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REVIEW

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Neonatal seizures

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Abstract The newborn brain is particularly vulnerable to seizures which are associated with poor neurodevelopmental outcome. The clinical manifestations of seizures in infants differ from those seen in older children and adults. The problem of electro-clinical dissociation, where there is no temporal correspondence between electrical paroxysms and repetitive stereotyped motor phenomena, is common in the newborn. There is at present very little information on which clinicians can base a rational decision about treatment which is often ineffective and does not alter neurodevelopmental outcome. This review summarizes current knowledge regarding investigation, treatment and prognosis of neonatal seizures.

Key words Seizures · Newborn infant · Review Therapy · Electroencephalography

Abbreviations GABA gamma aminobutyric acid · GAD glutamic acid decarboxylase · GMH-IVH germinal matrix haemorrhage-intraventricular haemorrhage

Introduction

The neonatal CNS is particularly susceptible to seizures. This vulnerability is thought to be due to a combination of enhanced excitability, and low levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [36]. Prompt diagnosis, investigation and treatment are vital as delayed recognition of a treatable cause can have a significant impact on the child's subsequent neurological outcome. Magnetic resonance imaging of the brain has shown markedly reduced myelination in children who had suffered from neonatal convulsions [32]. In infants seizures are associated with conditions such as periventricular haemorrhage, cerebral infarction (stroke), hypoglycaemia, infection, cerebral malformations and hypoxic ischaemic encephalopathy. Seizures represent the brain's final common response to insult. The initial injury may be brief, but membrane damage releases excitotoxic substances such as glutamate which trigger further epileptic activity.

Incidence

Seizures occur in 6%–13% of very low birth weight infants, and in 1–2 per 1,000 of infants born at term [10, 27, 28, 31, 44]. Older series did not usually discriminate between term and preterm infants and reported higher incidence figures because many of the cases were due to late-onset hypocalcaemia [5]. The incidence of early (< 48h) seizures in term infants also varies, being 0.87 per 1,000 in Dublin between 1980–1984 [10], 1.3 per 1,000 in Cardiff during 1970–1979 [34] and 2.8 per 1,000 in Fayette County, Kentucky in 1985–1989 [27]. Subtle seizures are the most common type, particularly in premature infants, being present in 75% of the cases described by Sher et al. [37].

Time of onset

Seizures apparent in the delivery room are rare being usually due to severe acute hypoxic ischaemic encephalopathy. Pyridoxine-dependent seizures can begin very early and mothers occasionally describe abnormal movements in-utero. Most neonatal seizures occur between 12 and 48 h after birth. Late onset seizures suggest meningitis, benign familial seizures or hypocalcaemia.

Diagnosis and classification

A seizure is a paroxysmal alteration in neurological function [42]. This can be behavioural, motor or auto-

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Table 1 Types of seizure in the newborn. Adapted from Volpe, 1989 [42]

Type	Clinical manifestation
Subtle	Eye signs – eyelid fluttering, eye deviation, fixed open stare, blinking. Apnoea. Cycling, boxing, stepping, swimming movements of limbs. Mouthing, chewing, lip smacking, smiling. Often no EEG changes – most likely with ocular manifestations
Tonic	Stiffening. decerebrate posturing. EEG variable
Clonic	repetitive jerking, distinct from jittering. Can be unifocal or multifocal. Usually EEG change
Myoclonic	Rare, sleep myoclonus is benign. EEG often normal, although background EEG can be abnormal

nomic. Four main types are recognised (Table 1) and within each type the seizures can be unifocal, multifocal or generalized. In the newborn there is the unusual problem of electro-clinical dissociation.

Subtle

Manifestations of subtle seizures include oro-facial manifestations such as eye deviation, eyelid blinking, sucking, chewing and lip smacking. Limb movements described as swimming, boxing or cycling can also indicate subtle seizure activity. Apnoeic episodes can be due to seizures. There can be difficulty distinguishing subtle seizures from jittering, an extremely common normal phenomenon in newborns. Jittering does not involve the face, is markedly stimulus sensitive, and ceases when the limb is held. The autonomic nervous system changes of a seizure, such as tachycardia or hypertension, are never seen in jittering.

Clonic

Clonic seizures involve one limb or one side of the face or body jerking rhythmically at a frequency of 1–4 times/s. Clonic seizures in the neonate can have more than one focus or migrate in a non-Jacksonian fashion; jerking of one leg can be followed by similar movements in the opposite hand. Clonic seizures are often a clue to an underlying focal lesion such as a cortical infarction, but they can be due to a metabolic cause. Infants are not usually unconscious during clonic seizures.

Tonic

Sustained posturing of the limbs or trunk, or deviation of the head or eyes are the usual manifestations of tonic seizures in the newborn. This type of seizure is usually associated with a characteristic EEG signature of high frequency sharp waves and spikes.

Myoclonic

Myoclonic jerks tend to occur in the flexor muscle groups. Generalised myoclonic seizures resemble salaam spasms and are the type most likely to be associated with EEG change. Any type of myoclonic seizure (focal, multifocal or generalised) can occur in benign neonatal sleep myoclonus [9]. Hyperekplexia is a rare disorder characterised by hypertonia and an exaggerated startle response [40]. The startles can look like myoclonic jerks and the high tone hyperreflexia and jitteriness can lead to an erroneous diagnosis of seizure [17]. Treatment with clonazepam or diazepam results in marked improvement.

Physiological changes during seizures

Blood glucose remains normal or rises during seizure but brain glucose falls markedly because brain transport mechanisms are unable to keep up with the increased demand. The cerebral blood flow rises to try to meet the need for oxygen and glucose. Magnetic resonance spectroscopic data show a shift in spectra from the high energy phosphate compounds towards inorganic phosphate suggesting that metabolic demand outstrips supply [46]. Glucose pre-treatment is effective in reducing the high mortality of status epilepticus in rats. Lactate accumulates during seizures and the arterial pH falls. Systemic blood pressure increases.

EEG Diagnosis of seizures

Electrographic seizures

Electrical seizures are usually brief in the newborn, lasting about 2 min in term infants, with about 8 min between seizures in most cases. Clancy and Ledigo [6] used an arbitrary cut-off of 10 s as a minimum duration and this definition was also adopted by Scher et al. [38]. Ideally an electrical seizure should have a clear onset and conclusion but these can be difficult to identify. Very short bursts of abnormal electrical activity have been termed BIRDS – brief intermittent rhythmic discharges. These are of uncertain significance.

Electroclinical dissociation

There is asynchrony between the clinical and electrical diagnosis of neonatal seizures: in only one third of cases studied with video surveillance were the clinical and electrical manifestations simultaneous [25, 45]. Subtle stereotyped behaviour may or may not be associated with characteristic EEG changes, and continuous electrical monitoring detects clinically silent seizures [7, 13, 21]. One explanation is that the motor manifestations arise because of discharges from the brain stem and

spinal cord which are ''released'' because of lack of inhibition from higher centres. An alternative explanation is that scalp electrodes are incapable of recording from every part of the brain; depth electrodes reveal an otherwise unsuspected electrical focus in 10% of adult patients. Of the oro-facial manifestations, only tonic horizontal deviation of the eyes is consistently associated with EEG paroxysms [35]. The neurological effects of clinically silent seizures are not known nor is it certain that treatment of clinically manifest seizures to electrical silence is required. This is an important question because phenobarbitone treatment frequently abolishes the clinical manifestations whilst the electrical paroxysms continue.

Aetiology

Hypoxic ischaemic encephalopathy is the most common cause of neonatal seizures at term, contributing over half the cases to most series (Table 2). The characteristic time of onset is within 24 h of birth, and seizures often begin in the first 12 h. Germinal matrix or intraventricular haemorrhage (GMH-IVH) is the most frequent cause of seizures in preterm infants: 45% of seizing preterm infants had GMH-IVH in one recent series [37], Seizures in term infants with normal Apgar scores are often due to focal lesions which may be missed on ultrasound, and require MRI for identification [33].

Maternal methadone addiction is more likely to be associated with neonatal withdrawal seizures than heroin [24]. Withdrawal seizures can occur for the first time at any age up to 3 weeks with a median time of onset of 10 days. They can persist for several months.

Hypoglycaemia can be the sole cause of neonatal seizures and other neurological symptoms such as apnoea, lethargy and jitteriness. Often hypoglycaemia complicates hypoxic ischaemic encephalopathy or infection, and hypoglycaemia is also common in infants who are small for gestational age. Disorders of neuronal migration such as lissencephaly, pacygyria and polymicrogyria can present with neonatal seizures. Diagnosis has been facilitated with the advent of MRI but is also possible with ultrasound.

Pyridoxine dependent seizures

These seizures can begin during intra-uterine life and are very resistant to treatment, stopping usually within minutes of parenteral pyridoxine (50 mg) and returning within days of withdrawal. This therapeutic trial can cause hypotonia requiring ventilatory support and should be carried out in an intensive care unit [26]. Atypical cases who respond more slowly and who have late-onset seizures requiring unusually high doses of pyridoxine have been described [2, 20]. Very large amounts of pyridoxine may need to be given for 2 weeks before this rare disorder can be excluded beyond doubt. The underlying defect is thought to be defective binding of the pyridoxal phosphate co-enzyme with glutamic acid decarboxylase (GAD), the rate limiting enzyme in GABA synthesis [18]. The condition is autosomal recessive and the gene for GAD resides on chromosome 2, although so far no specific mutation has been found. Supplementation of the diet with pyridoxine (vitamin B6) 20–100 mg bd is required for life. Unfortunately many of these children are retarded despite early diagnosis and treatment.

Glycine encephalopathy

Nonketotic hyperglycinaemia is a rare inborn error of metabolism in which large amounts of glycine accumulate causing intractable seizures. Hiccups can be trou-

Table 2 Causes of neonatal seizure

	1	2	3	4
Number of cases			**71**	**131**
Hypoxic-ischaemic encephalopathy	53%	16%	49%	30%
Intracranial haemorrhage	17%		14%	
Cerebral infarction (stroke)				
Meningitis	8%	3%	2%	7%
Maternal drug withdrawal			4%	
Hypoglycaemia	3%	2%	0.1%	5%
Hypocalcaemia, hypomagnesaemia				22%
Rapidly changing serum sodium				
Congenitally abnormal brain		8%		4%
Fifth day fits		52%		
Benign familial neonatal seizures				
Pyridoxine dependent seizures				
Hypertension			1.4%	
Inborn errors of metabolism				

Data in column 1 is from Levene and Trounce [30], column 2 from Goldberg et al. [15], column 3 from Andre et al [1] and column 4 from Bergman et al. [3]

blesome. Levels of glycine in blood, urine and cerebrospinal fluid are very high. In one case dextromethorphan monotherapy (35 mg/kg/day) was associated with cessation of seizures and normalisation of the EEG [39], but this regimen was not successful in another infant [47].

Benign familial neonatal convulsions

This fascinating autosomal dominant condition was first recognised in 1964. The seizures are dramatic and clonic, 80% beginning on the 2nd or 3rd day of life and ceasing at the age of 6 months. Genetic markers suggest mutation on chromosome 20 [29]. In contrast to pyridoxine dependent seizures these fits can be controlled by conventional medication and the prognosis for development is excellent.

Investigation

Essential laboratory investigations include:

(1) electroencephalogram; (2) blood glucose; (3) serum calcium; (4) serum magnesium; (5) arterial pH ; (6) serum sodium; (7) serum urea and creatinine; (8) lumbar puncture; (9) blood culture; (10) cranial ultrasound scan.

If the cause is not revealed, second line investigations include specimens for virology and a congenital infection screen, CT or MRI, samples such as hair or urine to look for maternal ''street'' drugs, urinary and blood amino acid estimation, chromosomal analysis, blood ammonia and measurement of urinary organic acids.

Treatment

Indications for treament

The special problems of electroclinical dissociation and the short duration of neonatal seizures make it difficult to be sure when to start and stop anticonvulsant treatment. There are good theoretical reasons for suppressing seizure activity but no clinical evidence that the generally poor outcome can be improved with anticonvulsant treatment. In part this may be because the available treatments are ineffective in suppressing abnormal electrical activity [8, 19]. Alternatively it may be that the prognosis is so completely determined by the underlying condition that treatment cannot influence the outcome. However, most neonatologists would treat if there were more than three brief seizures in an hour or the baby had a single seizure lasting more than 3 min. Current clinical practice is to treat to clinical rather than electrical silence.

General guidelines

Treatment is best given enterally or intravenously as intramuscular absorption is erratic and the neonate has little muscle mass. Facilities to site and maintain intravenous lines and to institute artificial ventilation are necessary as many of the available drugs depress respiration and ventilation can become inadequate due to frequent convulsions. The high total body water of the neonate means there is a large volume of distribution hence the relatively large loading doses required. Probably the best advice is to use phenobarbitone aiming to rapidly achieve a therapeutic level, and to follow with intravenous phenytoin, or rectal paraldehyde. Most would start with 15–20 mg/kg of phenobarbitone initially, but Gilman et al. [14] achieved seizure control with phenobarbitone alone in 77% of cases using a rapid sequential method in which they gave 15–20 mg/kg followed by further doses of 5–10 mg/kg every 30 min up to a maximum of 40 mg/kg in order to achieve a serum level of over 40 mg/l. Very large doses of phenobarbitone are not recommended in hypoxic ischaemic encephalopathy. Thiopentone coma did not improve the outcome in a controlled clinical trial [16] and in resistant cases I would currently consider sodium valproate, dexamethasone [4] or lignocaine [22].

Duration of treatment

Concern about the effects of anticonvulsant treatment on the developing brain means that many neonatologists would only discharge a baby on maintenance phenobarbitone if the neurological examination was abnormal, discontinuing treatment before discharge in those who were neurologically normal. Only 2 of 55 Swedish infants discharged without medication relapsed [23]. For infants who are discharged on anticonvulsants consider discontinuation of treatment if the baby is seizure-free at 9 months.

Prognosis

This is mainly related to the cause of the seizures. Following hypoxic-ischaemic encephalopathy at term 25% of those who develop grade II encepalopathy will suffer sequelae. The combination of a 5-min Apgar score < 5, fits and signs of encephalopathy was a poor one with 33% dead and 55% with handicap [11]. Seizure in very low birth weight infants has a poor prognosis with more than 50% dead, about 22% with major handicap [37, 41, 44]. The prognosis after hypocalcaemic seizure and in familial neonatal seizure is excellent. A normal interictal EEG at term is a good prognostic factor, with fewer than 10% of such infants experiencing sequelae [43].

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