 independent reviewers. Pooled sensitivities and specificities of investigated tests were calculated when possible.

**RESULTS:** Of the 259 relevant studies, 29 were included describing 13 prognostic tests conducted 1631 times in 1306 term neonates. A considerable heterogeneity was noted in test performance, cut-off values, and outcome measures. The most promising tests were amplitude-integrated electroencephalography (sensitivity 0.93, [95% confidence interval 0.78–0.98]; specificity 0.90 [0.60–0.98]), EEG (sensitivity 0.92 [0.66–0.99]; specificity 0.83 [0.64–0.93]), and visual evoked potentials (sensitivity 0.90 [0.74–0.97]; specificity 0.92 [0.68–0.98]). In imaging, diffusion weighted MRI performed best on specificity (0.89 [0.62–0.98]) and T1/T2-weighted MRI performed best on sensitivity (0.98 [0.80–1.00]). Magnetic resonance spectroscopy demonstrated a sensitivity of 0.75 (0.26–0.96) with poor specificity (0.58 [0.23–0.87]).

**CONCLUSIONS:** This evidence suggests an important role for amplitude-integrated electroencephalography, EEG, visual evoked potentials, and diffusion weighted and conventional MRI. Given the heterogeneity in the tests' performance and outcomes studied, well-designed large prospective studies are needed. *Pediatrics* 2013;131:88–98



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**KEY WORDS**

perinatal asphyxia, hypoxic-ischemic encephalopathy, prognosis, clinical test, systematic review


**ABBREVIATIONS**

aEEG—amplitude-integrated electroencephalography
CI—confidence interval
HIE—hypoxic-ischemic encephalopathy
MRS—magnetic resonance spectroscopy
SEP—sensory evoked potential
VEP—visual evoked potential

Drs van Laerhoven, de Haan, and Post all had full access to the meta-analysis data and take responsibility for the integrity and accuracy of all data and subsequent analysis; Drs Post and Offringa are responsible for the original design and concept of the study; Drs van Laerhoven, de Haan, van der Lee, and Post acquired the data; and Drs van Laerhoven, de Haan, and van der Lee analyzed and interpreted the data. Statistical analyses were performed by Drs van der Lee, de Haan, and Offringa. Drafting and revision of the manuscript were performed by Drs van Laerhoven, de Haan, van der Lee, Offringa, and Post. Drs de Haan, van der Lee, and Offringa supervised the study.


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Perinatal asphyxia is an important cause of acquired neonatal brain injury in term neonates leading to hypoxic-ischemic encephalopathy (HIE). It may lead to long-term neurologic sequelae or death.[1] In these critically ill neonates, a reliable evidence-based prognosis is of key importance to correctly inform parents and caretakers regarding the possible long-term neurodevelopmental consequences.

Clinical neurologic dysfunction immediately after HIE has long been regarded to be the best predictor of long-term neurodevelopmental outcome or death.[2–4]

Because neurophysiologic tests as EEG, amplitude-integrated electroencephalography (aEEG), and advanced neuroimaging modalities such as MRIs have become widely available, these tests have attained a significant role in the process of prognostication.

Nevertheless, uncertainty remains regarding the accuracy of these tests to predict long-term neurodevelopmental outcome or death in neonates with severe HIE. Most studies concerning prognostic tests are based on small case series or retrospective data or evaluate short-term follow-up (≤18 months).[3,5–8] In the era before the use of controlled hypothermia, 3 meta-analyses evaluated the prognostic value of biochemical tests,[9] aEEG,[10] and MRI or magnetic resonance spectroscopy (MRS)[11] in the neurodevelopmental outcome in term neonates with HIE. However, biochemical tests are not used in the clinical setting, and apart from that, these previous meta-analyses had methodologic limitations.

To investigate the prognostic value of currently used clinical tests for long-term neurodevelopmental outcome of neonatal patients suffering from perinatal asphyxia and HIE we performed a systematic review of the literature. If possible, results from studies concerning patients treated with controlled hypothermia were compared with normothermic patients.

## METHODS

### Information Sources

We followed the guidance from the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[12] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[13] A comprehensive electronic literature search was conducted in the MEDLINE (Pubmed), Embase, CENTRAL, and CINAHL databases for studies published between January 1980 and November 2011. Only studies including humans and reported in the English or Dutch language were eligible. We checked the citations of eligible studies for additional articles that might be included. In addition, experts were contacted for relevant articles concerning prognosis after HIE. The search strategies from the meta-analyses of Spitzmiller et al,[10] Ramaswamy et al,[9] and Thayyil et al[11] were used as examples of literature searches for studies on the use of aEEG, biomarkers, and MRI as prognostic tests. The Medical Subject Heading terms and keywords used for the search are included in the online-only material (see Supplemental Information eMethods 1).

### Eligibility Criteria and Definitions

Three reviewers (H.v.L., T.R.d.H., and B.P.) independently selected studies based on the following inclusion criteria: (1) observational prognostic studies that included neonates with a gestational age of 36 weeks or greater who had perinatal asphyxia and HIE (both perinatal asphyxia and HIE had to be clearly defined in the study methods section); (2) neurodevelopmental follow-up available for at least 18 months postnatal age; and (3) neurodevelopmental outcome clearly defined as good or adverse. Adverse neurodevelopmental outcome was defined by either 1 or more of the following criteria: (1) cerebral palsy, either described by standardized clinical neurologic examination or defined by the Global Motor Functioning Scale; (2) an abnormal test result on developmental test scores using the Bailey States of Infant Development test or the Griffith Mental Developmental Index (a test score of ≥2 SDs below mean was defined as adverse outcome); and (3) death during admission or during the specified follow-up period. Disagreements were resolved by discussion until consensus.

### Data Extraction

A standardized data extraction form was used to record study information (see Supplemental Information eMethods 2). Disagreements were resolved by discussion until consensus was reached. If the required data could not be extracted from the publication, the corresponding author was contacted and additional information was requested. If core data remained missing the study was excluded from the analyses.

### Methodologic Quality

Appraisal of the methodologic quality of the included studies was performed by 3 reviewers (H.v.L., T.R.d.H., and B.P.) with the use of a checklist (see Supplemental Information eMethods 3 and 4). Criteria were adapted from instruments developed by Kwakkel et al[14] and Borghouts et al[15] and general recommendations for prognostic studies.[16] A set of 14 items was obtained to evaluate the methodologic quality of studies. All 14 items were assumed to be of equal importance and were not weighed.

### Summary Measures and Synthesis of Results

The prognostic accuracy of each test was assessed on the basis of 2 × 2 tables for both normothermic and hypothermic neonates if available. Neurodevelopmental

outcome at the age of 18 months or older at follow-up was recorded as either "good" (ie, normal or mild disability) or "adverse" (moderate/severe disability or death) as defined by each individual study. In case of continuous variables, cut-off values for normal or abnormal test results were used as defined by the authors of the original studies and were stated as either positive or negative. Because the results of diagnostic tests predictive of cerebral damage can change over time after perinatal asfyxia, we documented the prognostic value of each test per time window of test performance if the published data allowed us to do so.

We calculated the sensitivity and specificity for each prognostic test in relation to good or adverse outcome. A meta-analysis of the results of included studies on the same prognostic test among either normothermic or hypothermic neonates was carried out by using Review Manager Version 5.0 (The Cochrane Collaboration 2008, The Nordic Cochrane Centre, Copenhagen, Denmark) in combination with the SAS (SAS Institute, Cary, NC) macro METADAS v 1.3 developed by Yemisi Takwoingi. Meta-analyses using the bivariate approach in which pairs of sensitivity and specificity are jointly analyzed, incorporating any correlation that might exist between these 2 measures using a random effects approach, were carried out when multiple studies addressed the same prognostic relation. In accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Version 1.0; 2010, http://srdta.cochrane.org), random effects analyses were performed and no indicator of heterogeneity was calculated.

## RESULTS

Our literature search yielded 3469 article abstracts, and 259 were selected for review of the full-text articles. Inclusion criteria were met by 46 studies. Checking citations and consulting experts yielded 6 additional studies, for a total of 52 inclusions. Despite contacting corresponding authors, adequate data for 2 × 2 tables could be retrieved only from 29 of 52 studies. Of these final 29 studies, 28 had included normothermic patients and 1 included both normothermic and hypothermic patients.[16] A flow diagram of the search and selection process is shown in Fig 1; Table 1 summarizes the characteristics of all included studies.

In 29 studies, 1411 term infants with HIE after perinatal asphyxia were investigated. Follow-up was available for 1306 (93%) infants. The degree of HIE (mild, moderate, or severe) was clearly described in 23 (79%) of 29 studies. The included studies contained 201 infants with mild HIE (grade 1), 469 patients with moderate HIE (grade 2), and 186 patients with severe HIE (grade 3). The remaining 450 patients were less clearly qualified as having either moderate or severe HIE.

In 19 (66%) of 29 studies, the outcome assessor was blinded for the test result. In 6 (21%) of 29 studies, the number of included patients was larger than 50, and 25 of 29 studies had 15% or less loss to follow-up. Five (17%) studies reported on the method or extent of the provided intensive care treatment or on end-of-life decisions. Twenty-one (72%) studies were of a prospective design.

The 29 included studies described 13 different clinically used diagnostic tests. These tests included different cerebral imaging modalities, neurophysiologic tests, and clinical neurologic examination. The age at test performance ranged from 1 to 30 days after birth. The age of neurodevelopmental outcome testing ranged from 18 months to 7 years. Table 2 reports the classification for positive or negative test as reported per study.

Results of the meta-analysis are reported in Table 3 (pooled sensitivities and specificities with confidence intervals) and Fig 2 (forest plots of sensitivity and specificity as calculated from the original reports). Figure 2 A and B reports the forest plots for neurophysiologic tests and clinical physical examination, and Fig 2C reports the forest plots for imaging tests.

The most promising neurophysiologic tests (performed in the first week) were aEEG (sensitivity 0.93, 95% confidence interval [CI] 0.78–0.98]; specificity 0.90 [95% CI 0.60–0.98]), EEG (sensitivity 0.92 [95% CI 0.66–0.99]; specificity 0.83 [95% CI 0.64–0.93]), and visual evoked

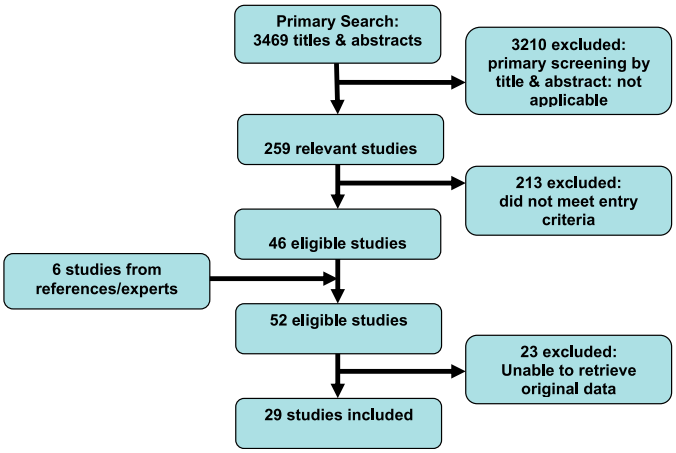


**FIGURE 1**
Flowchart of the search and selection process.

**TABLE 1** Characteristics of Included Studies

| Year of Publication | First Author | Prospective/ Retrospective Study Design | Blinded Y/N[a] | Female/ Male Ratio | HIE Stage 1/ 2/3 (n) | *n*/*N*[b] | Timing of Testing | Test | Follow-up | Outcome Studied |
|---|---|---|---|---|---|---|---|---|---|---|
| 2011 | Alderliesten[17] | R | N | 31/50 | 2/73/4 | 81 (122) | Days 1–8 | MRI: ADC and MRS | 18–46 mo | Griffiths and neurologic examination |
| 2011 | Ferrari[18] | P | Y | 14/20 | 9/11/14 | 34 (43) | Days 1–42 | MRI: T1/T2 and GM | 2 y | Griffiths and neurologic examination according to Amiel-Tison and Grenier and Touwen |
| 2010 | Twomey[19] | P | N | NA | 3/15/8 | 26 (26) | Days 1–14 | MRI: T1/T2, ADC, DWI and mCUS | 2 y | Bayley II and WPPSI |
| 2010 | Rutherford[20] | P | NA | 32/35 | NA | 130 (131) | Days 2–30 | MRI: T1/T2 | 18 mo | MDI, Bayley and GMFCS |
| 2010 | Ancora[21] | P | Y | 8/24 | 17/13/2 | 32 (33) | Days 1–14 | MRI: T1/T2 and aEEG | 2 y | Griffiths Mental Development Scale |
| 2009 | Liauw[22] | R | Y | 11/13 | 3/18/3 | 24 (24) | Days 1–8 | MRI: ADC | 2 y | van Wiechen examination |
| 2009 | Murray[23] | P | Y | 18/26 | 18/17/9 | 44 (54) | Days 1–2 | EEG | 2 y | Griffiths and neurologic examination |
| 2008 | Vermeulen[24] | P | Y | 19/(27 | 10/26/10 | 46 (46) | Days 1–8 | MRI: T1/T2, ADC and DWI | 2 y | Bayley II |
| 2006 | Toet[25] | P | Y | NA | 0/8/8 | 18 (21) | Days 1–2 | aEEG[c] | 2 y | Griffiths and Movement ABC |
| 2005 | L 'Abee[26] | P | Y | 6/14 | 0/4/7 | 11 (11) | Days 1–2 | MRI: T1/T2, DWI and MRS | 2 y | Griffiths and neurologic examination according to Amiel-Tison and Grenier and Touwen |
| 2005 | van Rooij[27] | R | Y | NA | NA | 160 (161) | Day 2 | aEEG | 2 y | Griffiths and neurologic examination |
| 2004 | Belet[28] | P | Y | 7/17 | 2/16/6 | 24 (24) | Days 5–14 | MRI: T1/T2 | 3.5–4 y | Bayley II and Denver developmental test |
| 2004 | Khong[29] | P | Y | 6/14 | 0/15/5 | 20 (20) | Days 2–14 | MRI: T1/T2,DWI and MRS | 18–24 mo | Amiel-Tison and Ellison evaluation |
| 2004 | ter Horst[30] | R | Y | 15/15 | 4/18/5 | 26 (30) | Days 1–3 | aEEG | 2 y | Touwen test |
| 2001 | Biagioni[31] | P | Y | 12/13 | 8/16/1 | 25 (25) | Days 1– 8 | MRI: T1/T2 and EEG | 2 y | Griffiths and neurologic examination |
| 2001 | Roelants-van Rijn[32] | P | NA | 7/14 | 6/12/3 | 19 (21) | Days 1–30 | MRI:T1/T2 and MRS | 2 y | Griffiths and neurologic examination |
| 1999 | Mercuri[3] | R | Y | NA | 16/37/5 | 47 (58) | Days 7–14 | Neurologic Examination | 1.5–5 y | Griffiths and neurologic examination. |
| 1999 | Toet[33] | P | N | NA | 27/17/20 | 68 (73) | Day 1 | aEEG | 5 y | Griffiths and neurologic examination |
| 1998 | Scalais[34] | P | Y | NA | 5/24/1 | 40 (40) | Days 1–7 | VEP, SEP and BAEP | 2 y | Griffiths anditems from Brunet-Lezine and neurologic examination |
| 1996 | Groenendaal[35] | P | N | NA | 5/20/7 | 31 (32) | Days 1–14 | MRS | 18 mo | Griffiths and neurologic examination |
| 1995 | Eken[36] | P | N | 16/18 | 11/7/16 | 34 (34) | Days 1–8 | CUS, SEP, VEP and aEEG | 2 y | Griffiths and neurologic examination |
| 1995 | van Lieshout[37] | R | Y | NA | NA | 18 (21) | Day 3 | EEG | 7 y | WHO disability staging |
| 1994 | Thornber[38] | P | NA | 24/14 | NA | 38 (38) | Days 1–3 | aEEG | 18 mo | Denver Developmental Test |
| 1993 | Bao[39] | P | NA | 52/93 | 49/57/8 | 133 (145) | Days 3–14 | NBNA | 2 y | Bayley modified by the Child Development Centre China |
| 1993 | Prechtl[40] | P | Y | 8/18 | 0/13/13 | 26 (26) | Days 1–8 | GM and EEG | 17–24 mo | Griffiths andneurologic examination |
| 1992 | Taylor[41] | R | Y | NA | NA | 57 (57) | Days 1–8 | SEP and VEP | 18 mo | Bayley II andneurologic, audiometric and visual examination |
| 1991 | de Vries[42] | P | Y | 8/26 | 4/12/18 | 34 (34) | Days 1–14 | SEP | 18 mo | Bayley Mental Developmental Scales and neurologic examination according to Amiel-Tison and Touwen |
| 1991 | Muttitt[43] | P | Y | 12/24 | 2/20/13 | 35 (36) | Days 1–7 | VEP | 2 y | Bayley Mental Developmental Scales and neurologic, audiometric and ophthalmologic examination |
| 1991 | McCulloch[44] | R | N | NA | NA | 25 (25) | Days 1–7 | VEP | 2.5–4.5 y | Clinical eye examination |

DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; CUS, cerebral ultrasound; GM, general movements; GMFCS, Gross Motor Function Classification System; MDI, Motor Development Index; NA, not available; WHO, World Health Organization.

[a] Blinded Y/N, outcome assessment blinded yes or no.

[b] *n*/*N*, number of cases with complete follow-up/total number of cases in study.

[c] Wechsler Preschool and Primary Scale of Intelligence.

**TABLE 2** Normal and Abnormal Findings as Defined per Study

| Year of Publication | First Author | Normal Findings | Abnormal Findings |
|---|---|---|---|
| 2011 | Alderliesten[17] | MRI: basal ganglia ADC $>1031 \times 10^{-6}$ mm$^2$/s | MRI basal ganglia ADC $\leq 1031 \times 10^{-6}$ mm$^2$/s |
| | | MRS: basal ganglia lactate/NAA $\leq 0.08$ | MRS: basal ganglia lactate/NAA $>0.08$ |
| 2011 | Ferrari[18] | Normal T1/T2-weighted MRI or | Abnormal T1/T2-weighted MRI in basal ganglia; white matter; cortex or PLIC |
| | | mild abnormalities cortex, no abnormalities basal ganglia or PLIC | GM: poor repertoire; abnormal movements for age. |
| | | GM: normal for age | |
| 2010 | Twomey[19] | Normal T1/T2-weighted | Abnormalities T1/T2-weighted or DW-MRI (diffuse, watershed, central, atypical) |
| | | Normal DW-MRI | Abnormal CUS (abnormal cortex/isolated gray matter hyperechogenicity, central hyperechogenicity) |
| | | Normal CUS | |
| 2010 | Rutherford[20] | Normal T1/T2-weighted MRI | Abnormalities on T1/T2-weighted MRI (basal ganglia; PLIC; white matter; cortical). |
| 2010 | Ancora[21] | Normal background aEEG | Abnormal background aEEG |
| | | No Lactate | Ratio MRS lactate/Cr $>0.3$ |
| | | Ratio MRS NAA/Cr $>0.5$ | Ratio MRS NAA/Cr $<0.5$ |
| 2009 | Liauw[22] | MRI: ADC Basal ganglia $>1018.5 \times 10^{-6}$ mm$^2$/s | MRI: ADC Basal ganglia $<1018.5 \times 10^{-6}$ mm$^2$/s |
| 2009 | Murray[23] | EEG normal background for age No seizures | Moderate, major abnormalities EEG background; seizures or inactive EEG |
| 2008 | Vermeulen[24] | Normal T1/T2-weighted or DW-MRI | T1/T2-weighted or DW-MRI abnormal cortex; basal ganglia; brainstem; PLIC or cerebellum |
| | | Normal ADC | Abnormal ADC cortex; basal ganglia; brainstem; PLIC or cerebellum |
| 2006 | Toet[25] | Normal aEEG pattern (continuous normal voltage, discontinuous normal voltage $>5$ $\mu$V), No seizures | Abnormal aEEG pattern (flat trace; continuous low voltage; burst suppression; seizures) |
| 2005 | L 'Abee[26] | Normal T1/T2-weighted or DW-MRI | Abnormalities T1/T2-weighted or DW-MRI |
| | | Normal ADC basal ganglia/white matter | (cortex, basal ganglia or white matter) |
| | | Normal MRS of basal ganglia. | Abnormal ADC (basal ganglia; white matter) |
| | | | Elevated lactate/*N*-acetyl aspartate (basal ganglia) |
| 2005 | van Rooij[27] | Normal aEEG pattern (continuous normal voltage, discontinuous normal voltage $>5$ $\mu$V) | Abnormal aEEG pattern (flat trace; continuous low voltage; burst suppression) |
| 2004 | Belet[28] | Normal T1/T2-weighted MRIs | Abnormalities T1/T2-weighted MRI (White matter lesions/deep gray matter lesions/ encephalomalacia-atrophy) |
| 2004 | Khong[29] | Normal T1/T2-weighted or DW-MRIs | Abnormal T1/T2-weighted or DW-MRIs |
| | | Normal ADC basal ganglia | (Diffuse white matter lesions, abnormalities in deep gray nuclei, lesions in brainstem) |
| | | Normal MRS basal ganglia | Abnormal ADC basal ganglia. |
| | | | MRS Lactate peak present in basal ganglia |
| 2004 | ter Horst[30] | Normal aEEG pattern (continuous normal voltage, discontinuous normal voltage $>5$ $\mu$V) | Abnormal aEEG pattern (flat trace; continuous low voltage; burst suppression), |
| | | No seizures | Seizures, status epilepticus |
| 2001 | Biagioni[31] | Normal EEG background for age, | Abnormal EEG |
| | | No seizures. | (low voltage; constant discontinuity,abnormal for age) Seizures |
| | | Normal T1/T2-weighted MRIs | Abnormal T1/T2-weighted MRI (abnormalities in basal ganglia, thalamus, PLIC, white matter). |
| 2001 | Roelants-van Rijn[32] | Normal T1/T2-weighted MRIs | Abnormalities T1/T2-weighted |
| | | MRS: lactate/NAA ratio $<0.09$ | (Moderate to severe Abnormalities in basal ganglia/thalamus/ PLIC/cortex) |
| | | MRS: NAA/Cho ratio $>0.62$ | MRS: Lactate/NAA ratio $>0.09$ |
| | | | MRS: NAA/Cho ratio $<0.62$ |
| 1999 | Mercuri[3] | Normal T1/T2-weighted MRIs | Abnormalities T1/T2-weighted |
| | | Neurologic exam: normal | (moderate to severe abnormalities in basal ganglia/thalamus/ white matter) |
| | | | Neurologic exam: abnormal |
| 1999 | Toet[33] | Normal aEEG pattern (continuous normal voltage, discontinuous normal voltage $>5$ $\mu$V) | Abnormal aEEG pattern (flat trace; continuous low voltage; burst suppression) |

**TABLE 2** Continued

| Year of Publication | First Author | Normal Findings | Abnormal Findings |
|---|---|---|---|
| 1998 | Scalais[34] | VEP/BEAP/SEP: normal for age | VEP: increased latency/missing components/absent<br>SEP: increased latency/absent cortical waves<br>BAEP: increased interpeak latency/abnormal amplitude ratio/ only Wave I identifiable |
| 1996 | Groenendaal[35] | MRS no lactate basal ganglia or periventricular white matter | MRS: Lactate in basal ganglia or periventricular white matter |
| 1995 | Eken[36] | CUS normal basal ganglia and white mater.<br>Normal SEP/VEP for age<br>Normal aEEG background pattern<br>No seizures on aEEG | CUS abnormal basal ganglia or white matter<br>VEP: latency P200 outside normal range for age or absent<br>SEP: latency outside normal range for age or absent response<br>Abnormal aEEG background (burst suppression/continuous low voltage/flat trace) Seizures on aEEG. |
| 1995 | van Lieshout[37] | EEG normal pattern for conceptual age<br>No seizures on EEG | Abnormal EEG (isoelectric,low voltage pattern, burst suppression, diffuse $\delta$ pattern, interhemispheric asynchrony)<br>Seizures on EEG |
| 1994 | Thornberg[38] | Normal aEEG background pattern (CNV)<br>No seizures | Abnormal aEEG background (burst suppression) or seizures |
| 1993 | Bao[39] | NBNA normal at 7 or 14 DPN (score >35) | NBNA abnormal at 7 or 14 DPN (score <35). |
| 1993 | Prechtl[40] | GM normal for age and developmental stage<br>EEG normal pattern for age, no electrical discharges | GM abnormal for age (abnormal quality of movements)<br>EEG electrical discharges, severely depressed and/or severely discontinuous interictal EEG |
| 1992 | Taylor[41] | SEP normal for age<br>VEP normal for age | SEP abnormal waveform or delayed latency/absent cortical components.<br>VEP delayed, unusual waveform, absent |
| 1991 | de Vries[42] | SEP N1 latency within normal limits according to Klimach and Cooke | SEP delayed N1 latency or absent response |
| 1991 | Muttitt[43] | Normal VEP for age | Abnormal VEP (unusual waveform persistent more then 7 d, delayed latency; missing components or absent) |
| 1991 | McCulloch[44] | Normal VEP for age | Abnormal for age or absent VEP |

Normal, normal test finding in study; abnormal, abnormal test finding in study; ADC, apparent diffusion coefficient; BEAP, brainstem auditory evoked potential; Chol, choline; Cr, creatine; CUS, cerebral ultrasound; DPN, days postnatal; NAA, *N*-acetyl aspartate; NBNA, Neonatal Behavioral and Neurologic Assessment; PLIC, posterior limb internal capsule.

**TABLE 3** Pooled Sensitivities and Specificities With Confidence Intervals for Tests Where Pooling was Possible

| Test | No. of Studies | No. of Patients | Pooled Sensitivity | | Pooled Specificity | |
|---|---|---|---|---|---|---|
| | | | Point Estimate | 95% CI | Point Estimate | 95% CI |
| aEEG first 6 h | 2 | 58 | 0.95 | 0.87–0.98 | 0.92 | 0.61–0.99 |
| aEEG first 24 h | 2 | 187 | 0.93 | 0.85–0.97 | 0.91 | 0.67–0.98 |
| aEEG first 72 h | 2 | 68 | 0.93 | 0.78–0.98 | 0.90 | 0.60–0.98 |
| EEG first 72 h | 2 | 48 | 0.92 | 0.66–0.99 | 0.83 | 0.64–0.93 |
| MRI DWI first week | 2 | 36 | 0.58 | 0.24–0.84 | 0.89 | 0.62–0.98 |
| ADC first week | 3 | 113 | 0.79 | 0.50–0.93 | 0.85 | 0.75–0.91 |
| T1/T2 first week | 3 | 60 | 0.84 | 0.27–0.99 | 0.90 | 0.31–0.99 |
| T1/T2 first 2 wk | 3 | 75 | 0.98 | 0.80–1.00 | 0.76 | 0.36–0.94 |
| T1/T2 first 6 wk | 3 | 120 | 0.83 | 0.40–0.97 | 0.53 | 0.31–0.73 |
| MRS first week | 3 | 66 | 0.75 | 0.26–0.96 | 0.58 | 0.23–0.87 |
| MRS first 2 wk | 3 | 56 | 0.73 | 0.24–0.96 | 0.84 | 0.27–0.99 |
| Cranial US | 2 | 60 | 0.79 | 0.30–0.97 | 0.55 | 0.39–0.70 |
| VEP | 5 | 181 | 0.90 | 0.74–0.97 | 0.92 | 0.68–0.98 |
| SEP 1st wk | 4 | 143 | 0.93 | 0.70–0.99 | 0.78 | 0.52–0.92 |

potential (VEP) (sensitivity 0.90 [95% CI 0.74–0.97]; specificity 0.92 [95% CI 0.68–0.98]). Of the imaging techniques, diffusion weighted MRI (first week) performed best on specificity (0.89 [95% CI 0.62–0.98]) and T1/T2-weighted MRI (first 2 weeks) performed best on sensitivity (0.98 [95% CI 0.80–1.00]). Early MRS demonstrated a sensitivity of 0.75 [95% CI 0.26–0.96] with poor specificity (0.58 [95% CI 0.23–0.87]). Clinical neurologic examination and cerebral ultrasound both performed poorly.

## DISCUSSION

To our knowledge, this is the first review to systematically evaluate currently used clinical tests for the prediction of outcome in term neonates with perinatal asphyxia and HIE. Although the literature contains a wide variety of studies on outcome in these patients evaluating a host of mostly new and relatively unknown test modalities, we have focused on tests used in everyday medical practice. Knowledge on the prognostic value of these tests is most helpful for the clinician. This review is, therefore, not an effort to provide a comprehensive overview of all available tests.

Although the initial search yielded 259 potentially relevant studies, we could only use the information on 13 different prognostic tests reported in 29 studies These 13 prognostic tests consisted of

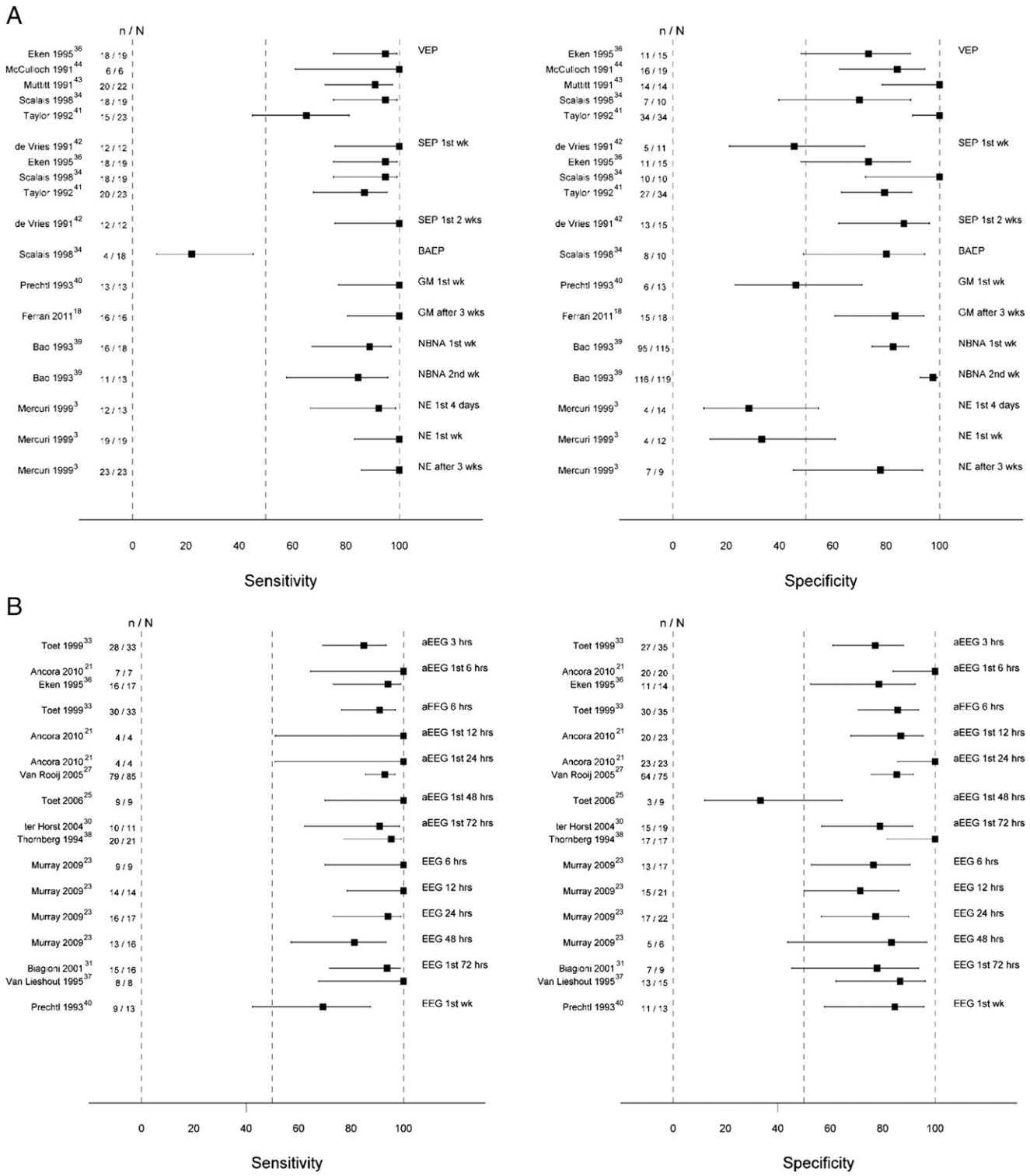


**FIGURE 2**

Sensitivity/specificity forest plots for (A) clinical neurologic tests (NE/NBNA/GM)- and VEP, SEP, BAEP studies; (B) aEEG and EEG studies; and (C) imaging studies (MRI/MRS/cranial). BAEP, Brainstem Auditory Evoked Potential; GM, general movements; NBNA, Newborn Behavioural Neurological Assessment; NE, neurological examination.

a wide array of tests such as imaging modalities, neurophysiologic tests, and clinical neurologic examinations.

According to our findings, the most promising neurophysiologic tests in the first week of life in neonatal patients with HIE after perinatal asphyxia are aEEG, EEG, and VEP. The 95% CIs are wide, due to small numbers. As far as we

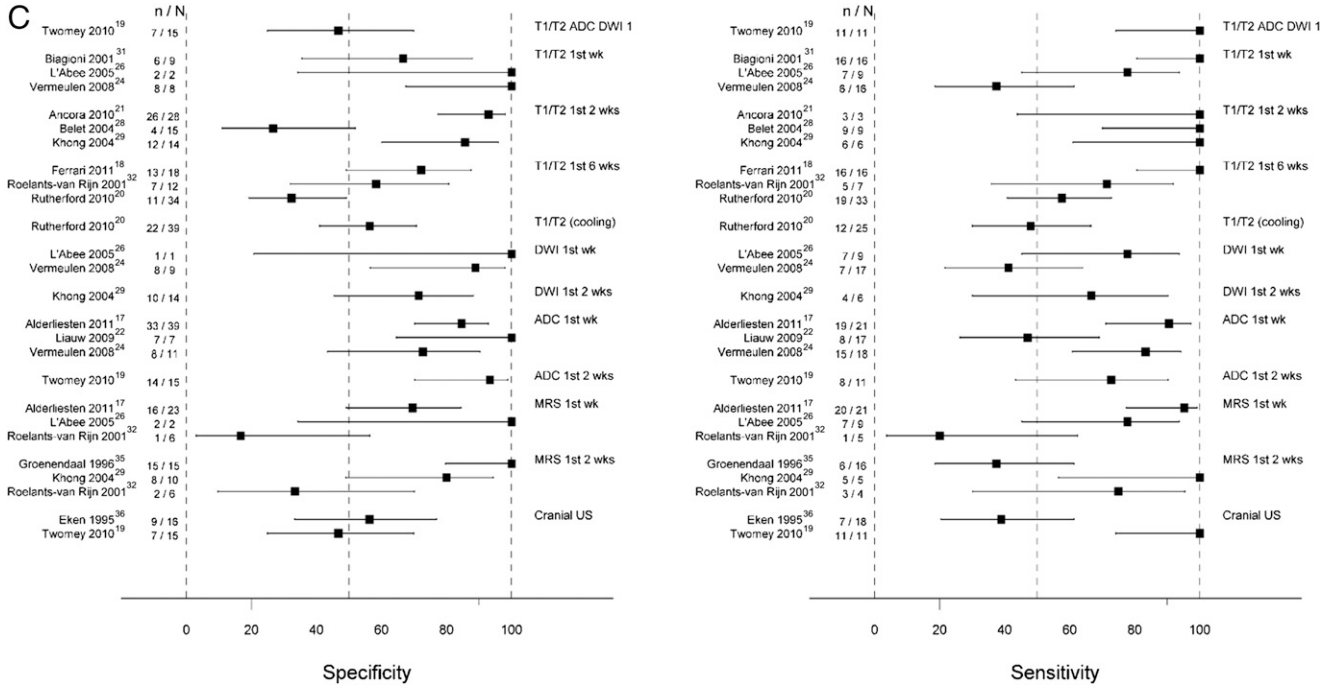


**FIGURE 2**
Continued

know, both sensory evoked potentials (SEP) and VEP are not used routinely in most NICUs, but both may provide important prognostic information. We did, however, find considerable heterogeneity in specificity, especially for SEP as can be seen in Fig 2A. This may be caused by differences in cut-off values used for positive or negative test results. In a meta-analysis by Zandbergen et al[45] concerning adults after hypoxia, the investigators concluded that in these patients the SEP is the most accurate early predictor of poor neurologic outcome or death. Additional investigation into the prognostic value of evoked potential tests after perinatal asphyxia is warranted.

Imaging studies of the brain in patients with HIE after perinatal asphyxia are essential in the process of prognostication nowadays. Although the original studies concerning imaging and outcome were heterogeneous and based on small numbers, we decided to perform meta-analyses. Of the imaging modalities, diffusion weighted MRI (performed in the first week) had the highest specificity and T1/T2-weighted MRI (performed in the first 2 weeks) had the highest sensitivity. An abnormal DW image is therefore highly predictive of adverse outcome (SPIN), and a normal T1/T2-weighted MRI is highly predictive of normal outcome (SNOUT). Outcome may, however, still be favorable in cases with early abnormal DW imaging. Cerebral ultrasound and clinical neurologic examination, both frequently used bedside screening methods, had a reasonable sensitivity but a poor specificity. Abnormalities on cerebral ultrasound or clinical neurologic examination may therefore lead to unnecessary apprehension due to the relatively large number of false positives.

## Comparison With Earlier Reviews

Three earlier meta-analyses, each focusing on a single prognostic test, have reported on the prediction of neurodevelopmental outcome or death in term neonates with HIE.[9–11] The meta-analysis by Spitzmiller et al[10] on aEEG included 8 studies,[27,30,33,36,38,46–48] of which 5 fulfilled our inclusion criteria.[27,30,33,36,38] We included 2 additional studies in our meta-analysis.[21,25] Spitzmiller et al's reported pooled specificity is in line with our findings (0.88 vs 0.90). The meta-analysis by Ramaswamy et al[9] on biochemical markers in serum, urine and cerebrospinal fluid is, in our opinion, inconclusive as the included studies are highly heterogeneous with regard to the type of biochemical test methods used and clinical outcome measures reported. Although biomarkers of cerebral cellular damage comprise a very interesting field of research, their value in the process of prognostication in daily practice needs to be evaluated.

Finally, the meta-analysis by Thayyil et al[11] evaluating the prognostic value of MRI and MRS concluded that basal ganglia or thalamic lactate/*N*-acetyl aspartate is a highly accurate marker for the prediction of adverse long-term neurodevelopmental outcome or death. Five studies addressing basal ganglia

lactate MRS complied with our inclusion criteria[17,26,29,32,35] of which 3 were also included in Thayyil et al's review. Based on our analysis and pooled sensitivities and specificities, taking into account the very wide 95% CIs, we conclude that there is insufficient evidence so far to advise either positively or negatively about the use of MRS. More prospective studies need to be done.

### Strengths and Weaknesses

The evidence from the studies we included seems applicable to the care and treatment policies for infants with HIE after perinatal asphyxia. A countereffect of our strict inclusion criteria is that our review includes only 1306 patients studied over 30 years. The major cause of the relatively small number of included patients is our inclusion criterion of a neurodevelopmental follow-up period of at least 18 months; many studies did not follow children beyond 12 months of age. In our opinion the relevance of the assessment of neurodevelopmental outcome at ages before 18 months is at least questionable as neurodevelopmental sequelae can become manifest at ages beyond 12 months, and mental and behavioral disabilities may appear at even later ages.[49]

The presence of bias is almost unavoidable in systematic reviews and meta-analyses of observational studies. Selection bias and information bias may be present in the original studies under review (by flaws in study design) or arise from the way studies were selected for inclusion. Several forms of bias may have influenced our results regarding the tests' accuracies. Language bias by restriction to the English and Dutch language sources may have led to an overestimation or underestimation of both sensitivity and specificity. However, the incremental value of searching for studies in other languages than English has not been fully investigated.[50] An overestimation of test accuracy may have occurred as it was not always clear if eligible patients in the included studies were entered in the cohort nonrandomly or consecutively. Overestimation of test result accuracy may also have occurred due to information bias as in a number of studies tests were analyzed in retrospect with knowledge of the clinical outcome. Selection bias by the possible exclusion of deceased patients in included studies may also have led to overestimation of the prognostic value of the tests. Publication bias, the selective publication of studies based on the magnitude and direction of their findings, represents a particular threat to the validity of meta-analysis of observational studies that may very well have inflated our results.

Last but not least, our results were most often based on small sample sizes; the CIs of our pooled data are therefore wide. Unfortunately, we could only retrieve useful data from 29 of the 52 selected studies due to poor reporting. A subgroup analysis of the prognostic value of the investigated tests in neonates with different grades of HIE after perinatal asphyxia was not possible with these limited data. This is of importance as tests may behave differently in different sub populations.

### Validity of Results in Patients Under Hypothermic Treatment

Controlled hypothermia has proved to be a major improvement in the care of newborns with HIE as it improves neurodevelopmental outcome and survival.[51,52] Studies incorporated in this review were mainly performed in the era before controlled hypothermia. Studies on EEG and aEEG during controlled hypothermia have reported an optimal time window of 48 hours after the hypoxic-ischemic event for optimal prognosis of outcome.[53,54] So far, there is no evidence that the optimal time window for MRI is essentially different due to this new hypothermia treatment protocol.[20,55] Therefore, based on the current state of knowledge, we believe that the results of this review concerning EEG, aEEG, and MRI can be used in infants treated with controlled hypothermia. It is not known whether VEPs are influenced by hypothermia and it is thus not certain if our results on VEP can be extrapolated to neonates undergoing controlled hypothermia.

## CONCLUSIONS

EEG and aEEG both perform well in predicting outcome for neonates with perinatal asphyxia and HIE even when performed in the first week of life. MRI is generally advised between the fourth and the eighth day after HIE. This time window is clinically essential to evaluate brain damage.[56] Our analysis shows considerable variation in the accuracy of MRI, either conventional, diffusion weighted, or spectroscopy. The clinician should be aware of the essence of test timing and the variability in sensitivity and specificity per time window of test performance. Cerebral ultrasound may be a quick and noninvasive bedside tool, but its specificity in children with HIE is unacceptably low. The prognostic value of SEP and VEP is promising but should be investigated in well-designed prospective studies before standardized clinical use is advocated. In general, we found large variability in the timing and cut-off values of the tests and in outcome assessment at follow-up, stressing the importance of clear definitions and harmonization of test methods and outcome measures in this field.

Finally, it seems clinically sensible that a combination of prognostic test results in individual patients, although correlated, will perform better than individual tests. From the available data we could not evaluate the accuracy of any combination of prognostic tests and therefore we cannot advise on the optimal test combination. A well-designed

prospective study is needed to test the joint accuracy of several complementary tests in prognostication. Results from such a study will not only aid in the clinical care of these patients but may also be used for the inclusion and stratification of patients in neuroprotective intervention trials that need to include patients at high risk of adverse outcome after HIE.

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# Prognostic Tests in Term Neonates With Hypoxic-Ischemic Encephalopathy: A Systematic Review

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