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Journal of Pediatrics & Neonatal Care

Editorial

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Seizure type in the newborn period and approaches to therapy

Volume 4 Issue 3 - 2016

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Received: March 20, 2016 | **Published:** March 21, 2016

Abbreviations: EEG, electroencephalogram; CFM, cerebral function monitor; HIE, hypoxic ischaemic encephalopathy; EIEE, early infantile epileptic encephalopathy; EMEE, early myoclonic epileptic encephalopathy

Epileptic seizures are relatively common in neonates. Estimated incidences are 1.5-3.5 per 100 live births and 10-130 per 100 preterm births.[1–3] They are usually a sign of neuronal compromise and prognosis will depend on the underlying cause. They can be difficult to diagnose as they can be associated with few or no clinical features.[4] The incidence of seizures in the neonatal period is higher than at any other time in life. Neonates also frequently exhibit non-epileptic movements that can be mistaken for epileptic seizures. Most neonatal epileptic seizures are provoked by an underlying condition, such as hypoxic brain injury (50%), haemorrhage (15%), stroke (5%), cerebral infections, cerebral malformations, metabolic, benign causes, drug withdrawal and family history.[5] These are acute seizures often with an underlying cause as opposed to true epilepsy which ordinarily is unprovoked.

Definitions and descriptions

An epileptic seizure is the transient appearance of signs or symptoms that arise from the brain because of excessive and abnormal activity of many neurons firing simultaneously.

Epilepsy is defined as a group of conditions involving recurrent, unprovoked seizures. Each epilepsy has its own variety of causes, treatments and prognoses.

Acute symptomatic seizures are epileptic seizures that are provoked by an insult or systemic illness. Examples of neonatal causes include intracranial haemorrhage, hypoglycaemia, hypocalcaemia or perinatal stroke.

Myoclonus is non-rhythmical, brief shock-like jerks caused by sudden, involuntary contraction or relaxation of one or more muscles.

Clonic seizures are repetitive, rhythmical, jerks of the limbs, face or axial muscles. These can be focal or multifocal in nature.

Clonus is an upper motor neuron lesion characterised by involuntary muscle contractions and relaxations in the muscles around a joint. It can be stopped by moving the position.

Tremor is an involuntary generalised movement that is rhythmical and oscillates around a fixed axis.

Jitteriness is recurrent tremors, reduced by holding or flexing the affected body part. It does not affect the face and is not associated with eye deviation or autonomic changes.

Unfortunately it does not end here. There are other descriptors often used: Dystonia is a movement disorder in which sustained or intermittent, involuntary contraction of muscles leads to abnormal postures, twisting or repetitive movements. Rigidity is stiffness and resistance in a joint during fast and slow passive movement that is not related to the angle of the joint. Unlike dystonia, the limbs do not return to odd postures when passive movement has stopped. Epileptic spasms involve contraction of the axial and proximal muscles leading to flexion of the neck, trunk, shoulders, elbows, hips and knees. Each spasm lasts around a second. They are shorter than tonic seizures but longer than individual clonic or myoclonic jerks. Tonic episodes are stiffening of the muscles for more than a few seconds. They can be focal or generalised.

Neonates will also startle, swim, pedal, lipsmack or tongue thrust. These may be brought on by external stimuli and need to be distinguished from true epileptiform movements.

Without an EEG many of these distinctions are difficult in the clinical setting. Myoclonus can be epileptogenic or non-epileptogenic. Generalised myoclonus is more likely to be epileptic than focal. Clonic jerking of hips, shoulders or elbows is likely to be epileptogenic. Focal tonic seizures or stiffening of one or more limbs is often epileptic in neonates, particularly when associated with eye deviation and autonomic features. Epileptic spasms can be seen in neonates with epilepsy, in some syndromes and early myoclonic epileptic encephalopathy.[6]

Many Neonatologists with the increased use of amplitude EEG (aEEG) or Cerebral Function Monitor (CFM) will have witnessed non-clinical seizure activity. This is characterised by electrical seizure activity without observable clinical signs. Less than 50% of seizures seen on aEEG have clinical manifestations.

There is no consensus about whether they cause harm or if treatment is required.[7] These decisions are often based on clinical condition and physician practice.

Tremor and Jitteryness occurs in many healthy term neonates who become jittery within a few days of birth. Jitteriness can occur in any infant at any time of the day. Typically in a very jittery infant a blood glucose and calcium are measured to try to explain the symptoms. If normal, then observation is commonly undertaken and reassurance given that this will resolve in time. Coarse tremor is more likely to be associated with an underlying cause and potential aetiologies should be considered, including hypoxic ischaemic encephalopathy, intracranial haemorrhage, sepsis, meningitis, hypocalcaemia, hypoglycaemia, hyperthyroidism and drug withdrawal.[8,9]

Benign conditions

Benign neonatal sleep myoclonus is a common non-epileptic condition where myoclonic jerks are seen during sleep, often just after falling asleep or on waking up. Onset is within 14days of birth in 89% of infants, and most obvious between day 15 and day 35 of life. Myoclonus resolves by 3months in 64% of infants, in 95% by 6months and in 97% by 1year of age.[10]

Benign myoclonus of infancy is a rare condition in which myoclonic jerks start from a few weeks to 15months of age in otherwise normal children. The prognosis is good, with episodes resolving within a few months and no increased risk of epileptic seizures or neurodevelopmental difficulties.

Symptomatic causes of myoclonus in the awake and sleep states include intraventricular haemorrhage, encephalomalacia, hypoxic and metabolic encephalopathies, encephalitis, hydrocephalus, hypertension, spinal pathologies, hyperekplexia and drug withdrawal.

When to treat?

Treatment needs consideration due to the nature of the medications in use. A pragmatic approach remains the most reasonable option.[11] There are side effects to consider and long-term cognition concerns with chronic use. If there is EEG confirmation this is ideal or if aEEG is available the trace prior to treatment can aid subsequent dosing.

Acute symptomatic or epileptiform

The timing of a seizure can help diagnostically. Family, antenatal, birth and postnatal histories can also help determine aetiology. Hypoxic ischaemic encephalopathy (HIE) is the commonest cause of neonatal acute symptomatic seizures but the fetus with metabolic or a neurological disorder may decompensate during labour and delivery and blur the picture. A number of investigations need to undertaken including metabolic, infective and structural screening.

The neonatal epileptic syndromes include, benign neonatal seizures (fifth day fits), benign neonatal familial seizures, early infantile epileptic encephalopathy (EIEE) (Ohtahara syndrome), early myoclonic epileptic encephalopathy (EMEE) and migrating partial seizures of infancy. The former is a diagnosis of exclusion with familial seizures related to timing, onset and family history. Early infantile seizures are rare and often associated with burst suppression on the EEG. Early myoclonic epilepsy has many causes.

It can be seen that neonates exhibit a wide range of paroxysmal movements. Some movements are epileptic seizures, some are not. As a result overdiagnosis and underdiagnosis of neonatal seizures occurs on every neonatal unit.

Treatment is often commenced with Phenobarbital even though in animal models this drug and others are associated with neuronal apoptosis.[11] Phenytoin is often used as a second line therapy but there are concerns about cardiac arrhythmias. Lidocaine appears to be a common second choice but concerns about its cardiac effect, especially if Phenytoin has already been administered, often leads to the addition of a benzodiazepine such as an infusion of midazolam. Benzodiazepines too lend concerns about their use with side effects including respiratory depression and hypotension. Other newer drugs favoured are Topiramate and Lamotragine but more recently Levetiracetam has been gaining favour although dosing regimens vary. Long-term anticonvulsant treatment continues to cause concern as to their effect on future neurodevelopment, so in benign syndromes and those coming quickly under control, medication should be rapidly withdrawn.

Conclusion

Most neonatal epileptic seizures are acute symptomatic, resulting from conditions like HIE. Investigations should be targeted, depending on what the differential diagnoses are following a full history and examination. Little evidence exists as to which antiepileptic drugs are most effective for acute symptomatic seizures or have the least short-term and long-term side effects. No international consensus exists on the correct pathway to treat neonatal seizures.

A limited number of neonatal epileptic syndromes exist, some with good and some with a poor prognosis. A careful history, noting the seizure type and EEG pattern, help to identify these syndromes. Where a benign syndrome is found, treatment for status epilepticus or frequent seizure clusters can be instituted, followed by a rapid withdrawal of medication. For the more severe syndromes, few treatment options are likely to be effective and prognosis is poor if no surgically resectable lesion is found. Vitamin-responsive seizures should always be considered early in refractory neonatal seizures and specialist advice sought.

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

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