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Differential diagnosis of epileptic seizures in infancy including the neonatal period

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SUMMARY

It is important to accurately diagnose epileptic seizures in early life to optimise management and prognosis. Conversely, however, many different movements and behaviours may manifest in the neonatal period and infancy that may not have at their root cause a change in electrical activity of the brain. It is important to distinguish them from epileptic seizures to avoid over- and inappropriate treatment. Some are physiological in the normal infant, such as neonatal tremor, benign neonatal sleep myoclonus, and shuddering attacks, whereas others may herald alternative rare neurological diagnoses with differing prognoses such as hyperekplexia, paroxysmal extreme pain disorder and alternating hemiplegia of childhood. Here are highlighted the key clinical features that distinguish some of these disorders, their management and prognosis.

1. Introduction

An epileptic seizure is defined as a clinical event, either a change in movement, or behaviour, the direct result of a primary change to the electrical activity in the brain. There are many events that can mimic seizures, either as events where electrical activity changes but where this is not the primary event, or where physiological movements are misinterpreted as the result of such. Seizures in the neonatal period are particularly important to recognise, their occurrence related to poor outcome when associated with many differing aetiologies. Although treatment can prove problematic, it is important to distinguish true seizures (movements that are the result of a change in the electrical activity in the brain) from movements of differing aetiology, often physiological in many cases. Term and preterm infants present with various abnormal movements that may be misinterpreted as seizures, for which prognosis may be very different and for many of which treatment is not required. It is therefore imperative to differentiate such movements to ensure appropriate clinical management, to avoid overtreatment and to provide optimal information for parents. By contrast with older children, a clinical diagnosis of seizures is unreliable in the neonatal period, particularly in the critically ill or sedated baby, and in such circumstances video electroencephalographic monitoring may be required. This article outlines the frequently and not-so-frequently occurring movement disorders in neonates that may be misdiagnosed as epileptic seizures (see Table 1).

2. Jitteriness

Jitters (or recurrent tremors) are the most frequently occurring movement encountered in the neonatal period, occurring in up to two-thirds of newborn babies in the first three days of life.[1] It is seen most frequently in sleepy or active infants, and least frequently in quietly wakeful infants. They are most pronounced during vigorous crying, and diminish during the course of the first weeks. Tremors are stimulus sensitive, diminish with passive flexion of the extremity, and are not associated with abnormality of gaze or eye movements. The exact cause of jitteriness is not established; one theory is that neonatal tremor is due to immaturity of spinal inhibitory interneurons causing an excessive muscle stretch reflex.[2] As time progresses, the interneurons mature and the tremors resolve. Another theory is that elevated levels of circulating catecholamines account for the tremor.[3]

Jitteriness in its pronounced form may be symptomatic of various conditions requiring specific attention. Underlying conditions that may give rise to excessive jitteriness include hypoglycaemia, hypocalcaemia, sepsis, hypoxic–ischaemic encephalopathy, intracranial haemorrhage and drug withdrawal. The quality and persistence of the tremor may give clues with regard to the underlying cause. Tremors associated with metabolic conditions are usually of high frequency and low amplitude, whereas the tremors associated with

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Table 1
Differential diagnosis of movement disorder in the infant.

Diagnosis	Age	Aetiology	Attack	EEG	Prognosis
Jitteriness/tremor	0–7 days	Physiological	Tremors, stimulus sensitive	Normal	Dependent on cause: excellent if no underlying condition with spontaneous resolution
Benign neonatal sleep myoclonus	0–3 months		Myoclonias confined to sleep in healthy infant	Normal	Excellent
Near-miss sudden infant death syndrome	Peak 1–6 months		Apnoea, hypo- or hypertonia, cyanosis etc.	Permanent EEG abnormalities may occur	
Startle disease (hyperekplexia)	Neonate–puberty	Genetic	Excessive startle, tonic spasms	Normal	Stiffness resolves by 3 years, exaggerated startle remains, developmentally normal
Paroxysmal extreme pain disorder	Neonate	Genetic	Autonomic phenomena, stiffening, bradycardia	Normal	Paroxysmal episodes of deep burning pain
Alternating hemiplegia of childhood	3 months– adult	Genetic	Initial eye movement abnormality, hemiplegic attacks from 12 months	No epileptiform features during attacks	Later epilepsy, cognitive impairment, ataxia
Breath-holding attacks (cyanotic spells)	6 months–5 years		Triggered by frustration, cries, holds breath in expiration: blue ± unconscious ± stiff	Normal except when slowed due to hypoxia during attack	Harmless
Reflex anoxic seizures (pallid spells)	Infants and toddlers	Due to cardiac asystole from vagal inhibition	Triggered by pain, fever, minor trauma etc., falls, pale, apnoeic. Hypoxia may induce a seizure	Normal except when slowed due to hypoxia during attack	Harmless
Masturbation/gratification phenomena	Infants and toddlers		Movements of masturbation, stereotypic movements while appearing withdrawn	Normal	
Cardiac arrhythmias		Long QT syndromes, Wolff–Parkinson–White, etc.		Hypoxic slowing during prolonged attack	
Other syncopes of cardiac origin		Cyanotic cardiopathies, valvular disorders, cardiomyopathy etc.		Hypoxic slowing during prolonged attack	

EEG, electroencephalography.

central nervous system disorders are low frequency, high amplitude movements.[4]

The neurological outcome of neonates is good as long as no perinatal complications, such as asphyxia, are identified. Two follow-up studies[5,6] have shown that jittery infants without a history of perinatal complications are likely to have normal neurodevelopmental outcome, regardless of whether the tremor was fine or coarse. Jittery neonates with a history of perinatal complications are at 30% risk of adverse neurodevelopmental outcome – in particular, those with coarse tremor as part of the 'neonatal hyperexcitability syndrome'.[5] Tremor can be differentiated from seizures if it can be induced with stimuli and can be ceased with gentle passive flexion and restraint of the affected limb; it is not associated with ocular phenomena, such as forced eye deviation; and is not associated with significant autonomic changes such as hypertension or apnoea.

Investigation will depend on the clinical history, examination and index of suspicion with regard to the wellbeing of the child. Should a neonate be a little jittery with no notable perinatal history, then a blood sugar and calcium should be all that is required. In one test that has been suggested to determine whether jitteriness is benign, the child is held supine and allowed to suck – the jitteriness should resolve.[7] Should there be a significant perinatal history, the tremor be coarse and not resolve with soothing, then consideration should be given to septic screen, imaging, thyroid function and a metabolic screen. Excessive tremor may also be the result of maternal drug withdrawal and therefore full consideration should be given to the possibility of this in the maternal history.[8]

3. Benign neonatal sleep myoclonus

Myoclonus is a brief limb movement, a jerk, caused by a muscle contraction. Benign neonatal sleep myoclonus (BNSM) is a condition where such jerks occur only in sleep. It is the most common condition misdiagnosed for epilepsy in the term neonate, and consequently overtreated. BNSM can be distinguished from epileptic myoclonus by the fact the jerks occur only during sleep, and settle on arousal.[9] It tends to occur in term healthy neonates, is bilateral and repetitive, and may involve all limbs but not the face. Onset is usually in the first few days of life, but it resolves by four months of age. As neonates may sleep for substantial periods of the day, florid jerks may cause alarm. Further, episodes may continue for up to an hour, and may be diagnosed mistakenly as status epilepticus.[10] However, the jerks resolve on arousal and are not associated with EEG change should this be performed during episodes. The key to diagnosis is their occurrence only in sleep, and the relatively normal behaviour of the neonate when awake. There are no sequelae; they resolve and long-term neurodevelopment is normal.

Benign myoclonus of early infancy comes on a little later, between three and nine months of age. However, it has been reported in the neonatal period. In this condition, the infant will have recurrent clusters of myoclonic jerks when awake but these are not provoked by stimuli. Again they are associated with a normal EEG, and relatively normal behaviour and neurodevelopment of the child. There is spontaneous resolution by 12 months of age.