

Investigation of seizures in infants

RICHARD E. APPLETON

The Roald Dahl EEG Unit, Paediatric Neurosciences Foundation, Alder Hey Children's NHS Foundation Trust, Liverpool

The investigation of seizures in infancy (i.e. within the first year of life) begins with establishing whether the seizures are epileptic or non-epileptic in origin. The 'broad' differential diagnosis of possible seizures and 'epilepsy' is multiple and is particularly difficult under the age of 12 months and includes:

- Gastro-oesophageal reflux (Sandifer's syndrome)
- Pallid syncopal attacks (reflex anoxic seizures)
- Cyanotic breath-holding attacks
- Cardiac arrhythmias
- Münchausen syndrome by proxy (passive or active – both representing a form of child abuse)
- Shuddering spells and jitteriness
- Hyperekplexia
- Benign neonatal sleep myoclonus
- Benign myoclonus of infancy
- Tonic reflex activity and involuntary movements (seen in children with neurological impairment including cerebral palsy or hydrocephalus).

Once a non-epileptic disorder has been excluded or the episodes are considered to be obviously epileptic, then the following conditions/investigations should be considered on a chronological basis.

Perinatal (first week of life) and neonatal (first month of life) seizures

The newborn period is the time of life with the highest risk of seizures¹⁻³. This is because of the relative lack, and immature development of inhibitory neurotransmitters and their pathways. The immature and developing brain is susceptible to a large number of both cerebral and systemic insults including:

- Asphyxia (hypoxic-ischaemic encephalopathy) – the most common and also most serious cause of neonatal seizures – particularly in term infants
- Intra- and periventricular haemorrhage – particularly in pre-term infants
- Metabolic dysfunction (e.g. hypoglycaemia, hypocalcaemia and hyponatraemia)
- Sepsis (most commonly septicaemia or meningitis but also congenital infections, particularly cytomegalovirus, herpes simplex and HIV-AIDS encephalopathy)
- Cerebral malformation
- Trauma.

The *onset* of perinatal seizures and timing of the cerebral insult are broadly as follows:

In utero Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 (and beyond)

Cerebral malformation/dysgenesis ----->
 Intrauterine (congenital) infection ----->
 Pyridoxine/pyridoxamine dependency/deficiency ----->
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Perinatal asphyxia
 Sepsis
 Hypoglycaemia
 Maternal drug withdrawal
 Periventricular haemorrhage

Hypocalcaemia
 Benign familial neonatal convulsions

Aminoacidopathies
 Galactosaemia
 Ketotic and non-ketotic hyperglycinaemia
 Early infantile epileptic encephalopathy
 Folinic acid-responsive neonatal seizures
 Glucose transport protein deficiency
 Migrating partial seizures (epilepsy) of infancy

Perinatal and neonatal seizures are both over- and under-diagnosed. Generalised tonic-clonic seizures do not occur in neonates, and most seizures are myoclonic or clonic and localised (focal or partial including Jacksonian) and fragmentary, again reflecting an immature brain. Even though almost two decades old, the classification of neonatal seizures remains a pragmatic classification²:

Seizure type	Relative frequency
Subtle (fragmentary) bicycling or boxing; oral-buccal-lingual (chewing, swallowing or tongue-thrusting); tonic eye deviation; apnoea (cessation of breathing); complex, purposeless movements	33%
Clonic	27%
Tonic	20%
Myoclonic focal; multifocal; generalised	20%

(Note: subtle seizures are more common in premature infants, i.e. before 37 completed weeks of gestation)

Not all abnormal movements (particularly in premature babies) are seizures and clinical differentiation of seizure from non-seizure activity may be very difficult. Electroencephalography (EEG) (particularly prolonged with simultaneous video-recording of the clinical episodes and abnormal movements), may resolve some of this difficulty. However, there is frequently an element of 'electroclinical dissociation' whereby electroencephalographic 'seizures' (i.e. epileptiform activity) have an uncertain and inconstant relationship with clinical seizures and this phenomenon is more likely the younger the infant.

The aetiologies of neonatal seizures are multiple. In most cases the underlying aetiology can be determined from preceding events, the clinical course (including the pregnancy), family history and physical examination. If there is no definite history of perinatal asphyxia, an initial 'screen' should be undertaken:

- Blood glucose, calcium, magnesium, urea, electrolytes and acid-base status
- Full blood count and film examination
- CSF analysis (glucose [with a simultaneous fasting blood glucose], protein, cell count)
- Cultures of blood, CSF, urine and faeces
- Cranial ultrasonography (only of use when looking for evidence of haemorrhage or a *major* cerebral malformation); CT is preferable to ultrasound and usually can be undertaken in 20–30 seconds, with the newer generation of fast-acquisition scanners.

Further investigations should be performed depending upon the clinical situation and results of the initial evaluations:

- Blood ammonia, lactate, uric acid and liver enzymes; biotinidase level; if the blood creatinine level is consistently low, further more detailed biochemical and genetic analyses should be undertaken looking for evidence of abnormalities of creatinine synthesis (e.g. GAMT deficiency)
- Blood and urine amino acids, urinary organic acids
- Urine-reducing substances; urine sulphite levels
- 'TORCH' antibody studies (for congenital infections)
- CT – or, ideally, MRI – of head (for cerebral malformations/dysgenesis)
- Diagnostic use of pyridoxine (vitamin B6)
- CSF analysis (glucose, lactate, amino acids)
- Chromosome and DNA analysis – particularly if the child has any dysmorphic features and/or microcephaly. Boys presenting with frequent and drug-resistant neonatal seizures and no obvious cause should have DNA analysed for Rett syndrome. Girls presenting with frequent myoclonic seizures and infantile spasms that persist and do not respond to antiepileptic medication should also have DNA analysis for Rett syndrome (specifically the CDKL5 mutation).

Note: CT may not reveal subtle dysgenesis (such as heterotopic grey matter) or abnormal patterns of myelination until the infant is 12 (or even 24) months of age; MRI is considerably more sensitive. However, early CT (within the first few weeks of life) should reveal major cerebral malformations (e.g. lissencephaly, schizencephaly and holoprosencephaly) and will also demonstrate haemorrhage and cerebral calcification (the latter frequently found in neonates and infants with a prenatally-acquired infection such as toxoplasmosis or cytomegalovirus [CMV]).

The condition of pyridoxine-dependent seizures is a rare autosomal recessive disorder that presents characteristically within the first week of life with intractable seizures and a markedly abnormal (almost hysarrhythmic-like, often with a burst-suppression pattern)

EEG⁴. However, it may also 'present' before birth with intrauterine seizures, or late, even up to 12 or 18 months of age. Clinical response to intravenous pyridoxine (vitamin B6) is usually immediate as is normalisation of the EEG, although the latter may be delayed for days or weeks. Therefore a trial of oral pyridoxine (20–30 mg/kg/day) should be given for at least three weeks. If there is a partial response to oral pyridoxine, it would be important to use a trial of pyridoxal phosphate⁶. Also, it is recommended that any infant under the age of 18 months with intractable seizures of unknown cause should receive a similar trial of pyridoxine. A biochemical marker (elevated levels of pipercolic acid in plasma, urine and/or CSF) and genetic abnormality have recently been identified in a number of infants with pyridoxine-dependent seizures and, if these early observations are confirmed, this would represent a significant advance and importantly, replace the 'therapeutic challenge', in providing a definitive diagnosis of this rare syndrome⁷.

The treatment of perinatal and neonatal seizures depends largely on the aetiology. Any underlying cause such as drug withdrawal, electrolyte disturbance or a treatable metabolic disorder (including hypoglycaemia and hypocalcaemia), should be corrected. Antiepileptic drug (AED) treatment is virtually always indicated if a correctable metabolic cause is not identified; pyridoxine should be given early if seizures are resistant to conventional AED therapy and biotin also given, pending the result of a serum biotinidase level. Phenobarbitone and phenytoin are the usual first-line drugs, but ideally only in the acute situation where early seizure-control is required. The metabolism of phenytoin in neonates is rapid and doses often need to be in excess of 15–20 mg/kg/day and given at eight, rather than 12-hourly intervals (for this reason serum level monitoring must be frequent and particularly if the infant is receiving a number of other drugs).

Paraldehyde, lignocaine and clonazepam are other useful drugs, often given as infusions (rather than as boluses) in 'refractory' neonatal status epilepticus. If seizures persist the infant **must** be discussed with a paediatric neurologist as rare conditions, including a mitochondrial cytopathy, glucose transport protein deficiency, carbohydrate deficient glycoprotein syndrome, sulphite oxidase deficiency or folinic acid-responsive seizures, must be considered and either confirmed or excluded by the relevant investigations.

Most neonatal seizures are acute symptomatic in origin with the seizures tending to resolve, usually spontaneously. In this situation it would be reasonable to withdraw medication four or at most six weeks after the 'symptomatic' insult (assuming the infant is seizure free) – and to restart an AED if seizures then recurred. The drug of choice then would be dependent upon the seizure type (or types), and the overall neurological/developmental status of the child. Drugs of first choice would include carbamazepine (partial or tonic-clonic seizures), sodium valproate (myoclonic, atonic or tonic-clonic seizures) and vigabatrin (infantile spasms); phenobarbitone and phenytoin would **not** be drugs of first choice for treating 'late' epilepsy. Sodium valproate should be avoided in any infant with frequent myoclonic seizures, in whom the cause of the seizures is as yet unknown, or if there is any suspicion that the infant may have an underlying metabolic disorder and specifically a mitochondrial cytopathy.

A number of outstanding issues remain to be answered regarding neonatal seizures:

- There are inadequate data indicating whether neonatal seizures produce cerebral damage or are completely 'harmless'. There is some circumstantial evidence that neonatal seizures increase the risk of later epilepsy and, possibly, cognitive impairment in children who subsequently develop cerebral palsy (CP)⁸. However, it is likely that the aetiology of the seizures is more important than the seizures themselves.
- There is almost no information on the effects of AEDs on the developing brain.
- Many pharmacokinetic properties of AEDs (particularly phenytoin) are unique to the

- neonatal period and may result in problems of both drug efficacy and toxicity.
- The value of AED treatment beyond the neonatal period to prevent later epilepsy is unknown.

Benign familial neonatal convulsions (seizures)⁹

As already stated, this syndrome may present in the newborn period (characteristically in the first week of life), and is rarely seen after eight weeks of age. Seizures are usually generalised and rarely subtle. There is no known cause for this condition, but it is believed to be inherited with autosomal dominant inheritance and at least two genes have been identified – one on chromosome 20q and one on 8q. Some consider this syndrome to be the earliest form of idiopathic generalised epilepsy. Neurological and developmental outcome is normal, but approximately 10–12% of these infants develop later epilepsy (in adolescence or in early adult life), usually generalised tonic-clonic seizures. In most infants, seizures resolve between six weeks and six months of age. The precise incidence (and prevalence) of this syndrome is unknown. The inter-ictal EEG is usually normal.

Benign non-familial (sporadic) neonatal convulsions (seizures)⁹

This is another rare type of neonatal convulsions, again with no obvious cause. It is likely that this represents the entity known previously as ‘fifth day fits’, which was once considered (entirely erroneously), to be due to zinc deficiency. Seizures may persist for longer than in the familial form but late epilepsy is much less common (under 1%), and may have no causal relationship.

Migrating partial seizures (epilepsy) in infancy¹⁰

Although this would appear to be a rare syndrome it is probably under-recognised, like most new epilepsy ‘syndromes’. Again, as with many syndromes, it is waiting for a biochemical or genetic marker to confirm its identity, and possibly to explain its pathogenesis. Most infants present at less than six months of age and the majority at less than six weeks of age. The seizures are brief but multiple and at their peak may occur over 50 or 60 times per day. Eye and/or head deviation, autonomic features (facial flushing and epiphora) and some facial/limb clonic activity characterize the seizures. As the name implies, the seizures originate from (and migrate to) different parts of the brain – both clinically and electrically, in the EEG. Developmental progress is generally very poor (from the onset of the seizures) and survivors usually have moderate or severe learning difficulties. Many infants die under two or three years of age. Thus far no abnormality has been consistently identified, despite exhaustive biochemical, radiological and genetic investigations, including mutations associated with channelopathies. Seizure-control is usually very poor and no one anticonvulsant has proved to be any more effective than another.

Myoclonic epilepsy in infants

Early onset, severe. The condition may be independent from, or, far less likely, may overlap with Ohtahara’s syndrome¹¹ (early infantile epileptic encephalopathy with burst-suppression on EEG). Both syndromes (whether separate or allied) have a poor prognosis; seizures are typically resistant to treatment and psychomotor retardation is both inevitable and profound. Speech and language impairment is particularly marked – and usually persistent. In true Ohtahara’s syndrome most children do not survive beyond their second or third birthday. Familial cases are common, suggesting an underlying metabolic defect. Structural abnormalities (disorders of neuronal migration) and a number of metabolic diseases have been identified (rarely), including:

- Hyperglycinaemia (ketotic and non-ketotic)
- Methylmalonic acidaemia
- Propionic acidaemia
- Sulphite oxidase deficiency
- D-glyceric acidaemia
- Mitochondrial cytopathy (e.g. cytochrome oxidase deficiency).

A number of infants with this syndrome may develop infantile spasms and West syndrome in the second half of the first year of life. Valproate, the benzodiazepines (clonazepam, nitrazepam), and prednisolone (for short courses) and phenobarbitone are the drugs of choice. Piracetam is also worth considering. Importantly, lamotrigine may exacerbate the myoclonic seizures in severe myoclonic epilepsy of infancy. Early – and as yet anecdotal – evidence suggests that levetiracetam and topiramate may be effective in treating myoclonic seizures in infants and young children although clearly, further data will either confirm or refute these early observations.

Late-onset, severe. Severe myoclonic epilepsy in infancy (SMEI) is a rare syndrome with an estimated frequency of one in 40,000¹², although it may turn out to be more common. Otherwise normal infants develop generalised or focal myoclonic seizures in the first few weeks or months of life; rarely the onset may be as early as the first week. Infants far more commonly present at 6–9 months of age with isolated but prolonged and often focal ‘febrile seizures’ or febrile status epilepticus. Myoclonic, tonic-clonic and partial seizures then develop, often explosively, in the second or third year of life. The child’s development may stagnate and may even regress, particularly in receptive and expressive speech and language skills. Severe myoclonic epilepsy in infancy (SMEI) is also known as ‘Dravet syndrome’, although in the author’s opinion eponyms are not that helpful in describing newly-described specific epilepsy syndromes. SMEI is recognised to be a sodium channelopathy, and specifically due to (at least) one mutation in the alpha (α) subunit of the first neuronal sodium channel gene (SCN1A) on chromosome(s) 19 and/or 2. Sodium valproate, clonazepam and stiripentol are probably the more effective anticonvulsants in treating this syndrome. Topiramate, levetiracetam and the ketogenic diet have also been reported to be helpful. Importantly, lamotrigine, even in relatively low doses, may significantly exacerbate the myoclonic seizures – and this observation is often used as a clue in establishing a diagnosis of SMEI. There is a real danger of inappropriate and excessive ‘polypharmacy’ in treating children with this epilepsy syndrome with the consequence of significant side effects, particularly affecting concentration, learning, behaviour and sleep. There are no data to indicate that the simultaneous use of three antiepileptic drugs (AEDs) is more effective than two in controlling seizures. Stiripentol, in association with sodium valproate or clobazam may be particularly effective in treating most of the seizure types in SMEI. However, its use must be carefully monitored because of its potential serious side effects on the central nervous system¹³, mainly due to its interactions with the other anticonvulsants used to treat this specific epilepsy syndrome.

*Benign*¹⁴. This is also a rare and a somewhat more disputed syndrome. It is characterised by brief episodes of generalised myoclonic seizures which may commence in the first (or more commonly in the second) year of life in otherwise normal children who frequently have a family history of epilepsy. The myoclonic seizures are brief, may be massive and usually occur on or soon after falling asleep. The only relevant investigation is the EEG, which shows generalised spike-wave or polyspikes occurring in brief bursts during the early stages of sleep. Generalised tonic-clonic seizures may develop in adolescence. Valproate readily controls the infantile myoclonus. Lamotrigine may be a useful alternative. Some consider this syndrome, rather than benign familial neonatal convulsions, as the earliest expression of idiopathic generalised epilepsy. In most children, seizures either remit spontaneously or

are relatively easily controlled with anticonvulsants.

West syndrome^{15,16}

This syndrome is one of the most severe that occurs in the first year of life; the usual age of onset 3–10 months (peak 6–8 months). The full syndrome comprises an electroclinical triad, although only the first two features are required to diagnose the syndrome:

- Infantile spasms (flexor and extensor seizures occurring typically in clusters, with between five and 50 per cluster usually on or soon after waking).
- Hypsarrhythmia on the EEG (occasionally demonstrated only during sleep, particularly in the early stages of the syndrome).
- Developmental delay (not invariable at the onset of the spasms and therefore not essential for the diagnosis of the syndrome).

Approximately 80% are ‘symptomatic’ and are due to an identified aetiology. Common causes include:

- A neurocutaneous syndrome, specifically tuberous sclerosis and neurofibromatosis type 1
- A sequel to hypoxic-ischaemic (perinatal asphyxia) encephalopathy
- Cerebral dysgenesis (including tuberous sclerosis and Aicardi syndrome)
- Cerebral tumour
- The result of infection (pre- and postnatal meningoencephalitis)
- Metabolic disorders (e.g. biotinidase deficiency, Menke’s disease, phenylketonuria, non-ketotic hyperglycinaemia, a mitochondrial cytopathy)
- Degenerative disorders (e.g. PEHO syndrome – progressive encephalopathy, peripheral edema, hypsarrhythmia and optic atrophy).
- Genetic causes including the CDKL5 mutation in Rett syndrome and abnormalities in the homeobox genes.

There are however many other causes¹⁵.

The remaining 20% is ‘cryptogenic’ (or, ‘presumed symptomatic’, using the new, proposed ILAE terminology), with no obvious cause. Almost certainly this number will fall over the forthcoming years with further advances in functional neuroimaging (MRI, tractography and magnetoencephalography [MEG]), molecular genetics and biochemistry. In the author’s opinion genetic and ‘new’ metabolic disorders are likely to be responsible for a larger number of infants with infantile spasms (and other seizure types) than is currently recognised, including some as yet undiscovered enzyme/substrate deficiencies.

The investigation of infantile spasms depends largely on the individual child and its previous medical (particularly perinatal) history. All infants require imaging with MRI. A negative (normal) CT should never be regarded as excluding a structural lesion. If initial CT is undertaken this should always be followed by MRI undertaken at approximately two or three years of age (by which time cerebral myelination should be largely complete), to demonstrate any subtle dysgenesis, or evolving metabolic disorder.

Vigabatrin remains one of the initial drugs of choice for West syndrome irrespective of cause among many, but not all, paediatric neurologists in the UK and Europe. It is particularly effective in treating infantile spasms caused by tuberous sclerosis. The drug may not be as effective as the other drugs of first choice (adrenocorticotrophic hormone – ACTH, now available as tetracosactide in the UK, or prednisolone) in treating spasms

caused by other aetiologies¹⁷. Vigabatrin may be associated with a lower rate of relapse than hormonal treatments when the drug is discontinued. Vigabatrin also appears to be considerably safer with much less serious and toxic side effects (see also Chapter 30), although the reported visual field constriction in association with at least six months' (and usually longer) exposure to this drug is clearly of concern; the incidence of the visual field defect in children is unclear but is considered to be approximately 20–25%, although these data are predominantly based on older children who received the drug for treating partial seizures and not in infants who were treated for infantile spasms. In the author's experience, nitrazepam and, to a lesser extent, sodium valproate may be the most 'effective' drugs in treating infantile spasms caused by perinatal hypoxic-ischaemic encephalopathy or non-accidental brain injury. Anecdotally, topiramate and levetiracetam may also have a role, at least in treating refractory symptomatic infantile spasms. It is important to realise that unfortunately, neither vigabatrin nor any other single drug will ever prove to be effective for all children with infantile spasms, given the marked heterogeneity of both the semiology of the spasms and their aetiology.

Febrile convulsions (seizures)¹⁸

Defined as 'convulsions with fever in children aged between six months and five years without evidence of serious acute symptomatic brain disease (e.g. meningitis, encephalitis)' (see also Chapter 8).

Although by *definition* children as young as six months of age may have febrile seizures, the author would not accept the diagnosis in infants less than one year of age, and would consider the following diagnoses first, and undertake the appropriate investigations:

- Meningitis/encephalitis
- Metabolic disorder
- Cerebral dysgenesis.

Clearly the number and type of investigations undertaken would depend upon the age of the infant and whether the febrile seizure was 'simple' or 'complex' (complex means a seizure which is focal, serial, longer than 15 minutes, or followed by a neurological deficit). For example, a complex febrile seizure in a six-month-old infant should at least raise the possibility that the child may be developing severe myoclonic epilepsy in infancy (SMEI, described above) and would justify *at least* the exclusion of meningitis by CSF analysis and urine culture. It would also merit neuroimaging (preferably MRI) to exclude or demonstrate a structural lesion (including cerebral dysgenesis). A simple febrile seizure in a one-year-old with no obvious focus of infection would justify CSF and urine analysis however. A simple febrile seizure in a two or three-year-old child with otitis media probably needs no investigation and specifically there is no indication for undertaking an EEG in this situation.

Frequently a complicated febrile seizure may actually represent a first epileptic seizure that has been provoked by an intercurrent infection. Over the past few years, there has been the identification of a 'syndrome' of generalised epilepsy and febrile seizures plus (GEFS+) which may present with febrile seizures in the first two years of life. The word, 'plus' in this syndrome refers both to the fact that febrile seizures may still occur after the age of five years *and* that other afebrile seizures (of multiple types) may occur in later childhood or adult life. Inheritance is said to be autosomal dominant with at least one abnormal gene lying on chromosome 9^{19,20}. In the author's opinion, febrile seizures are over-diagnosed and the entire concept of what precisely constitutes a 'febrile seizure' requires re-evaluation.

Summary and conclusions

- Although the newborn period is the time of life when epileptic seizures occur most

commonly, firstly not all involuntary including ‘jerky’ or ‘twitchy’ movements are epileptic and secondly, most causes of genuine epileptic seizures are secondary to (or symptomatic of), an underlying cause. If in doubt that the movements or other paroxysmal events (e.g. autonomic changes) are epileptic – do not diagnose epilepsy

- There are a relatively large number of epilepsy syndromes that have an onset in infancy (the first year of life) and most are associated with a poor prognosis, both in terms of seizure control and eventual spontaneous remission but also development and cognitive functioning
- Never overlook a simple biochemical or metabolic cause of seizures in neonates and infants (specifically, glucose, calcium and sodium)
- Cranial ultrasound and skull radiographs are of little diagnostic value when evaluating the cause of an infant’s seizures. MRI is the imaging modality of choice – particularly when considering cerebral dysgenesis as a cause of the epilepsy
- Genetic investigations, such as the Rett syndrome mutations (MECP2 and CDKL5) should be considered early when confronted with a child with intractable seizures and no obvious cause
- Avoid polypharmacy (the simultaneous use of more than two AEDs) in treating seizures in infancy. When about to add another AED, always try and withdraw another one first or simultaneously – this is always easier said than done.

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