Investigation of seizures in infants

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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 seizures[1-3]. 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 l Day 2 Day 3 Day 4 Day 5 Day 6 (and beyond)

Cerebral malformation/dysgenesis -->
Intrauterine (congenital) infection --->
Pyridoxine/pyridoxamine dependency/deficiency --->

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 classification[2]:

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).

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)
- MRI head (for cerebral malformations/dysgenesis)
- Diagnostic use of pyridoxine (vitamin B6) and/or pyridoxal-5-phosphate
- CSF analysis (glucose, lactate, amino acids)
- Chromosome and DNA analysis. There are an increasing number of gene abnormalities associated with infantile epilepsies – discuss with genetics team.

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 hypsarrhythmic-like, often with a burst-suppression pattern) EEG[4]. However, it may also 'present' before birth with intrauterine seizures, or late, even up to 12 or l8 months of age. Clinical response to intravenous pyridoxine (vitamin B6) is often 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. Some infants have an abnormality further down the metabolic pathway and require treatment with pyridoxal-5-phosphate as pyridoxine will not be effective in these infants. Some clinicians now would recommend using pyridoxal-5-phosphate instead of pyridoxine to ensure that all infants who have a defect in this metabolic pathway will be treated in an appropriate manner[6]. Also, it is recommended that any infant under the age of l8 months with intractable seizures of unknown cause should receive a similar trial of pyridoxine. A biochemical marker (elevated levels of pipecolic acid in plasma, urine and/or CSF) and genetic abnormalities 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 syndrome[7].

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/pyridoxal-5-phosphate 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).

Levetiracetam, lignocaine and benzodiazepines (clonazepam or midazolam) 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 steroids/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 (KCNQ2) and one on 8q (KCNQ3). 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.

Epilepsy of infancy with migrating focal seizures (migrating partial seizures in infancy[10,11])

Although this would appear to be a rare syndrome it is probably under-recognised, like most new epilepsy 'syndromes'. 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. There is emerging evidence of a genetic aetiology to this disorder with mutations in KCNT1 being the most frequently reported but also cases with SLC25A22, SCN1A, SCN2A, TBC1D24, SCN8A and CHD2 mutations. Seizure-control is usually very poor and no one anticonvulsant has proved to be any more effective than another. Ketogenic diet and vagal nerve stimulation also are generally ineffective. There has been some recent interest in gene-targeted treatment in children with KCNT1 mutations using quinidine, however further evaluation of this is required[12].

Myoclonic epilepsy in infants

Early onset, severe (early myoclonic encephalopathy) (EME). The condition may be independent from, or, far less likely, may overlap with Ohtahara syndrome[13] (early infantile epileptic encephalopathy with burst-suppression on EEG). Both syndromes are severe epileptic encephalopathies with a poor prognosis; seizures are typically resistant to treatment, psychomotor retardation is both inevitable and profound and life expectancy is limited. In EME seizures typically start in the first two months of life (with the majority starting in the first ten days) and myoclonic seizures are frequent (distinguishing the condition from Ohtahara syndrome). Metabolic aetiologies are common (non-ketotic hyperglycinaemia is the commonest metabolic aetiology, and amino and organic acidopathies, urea cycle disorders, mitochondrial disorders, pyridoxine and pyridoxal-5-phosphate disorders, molybdenum cofactor deficiency, sulfite oxidase deficiency, Menke syndrome, Zellweger syndrome and other disorders are also seen) and structural abnormalities are rare. A number of familial cases have been reported raising the possibility of a genetic aetiology. Gene mutations have been found in ErbB4.

Treatable metabolic aetiologies should be investigated at presentation and all infants should have a trial of pyridoxal phosphate. AEDs are generally ineffective and ketogenic diet has not been particularly beneficial in this condition.

Late-onset, severe. Dravet syndrome (also known as severe myoclonic epilepsy of infancy, SMEI) is a rare syndrome with an estimated frequency of one in 40,000[15], 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. Around 70–80% of patients with SMEI have a mutation in the alpha (α) subunit of the first neuronal sodium channel gene (SCN1A) on chromosome(s) 19 and/or 2 (95% de novo; 5% inherited). 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 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 system[16], mainly due to its interactions with the other anticonvulsants used to treat this specific epilepsy syndrome. There is anecdotal evidence that cannabidiol may be an effective treatment for Dravet syndrome, and clinical trials are currently under way.

Benign[17]. Benign myoclonic epilepsy in infancy 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 or febrile seizures. 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, and 20% have photosensitivity. Valproate readily controls the infantile myoclonus. Lamotrigine may be a useful alternative. While it is considered most likely to have a genetic basis, no genes have been identified to date. In most children, seizures either remit spontaneously or are relatively easily controlled with anticonvulsants. Febrile seizures occur in about 10% and generalised tonic-clonic seizures may develop in adolescence.

Ohtahara syndrome

Ohtahara syndrome presents in the first three months of life and is a severe epileptic encephalopathy. It can be distinguished from EME due to the predominance of tonic seizures and the relative infrequency of myoclonic seizures. However, like EME it has a poor prognosis with a drug-resistant epilepsy, severe psychomotor retardation and limited life expectancy. Structural brain abnormalities are the commonest cause of this epilepsy syndrome (e.g. hemimegalencephaly, porencephaly, Aicardi syndrome, olivary-dentate dysplasia, cerebral dysgenesis and focal cortical dysplasia) but genetic mutations (STXBP1 [10–15% of cases], SLC25A22, CDKL5, ARX, SPTAN1, PCDH19, KCNQ2, and SCN2A) are being increasingly reported. Metabolic aetiologies also occur (mitochondrial disorders, non-ketotic hyperglycinaemia, pyridoxine/pyridoxal-5-phosphate disorders, carnitine palmitoyl transferase deficiency, and biotinidase deficiency).

In terms of treatment AEDs are often not effective. Sodium valproate, phenobarbitone, vigabatrin, benzodiazepines and zonisamide have all demonstrated some limited effectiveness, as has the ketogenic diet. Treatable metabolic disorders should be identified early as appropriate treatments are of clinical benefit. Children with focal structural brain malformations should be referred to an epilepsy surgery programme as epilepsy surgery may be effective in terms of both seizure control and neurodevelopmental outcome.

Prognosis is poor in this condition with 25% of children dying in infancy. Many infants with Ohtahara syndrome will evolve into West Syndrome during infancy.

West syndrome[18,19]

This syndrome is one of the most severe that occurs in the first year of life with typical age of onset between 3 and 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:

- Epileptic 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 (though this is not present in all infants with West syndrome at presentation and may be demonstrated only in sleep).
- 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:

- Structural brain disorders
  - Malformations of cortical development (e.g. lissencephaly, cortical dysplasia)
  - Neurocutaneous syndromes (tuberous sclerosis, incontinentia pigmenti, neurofibromatosis)
  - Acquired brain injury (e.g. a sequel to hypoxic-ischaemic (perinatal asphyxia) encephalopathy, post- meningoencephalitis)

- Metabolic disorders (e.g. biotinidase deficiency, Menke's disease, phenylketonuria, non-ketotic hyperglycinaemia, mitochondrial cytopathy)
- Chromosomal disorders (Down syndrome, Miller-Dieker syndrome)
- Genetic causes (ARX, CDKL5, SPTAN1, STXBP1).

There are however many other causes.

The remaining 20% is 'cryptogenic' with no obvious cause. Almost certainly this number will fall over the forthcoming years with further advances in functional neuroimaging (MRI, tractography and magnetoelectroencephalography [MEG]), molecular genetics and biochemistry.

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.

First-line treatments for West syndrome are ACTH tetracosactide, prednisolone and vigabatrin[20,21]. ACTH/prednisolone is more effective than vigabatrin in controlling spasms early on (at 14 days), but is similar in efficacy in long-term follow-up (12–14 months)[22]. Vigabatrin appears to be particularly effective for infants who have West syndrome caused by tuberous sclerosis. Vigabatrin appears to be safer than ACTH/prednisolone, 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. A study evaluating the use of combination treatment with ACTH/prednisolone and vigabatrin compared to ACTH/prednisolone alone (the ICISS – International Collaborative Infantile Spasms Study) has just completed recruitment and early reports are of improved early seizure control on combination treatment, but these are yet unpublished. Other treatments that are of benefit include nitrazepam (which in a historic comparator trial has been shown to have similar efficacy to ACTH, but fewer side effects[23]), sodium valproate, topiramate, levetiracetam, zonisamide and pyridoxine. The ketogenic diet should be considered in infants with West syndrome which is resistant to medication. Children who have focal structural abnormalities and drug-resistant spasms should be referred to an epilepsy surgery centre to consider whether they are suitable candidates for resective epilepsy surgery.

Febrile convulsions (seizures)[24]

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
- Malformations of cortical development.

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 malformations of cortical development). If these investigations are negative it would be appropriate to screen for SCN1A mutations. 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. Mutations in a number of genes have been associated with this disorder including SCN1A, SCN1B, GABARG2 and PCDH19.

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 malformations of cortical development 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; infantile gene panels using next-generation sequencing of increasing numbers of known genes are becoming available and are likely to replace single-gene testing in time.
- 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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