

The only place to start: making the diagnosis of epilepsy

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Epilepsy is defined as the tendency for recurrent seizures to occur without acute provocation. Every child's (and adult's) brain is capable of generating a seizure with certain pro-convulsive drugs and it should therefore be of no surprise that seizures may be provoked by numerous other factors including: an acute metabolic (biochemical) disturbance, central nervous infection, drug intoxication or acute head trauma. The risk of epilepsy developing after acute and provoked (symptomatic) seizures is low (3–5%) and therefore the occurrence of acute seizures cannot contribute to, and should not influence, the diagnosis of epilepsy. Emotional stress is not considered to be a provoking factor.

Epilepsy has protean manifestations. Some children present with generalized tonic-clonic seizures (convulsions), while others present with staring spells (usually absence seizures), periods of confusion with or without automatisms (usually complex partial [focal] seizures), limb or body jerks (myoclonus), spasms (infantile or epileptic spasms), falls or drops (usually atonic or astatic but also tonic seizures), loss of speech and social interactions and/or cognitive function (Landau–Kleffner syndrome), and variants of paroxysmal events during sleep (often frontal lobe or, less commonly, temporal lobe seizures).

Epilepsy and some epilepsy syndromes may be diagnosed relatively quickly after a few tonic-clonic seizures (as these are usually dramatic and understandably frighten the family). Conversely, other syndromes may be diagnosed after some considerable time and only after the child has experienced a number of seizures. This is often because infrequent or only subtle seizures usually do not prompt parents to seek medical advice. Once seizures have been seen to occur very frequently, and specifically absence or myoclonic seizures, the diagnosis may be more straightforward; however, when patients present with only a few seizures the

2 Chapter 1: The only place to start: making the diagnosis of epilepsy

diagnosis is more challenging. A common scenario is the child presenting after a first, unprovoked ‘major seizure,’ i.e., a generalized tonic-clonic or prolonged complex partial seizure. After a first unprovoked ‘major seizure’ the chances of a recurrence are about 50%, and usually within the following six to 12 months. Clearly there are many children who will have an isolated unprovoked seizure and do not have a ‘tendency for recurrent seizures’; they should not be diagnosed as having epilepsy, regardless of the results of investigations. However, in many cases the first ‘major seizure’ is not in fact the first seizure and a careful history may reveal preceding ‘minor seizures’ (and usually collectively and erroneously termed ‘petit mals’), such as myoclonus or absence that had not worried the family sufficiently to prompt them to seek medical advice. If there is a convincing history of ‘minor seizures,’ alongside a clear history of a first ‘major’ (tonic-clonic) seizure, then it would be appropriate to make a diagnosis of epilepsy.

If a person has two unprovoked seizures then the chance of further seizures increases significantly to 80–90%, a recurrence risk that justifies the diagnosis of epilepsy. Consequently, the operational diagnosis of epilepsy is usually defined as the occurrence of two or more unprovoked seizures – and irrespective of the seizure type.

The diagnosis of a seizure – and epilepsy – is a clinical diagnosis in nearly all cases. In most situations, most seizures will have stopped long before the child is seen for medical advice. A careful history is the only diagnostic test and there are numerous paroxysmal disorders that may, on only limited ‘sound-bites’ of a history, mimic epileptic seizures. The most common is the brief, generalized, total body stiffening with or without a few myoclonic or clonic movements that characterizes vasovagal syncope or a reflex anoxic seizure. The clinical history must include where the episodes occurred and at what time, what the child was doing at the time and whether there was any possible provoking factor. For syncope, a typical scenario will be a dentist’s surgery, the sight of blood or sudden pain, or in a particularly hot environment. The patient often reports the premonitory symptoms of syncope such as light-headedness and feeling cold and clammy. This is followed by gradual graying and loss of vision. Observers will note extreme pallor with a limp fall and then stiffening with a few body jerks – myoclonic or clonic movements. Thus a history must be obtained from the patient and a witness. Incontinence more commonly occurs during a seizure but also occurs during syncope if the child has not recently urinated. The finding of a carpet burn on the face or a limb and an unexplained bitten tongue, particularly the side of the tongue, is much more suggestive of a generalized tonic-clonic seizure.

There are no investigations that can replace or short-cut the medical history. The results of an electroencephalogram (EEG) may be particularly misleading. If the patient has an actual seizure during the EEG recording then the diagnosis of epilepsy will be confirmed or refuted, in most cases; focal seizures arising from the mesial frontal lobe are an exception and the surface EEG may show no obvious change during or following the seizure. Unfortunately, other than in childhood-onset absence, photosensitive epilepsy or, occasionally, West syndrome a child is unlikely to experience a seizure and the EEG is nearly always undertaken when the patient is well. The hope is to find either focal or generalized ‘epileptic

Chapter 1: The only place to start: making the diagnosis of epilepsy**3**

discharges' (traditionally defined as spikes, spike and wave, or sharp waves on the EEG). It is important to understand the limitations of the EEG in the diagnosis of epilepsy:

- Approximately 3–5% of 'normal' children who never have experienced, and never will experience, a seizure will show spike activity or spike and slow-wave activity on the EEG.
- Conversely, approximately 20–25% of children with definite epilepsy will show no epileptic discharge on a routine EEG.

Consequently, the finding of epileptic discharges on EEG is neither sufficiently sensitive nor specific to make the diagnosis of epilepsy. Again, the diagnosis can only be achieved by the clinical history. If the history is vague, incomplete or non-diagnostic, we are of the opinion that it is best to defer the diagnosis until there are more obvious epileptic attacks or if additional history, with or without video footage of the episodes, becomes available. There is good evidence that epilepsy is often falsely diagnosed and even pediatric neurologists may occasionally disagree, when the history from frightened or inarticulate parents is unusual or incomplete – or the history has not been obtained from an eye-witness of the episodes. A false diagnosis of epilepsy may result in significant and considerable harm by inducing stigma, exposing the child to potentially dangerous medications, restricting the child's activities and adversely affecting both the child's psyche and that of their family.

The role and the importance of the EEG are not in making the diagnosis of epilepsy but in:

- helping to identify and define the specific epilepsy syndrome
- identifying areas of focal brain dysfunction that will assist the interpretation of brain imaging studies (magnetic resonance imaging [MRI])
- the confirmation (or exclusion) of non-convulsive status epilepticus.

For example, a 'normal' early school-aged child who presents with characteristic focal seizures at night may show the characteristic broad, central EEG spikes or sharp waves that, together with the clinical history, will establish the diagnosis of benign partial epilepsy with centro-temporal spikes (BECTS). However, another 'normal' child of the same age but with a different semiology to their nocturnal seizures and with an EEG that demonstrates discrete frontal spikes and a slow-wave abnormality might have a frontal brain tumor.

An epilepsy syndrome is currently defined on the basis of largely subjective criteria, including:

- the age at onset of the seizures
- the seizure type or types
- the child's neuro-developmental profile
- the EEG (and ideally, both an inter-ictal and ictal recording).

In the future, it is possible, if not likely, that with the identification of specific genetic or biochemical markers, or both, the term 'epilepsy syndrome' may be more appropriately replaced by the term 'epilepsy disease.'

Neuro-imaging, even with MRI, also does not contribute to the diagnosis of epilepsy. An abnormal computed tomography (CT) or MRI scan in a child with

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4 Chapter 1: The only place to start: making the diagnosis of epilepsy

uncertain paroxysmal episodes does not necessarily mean that the episodes are epileptic in origin. The role of CT in the investigation of epilepsy is now largely redundant and, in addition, involves unnecessary irradiation that is equivalent to over 100 chest x-rays. Magnetic resonance imaging is far more effective than CT in detecting significant cortical abnormalities that may cause epilepsy and MRI is generally recommended once a child has been diagnosed with a non-benign focal or non-idiopathic generalized epilepsy.

In summary, epilepsy has many manifestations and its correct diagnosis depends on a comprehensive and accurate history obtained from an eye-witness of the child's paroxysmal episodes. Information on the diagnosis, prognosis and management of specific epilepsy syndromes and other, non-syndromic epilepsies requires the additional and specialist knowledge that is illustrated in this book.

Epilepsy beginning in infancy

Stewart Macleod and Elaine Wyllie

Introduction

Epilepsy and epileptic seizures are common in infancy. A population-based study of Canadian children found an incidence of epilepsy of 118/100,000 infants aged less than one year (excluding neonates), falling to 42/100,000 in the second year of life (1). Seizures that are considered epileptic are of course even more common. Approximately 3% of all children will have at least one febrile seizure, the majority of which will occur in the first two years of life. Acute symptomatic seizures are also common in this age group with common etiologies including CNS infection, trauma and transient biochemical impairment (e.g., hyponatraemia, hypoglycemia and hypocalcemia). Clearly, evaluation of infants with seizures must always include a careful search for an underlying and potentially treatable cause.

As in any age group, the diagnosis of epilepsy in infants relies on an accurate history and second-by-second and minute-by-minute account of the event as it starts, progresses and ends. It may be easier to obtain good first-hand witness accounts of paroxysmal events in this age group as young infants spend the majority of time with their immediate care-givers. Seizure semiology in infants can be complex:

- Generalized tonic-clonic seizures, although rare in this age group (particularly before the age of one year), should be easy to diagnose.
- Myoclonic seizures may be more difficult to recognize and usually occur in a number of symptomatic and presumed symptomatic epilepsies, often with a metabolic etiology.
- Infantile spasms are usually easily recognized although the seizure semiology is not familiar to parents and primary care clinicians (general practitioners).
- Focal seizures may be particularly difficult to recognize, even by pediatricians with some experience in treating epilepsy.

6 Chapter 2: Epilepsy beginning in infancy

Home video recordings can be very useful to fully appreciate subtle motor phenomena including head and/or eye deviation (2). It is always valuable to obtain as detailed a history as possible, including the ante- and peri-natal history, developmental history and specifically whether there is a family history of early infantile seizures. The oldest surviving female family member usually provides the most information when obtaining an accurate family history. The benign idiopathic epilepsies of early infancy are inherited in a dominant fashion (with variable penetrance), making an extended family history invaluable.

The investigative process should not stop with the diagnosis of 'epilepsy.' Whenever possible any underlying epilepsy syndrome should be diagnosed but it is probably more important to try to identify an underlying etiology. An etiology will be found in approximately 70–80% of infants (< 12 months) with symptomatic seizures. These will include structural brain lesions and biochemical abnormalities. Current brain imaging techniques, particularly magnetic resonance imaging (MRI) has increased the number of identified cerebral lesions in this age group. A wide spectrum of abnormalities may be seen, but most are acquired (destructive) or developmental (malformations). Genetic abnormalities are increasingly recognized, ranging from small chromosomal microdeletions to single gene mutation syndromes such as those found in severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome) with mutations in sodium ion channels or GABA-receptor genes. Finally, there are a number of potentially treatable neurological disorders which present at this age with epileptic seizures. There should be a high index of suspicion when considering these conditions; it is important that they be diagnosed as early as possible because early treatment may improve the long-term developmental and cognitive potential.

It is important to emphasize that many epilepsy syndromes which occur in infancy are rare and clinicians may only see one or two cases during their careers.

An important concept that is particularly poignant in epilepsy in infants is the 'epileptic encephalopathy,' or 'catastrophic epilepsy' as termed by other epilepsy specialists. An encephalopathy is any process which disturbs cerebral function. The list of conditions in pediatrics that can cause an encephalopathy is long but by definition an 'epileptic encephalopathy' is a disorder in which the cerebral dysfunction is considered to be primarily caused by the patient's epileptic seizures or frequent paroxysmal EEG abnormalities, rather than the underlying etiology of the epilepsy. The effects of an epileptic encephalopathy may sometimes be permanent with neurological and cognitive deficits persisting even if the seizures are fully controlled. A number of these disorders occur throughout all age ranges. Although each one is rare, collectively they constitute a significant proportion of epilepsy practice. Finally, most of the epileptic encephalopathies present in infancy, including pyridoxine-dependency and Ohtahara, West and Dravet syndromes.

Symptomatic epilepsies in early infancy

Symptomatic epilepsies constitute the majority of cases in this age group, which reflects the large number of symptomatic etiologies which can potentially present

with epileptic seizures. Obviously, some of the etiologies can present with epilepsy at any age (e.g., epilepsy associated with congenital hemiplegia or epilepsy as a manifestation of a malformation of cortical development). In contrast, there are many etiologies that invariably present with epileptic seizures in infancy (e.g., the seizures in pyridoxine-dependency, migrating partial seizures [epilepsy] in infancy, and Rett syndrome caused by mutations in the CDKL5 gene).

A comprehensive protocol or guideline-driven approach to the investigation of infantile seizures will help the clinician to undertake the relevant investigations. However, such an approach means that the infant will be subjected to a number of potentially invasive and unpleasant, costly and unnecessary investigations with little chance of identifying the etiology. Consequently, it may be very useful to consider a rational framework or algorithm for the investigation of these infants using the following approach:

- a structural abnormality
- a genetic disorder
- a metabolic disorder.

Obviously, there may be some disorders that overlap with this rather arbitrary classification; this is well illustrated by the tuberous sclerosis complex which has well-defined imaging features on MRI, as well as an identifiable genetic mutation in approximately 80% of children. This overlap is also seen in a large number of metabolic disorders.

Disorders of brain structure

Structural brain lesions are the most common cause of epilepsy in infants. The lesions can be pre-natal (e.g., congenital malformations including cortical dysplasias, neuronal migration abnormalities, or destructive lesions caused by maternally acquired infection), peri-natal (e.g., caused by moderate or severe neonatal hypoxic-ischemic encephalopathy), or post-natally acquired (e.g., caused by meningitis/encephalitis or trauma, or a brain tumor). Brain tumors in infants and young children typically occur in the posterior fossa (cerebellum and brain stem) and present with symptoms and signs of raised intracranial pressure. However, they may also present with behavioral problems and focal seizures, particularly if arising within a temporal lobe. Magnetic resonance imaging is the imaging modality of choice and in many cases will be diagnostic or at least give valuable clues as to which other investigation should be undertaken. Cerebral computed tomography (CT) should be avoided wherever possible because it does not reveal the same range of abnormalities as MRI and subjects the infant to considerable radiation (3). There are certain circumstances in which imaging may not be mandatory (e.g., a patient with neonatal hypoxic-ischemic encephalopathy and previous [diagnostic] imaging, who subsequently develops epilepsy will probably not require repeat MRI unless epilepsy surgery is being considered as a treatment option). Where the initial imaging is reported to be normal in the early infantile period, repeat scanning may be indicated at a later date if seizures persist. Subtle developmental lesions may be difficult to visualize on MRI until myelination is more complete at the age of 18–24 months. It is

8 Chapter 2: Epilepsy beginning in infancy

important to understand that high-resolution (at least 3.0 Tesla) MRI may be the most relevant repeat scanning technique and this will necessitate referral to a tertiary epilepsy centre.

Chromosomal disorders

In the absence of a readily recognizable cause for the infant's epilepsy, chromosome analysis should be a mandatory investigation. Chromosomal anomalies are quite frequent when epilepsy is accompanied by other major congenital abnormalities such as congenital heart disease or cranio-facial abnormalities. However, even in the absence of other somatic abnormalities (including dysmorphic facial features), current high-resolution chromosome analysis may identify small deletions or duplications.

Some chromosome abnormalities have a very high rate of epilepsy as part of their phenotype:

- The majority of patients with Wolf–Hirschhorn syndrome caused by deletions in the short arm of chromosome 4 have early-onset epilepsy along with other congenital abnormalities and characteristic facial features (Greek helmet-shaped face).
- Approximately 8–10% of children with trisomy 21 will develop West syndrome (infantile spasms).
- Ring chromosome 20 is commonly associated with drug resistant seizures, although the onset is rarely in early infancy but usually in early childhood.

More detailed genetic investigations may be warranted for infants with unclassified epilepsy and a learning disability (mental retardation), with or without any soft dysmorphic features. Telomere studies and Multiple Ligation-dependent Probe Amplification (MLPA) are relatively new techniques which can detect microscopic deletions in specific regions. These investigations should always be taken in conjunction and following discussion with clinical geneticists.

Metabolic disorders with epilepsy in infancy

Although many children with inborn errors of metabolism may develop epilepsy, most do not present primarily with epileptic seizures, or manifest seizures in isolation. Inborn errors of metabolism are extremely important to consider and diagnose because many are potentially treatable. Potential clues to an underlying metabolic etiology include:

- a family history of neonatal or infantile death
- parental consanguinity
- micro- or macrocephaly
- developmental impairment
- failure to thrive or short stature
- hepatomegaly

- other organ dysfunction
 - uncommon seizure types, and specifically myoclonic or tonic seizures.
- Mitochondrial and peroxisomal disorders are becoming increasingly recognized as a cause of infantile epilepsy.

Potentially treatable causes of early infantile epilepsy which may significantly improve developmental and cognitive functioning include:

- **biotinidase deficiency** (4). This diagnosis is suggested by the combination of alopecia, eczema and neurological problems including seizures. However, many infants may show only some of these features. Urine organic acid analysis and measurement of the biotinidase level will establish the diagnosis and prompt but lifelong treatment with biotin supplementation may allow a relatively good outcome
- **disorders of glucose transportation** (5) into the central nervous system. This is diagnosed by finding inappropriately low levels of glucose in the cerebrospinal fluid (CSF) (neuro-glycopenia) or a low fasting CSF: blood glucose ratio (< 0.35). The phenotype of this relatively recently described disorder is expanding rapidly (including patients with what appears to be drug resistant absence epilepsy or patients without epilepsy) and is potentially treatable by the ketogenic diet
- **pyridoxine-dependency** (6). This rare disorder **must** always be considered in any infant with drug resistant epilepsy and usually without an identified etiology. Approximately two-thirds of patients present with neonatal seizures but pyridoxine-dependency can also present at any time in the first 18–24 months of life with developmental impairments and epilepsy. The usual presentation after the neonatal period is with very frequent myoclonic seizures or infantile spasms; the EEG may show a burst-suppression or atypical hypsarrhythmic pattern.

Most common specific epilepsy syndromes in early infancy

The most common – and also potentially the most difficult to treat – include the following:

- West syndrome
- severe myoclonic epilepsy of infancy (Dravet syndrome)
- migrating partial seizures in infancy
- benign infantile convulsions.

West syndrome

This is probably the most common recognizable epilepsy syndrome which occurs in early infancy with an incidence of approximately 0.31/1,000 live births. The earliest description in modern medical literature was provided by Dr William West. Dr West wrote a heartbreaking letter to the editor of the *Lancet* asking for advice about his own son. In this letter he exquisitely describes the seizure semiology, the

10 Chapter 2: Epilepsy beginning in infancy

clustering pattern of the seizures and the associated developmental stagnation/regression. In the 1950s, various authors, notably Gibbs and Gibbs, described the associated EEG abnormality, hypsarrhythmia.

West syndrome (WS) is commonly defined on the basis of infantile spasms and a hypsarrhythmic EEG; developmental impairment or regression, if not already present at the time of the diagnosis of WS, nearly always evolves and will be obvious before the end of the first year of life. The onset is usually within the first year of life with a peak around six to eight months of age. Rarely, WS can present after the first year of life with infantile spasms in isolation and without a hypsarrhythmic EEG or developmental regression or, even less commonly, with a hypsarrhythmic EEG but no spasms. These situations usually occur in the context of a child with severe preceding neurological disability and the symptoms or signs may be overlooked by parents, care-givers or health professionals.

Presenting symptoms: The most common presenting symptom is with the pathognomic seizure type – the infantile spasm. Infantile spasms have been called various names including jack-knife seizures, and salaam attacks. The seizures have an insidious onset, gradually increasing in frequency before presentation. They may initially be mistaken for infantile colic or an exaggerated startle response even by healthcare professionals. Spasms have various appearances. In a time-synchronized video/polygraphic monitoring study, Kellaway *et al.* described different types of spasms including flexor, extensor, asymmetrical and spasms associated with motor arrest (7). The majority exhibited a mixture of different types of spasms. In practice, differentiating between different types of spasms does not usually provide clues to the underlying etiology with the exception that persistently asymmetrical spasms may be associated with a unilateral hemispheric abnormality. The ‘classical’ description of a spasm that accounts for 50–70% of cases is with sudden flexion of the head, neck and trunk with abduction of the arms followed by a few seconds of sustained tonic contraction. The infant recovers but may be upset for 10–30 seconds and then another spasm occurs. This may be repeated with three to four to over a hundred spasms occurring in a cluster. Spasms can be much more subtle, sometimes involving isolated muscle groups such as the abdominals or ocular muscles or the neck. These spasms are obviously much harder to recognize and may require simultaneous video–EEG monitoring to be well defined. There are often other clinical manifestations associated with the spasms. The child is upset and cries after a spasm or may be relatively unresponsive. The clustering of infantile spasms is typically within a few minutes after waking or, slightly less frequently, as the infant is falling asleep. Spasms rarely occur during sleep.

Some degree of developmental regression usually accompanies the onset of the spasms, although more commonly it develops after the onset of the spasms. The developmental regression can manifest itself in a number of ways. In cryptogenic infantile spasms the infant may have been developing normally before the onset of spasms and then becomes progressively lethargic, disinterested in their surroundings and eventually appears to be blind. This may occasionally result in the infant being referred to ophthalmology services with visual loss, particularly if the spasms