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Expert Lecture

Neonatal seizures: diagnosis and management

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Abstract: The recognition of epileptic seizures in newborns is challenging as neonates exhibit a variety of paroxysmal motor phenomena, some epileptic but others not. The distinction, frequently requiring video-EEG monitoring, is crucial for management. Causes are often multi-factorial, specific to country/region, and change over time. Hypoxia-ischemia and infection are still common in both developed and developing countries. Venous and arterial strokes are being increasingly recognized. Treatable conditions, including inborn errors of metabolism, must be anticipated and considered early in the course. Etiology is the principal determinant of outcome. Management is based on uncontrolled studies and expert opinions. Information on neonatal seizures is reviewed, and suggestions for management provided. Phenobarbital remains the first anti-epileptic drug of choice, worldwide. Pharmacogenetic information and hepatic or renal dysfunction will influence doses of all drugs. The toxicity of excipients present in intravenous medicines should be kept in mind, especially when infusions are given to critically ill neonates. Therapeutic trials with pyridoxine or ideally pyridoxal phosphate, folinic acid and biotin should be considered early, if seizures are intractable. The management of electrographic seizures without clinical seizures needs critical study. When anti-epileptic drug treatment is required, maintenance should be for a short duration if seizures are of an acute symptomatic nature. [**Chin J Contemp Pediatr**, **2011**, **13** (**2**):**81 – 100**]

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Introduction

The risk of seizures is relatively high in the first month of life [1-2]. In 1987, Mizrahi & Kellaway[3] discussed the limitations of identifying and characterizing neonatal seizures without simultaneous polygraphic video-electroencephalographic (EEG) recordings. In 1990, Shewmon[4] pointed out that a standard operating definition for neonatal seizures was lacking, and that most studies to that time were "undermined by inadequate or inconsistent criteria". Despite the proliferation of literature on neonatal seizures, Shewmon's comments are still valid. Additionally, the challenges of differentiating epileptic from non-epileptic events, together with poor inter-observer agreement, even among experts[5], also confound published information.

To our knowledge, with one exception[6], nationally or universally accepted guidelines for the management of neonatal seizures, are not available. Our aim is to present an approach to management based on current information. To do so, a review of the relevant background is essential.

A neonatal epileptic seizure refers to an abnormal, stereotypical clinical event, that results from an abnormal 'hypersynchronous' discharge of neurones , located in the cerebral cortices or thalami. The event is most often relatively sudden in onset and self-limiting (paroxysmal). Abnormal paroxysmal clinical events

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arising from basal ganglia, brainstem, and cerebellum, are generally not considered epileptic. Certain clinical characteristics strongly suggest an epileptic seizure. However, as in older children and adults, a definitive diagnosis of an epileptic seizure can often be made only when there is a time-locked, usually stereotypical, EEG correlate to the clinical event. Polygraphic video-EEGy is considered the gold standard test for differentiating between epileptic and non-epileptic events[7-9]. The absence of an EEG correlate to the clinical episode suggests that it may not be epileptic; but this is not absolute[3,4,7,10], adding to the challenge for clinicians.

In this review, neonatal seizure refers to an epileptic event. When the clinician is unable to determine if an event is epileptic or not, then it is best to label it as 'undetermined', until a more definitive diagnosis can be made.

Factors contributing to risk

Factors reported to contribute to the risk of neonatal seizures include: prematurity, birth weight <2500 g, delivery $\geqslant 42$ weeks, maternal age >40 years, nulliparity, maternal diabetes mellitus, intrapartum fever or infection, especially chorioamnionitis, and catastrophic delivery (placental abruption, uterine rupture and cord prolapse)[11-13].

Clinical differentiation of epileptic from non-epileptic events

Clinical judgment is essential in assessment[3]. Non-epileptic events that may be mistaken for epileptic seizures are listed in Table 1, and have been discussed by us[14-15]. Jitteriness and tremor can be stopped with light pressure[10,14-16]. Benign neonatal sleep myoclonus should be suspected when the event occurs only during drowsiness or sleep. It will stop promptly when the neonate is aroused with a sufficiently painful stimulus[17].

Apnea, especially related to prematurity, is unlikely to be epileptic. However, if the neonate is unresponsive to a painful stimulus during apnea, exhibits ocular jerks, ocular deviation, eyelid contractions or pupillary change, is full-term, and there is no alternative explanation, then the probability of epileptic apnea is enhanced[10,18].

Table 1 Non-epileptic motor events that may be mistaken for neonatal epileptic seizures

Events	Clinical details
Tremor	May be fine (high frequency > 6 Hz; low amplitude < 3 cm) or coarse (lower frequency and higher amplitude); jitteriness refers to recurrent tremor.
Benign sleep myoclonus	Myoclonus, often multi-focal, migrating, during drowsy and sleep states only. Stops on arousal with painful stimulus. May worsen with light touch, sound or anti-epileptic drugs.
Hyperekplexia	Exaggerated startle to stimuli; associated with generalized muscular rigidity; life threatening apnea may occur during spasms.
Benign myoclonus of infancy	Recurrent non-epileptic myoclonus while awake; neonate otherwise normal; not usually provoked by stimuli.

Note: EEG normal during events; see Huntsman et al[14-15] for details.

Classification

Mizrahi[3,7] and Lombroso[19] classified neonatal events, incorporating EEG information, building upon the earlier observations of Rose[20] and Volpe[10,16]. Episodes with and without EEG correlate can occur in the same neonate, and neonates may have more than one type of epileptic seizure[3,7,20]. Tonic posturing, especially when generalized, is rarely epileptic; the tonic seizures in Ohtahara's syndrome are an exception. Decerebrate (tonic) posturing is often intermittent, and therefore mistaken for epileptic seizures. It is often difficult to differentiate between clonic and myoclonic seizures; the rate of movement in clonic is slower than in myoclonic. Multi-focal clonic and myoclonic seizures in neonates often migrate from one part of the body to another, generally in an unorganized manner. Various automatisms, especially of mouth and tongue are seen frequently in newborns with diffuse forms of brain injury, such as hypoxic-ischemic encephalopathy (HIE). Well formed generalized tonic-clonic seizures and organized progression of a focal seizure (Jacksonian march) do not occur in neonates[3,19,20]. See Table 2.

Table 2 Neonatal events, probability of their being epileptic and clinical associations

Events	Probability of being epileptic	Clinical associations
High probability of being epileptic *		
(i) Consistently focal motor (usually clonic but can be myoclonic, tonic), including focal ocular deviation, and hemiconvulsive	100%	Usually focal structural lesion
(ii) Generalized asymmetric tonic episodes	100%	Metabolic/diffuse structural
(iii) Generalized flexor spasms (? myoclonic)	100%	Metabolic; diffuse structural; EME; EIEE
May or may not be epileptic *		
(i) Multifocal clonic	50%	Metabolic; diffuse structural
(ii) Generalized myoclonus or multifocal myoclonus	50%	Benign sleep; metabolic; diffuse structural (example HIE); EME.
Unlikely to be epileptic *		
(i) Generalized symmetric tonic or dystonic posturing	Low	IVH-grade 4; diffuse structural or Metabolic; often seen in EIEE
(ii) Other motor (subtle; minimal): repetitive blinking; stare, oral, buccal, lingual automatisms (sucking; swallowing)	Low	Usually diffuse structural
(iii) Generalized bicycling, pedaling, swimming movements	Low	Diffuse structural
(iv) Apnea	Rare	If epileptic, associated with other subtle features to suggest epileptic event
(v) Combinations of above	Mixed	Diffuse structural, specially inborn errors of metabolism

Note: * based on EEG confirmation. HIE: hypoxic-ischemic encephalopathy; IVH: intraventricular hemorrhage; EIEE: early infantile epileptic encephalopathy (Ohtahara's syndrome); EME: early myoclonic epilepsy. Diffuse structural: most common cause is HIE; however, diffuse abnormalities of brain development, neurocutaneous syndromes and inborn errors of metabolism also fall in this category. Probabilities are for rough guidance.

Table 3 Etiology of neonatal seizures

Cause	Age seizure onset
Symptomatic	
Infection	
i) Antenatal (AIDS/HIV; STORCH; TB)	Any
ii) Post-natal	
a) Bacterial meninigits	Usually after the first week
b) Viral encephalitis (especially herpes simplex)	Usually after the first week
c) other: example malaria, TB.	Rare in the newborn
d) Sepsis	Any age
Hypoxic-ischemic encephalopathy	Birth- 2 days
Birth trauma	< 2 days
Post-natal trauma	Usually < 3 days of trauma
Vascular	
i) Arterial stroke	Variable
ii) Venous thrombosis/hemorrhage	Variable
iii) Subarachnoid hemorrhage	<2 days
iv) Intracranial hemorrhage	Usually within 7 days
Metabolic	
i) Simple metabolic (hyocalcemia, hypomagnesemia)	Usually 4th-10th day
ii) Simple metabolic (hyponatremia, hypernatremia)	Usually after first week
iii) Isolated hypoglycaemia	<3 days
iv) Pyridoxine related, including folinic-acid responsive	Intrauterine period to anytime post-natal
v) Other inborn errors of metabolism	Variable (early to later)
Neurocutaneous syndromes	Any time in neonatal period
Congenital abnormalities of brain development	Any time
Maternal drug abuse/withdrawal syndromes	Hours of birth < 2 days; sometimes later
Toxic (example lead; antenatal exposure)	Usually < 2 days
EIEE	Any time
EME	Anytime
Idiopathic/genetic	
Benign familial neonatal epilepsy syndromes	Anytime
Benign idiopathic neonatal convulsions	5th-7th day

Note: Only selected causes, listed, especially under "Metabolic" Some inborn errors of metabolism are associated with abnormalities of brain development, and both can present as EIEE (early infantile epileptic encephalopathy) or EME (early myoclonic encephalopathy). HIV: human immunodeficiency virus; STORCH: syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex; TB: tuberculosis.

Etiology

See Table 3. Neonatal seizures are often multi-factorial[19]. The relative frequencies of the various causes for neonatal seizures are country and region specific and can change over time. Intracranial hemorrhage associated with hemorrhagic disease of the newborn (HDN), a disorder preventable with vitamin K administration soon after birth, is now rare in the west. A primary disturbance of mineral metabolism (calcium, magnesium, phosphorus) occurred in 55% of 75 neonates with seizures admitted to a neonatal unit in Scotland in the early 1970s[21], but is now uncommon in western countries. These conditions, together with hypoglycemia, hypo- and hyper-natremia (due to inappropriate formulae, errors in dilution and concentra-

tion, poor feeding; dehydration) should be considered high on the list of causes for neonatal seizures in developing countries, especially rural areas. However, electrolyte abnormalities may be secondary to etiologies such as HIE or meningitis[20-21]. Maternal Vitamin D deficiency or insufficiency, common among women with inadequate exposure to sunlight or intake can be associated with hypocalcemia and seizures in the neonate[22-24]. Congenital hypothyroidism, a treatable disorder, can present with neonatal seizures[25].

HIE is the most common cause in most series[10], accounting for 35% to 70% of all cases[2,11,12,26]. Two of us (MMKS, KS) found HIE and hypoglycemia to be common causes of neonatal seizures in the Chinese neonatal units we visited.

Infection is also a frequent and important etiology[10-11,26-27]. Sepsis (60%) and meningitis (15%) accounted for 75% of 142 neonates with seizures from a district hospital in Kenya[27]. Herpes simplex encephalitis is another potentially treatable cause in neonates[10,28]. Infective agents are often country and region specific

Maternal lead exposure can cause seizures in the neonate[29]. Neurocutaneous syndromes such as tuberous sclerosis, Sturge-Weber syndrome and incontinentia pigmenti may present in the neonatal period with seizures[30-31]. Tumors and vascular malformations are rare[32-33]. Abnormalities of brain development, especially cortical/hemispheric (such as disorders of neuronal migration, including hemi-megalencephaly), can result in neonatal seizures. However, abnormalities of brain development, particularly migrational and of the corpus callosum, may be clues to an inherited metabolic disorder or chromosomal abnormality[34-35].

New and important information on some causes of neonatal seizures is briefly discussed below.

Inherited metabolic diseases affecting the nervous system (including mitochondrial encephalomyopathies[35-37]

Inherited metabolic diseases may be uncommon but relatively under-estimated causes of intra-uterine and neonatal seizures. In many, early diagnosis and treatment can result in a normal outcome. Readers are directed to two excellent reviews for details to approach and management[36-37].

Vitamin B6 (pyridoxine) related epilepsy

Currently, four inborn errors of metabolism reduce vitamin B6 concentrations in the brain[38-45]. These include: hyperprolinemia type 2, pyridoxine dependent epilepsy (PDE; antiquitin deficiency; mutation in the ALDH7A1 gene), pyridoxine phosphate oxidase (PNPO) deficiency (mutations in the PNPO gene) and perinatal hypophosphatasia (deficiency of aromatic amino acid decarboxylase). All present in the prenatal/neonatal period with status epilepticus (SE) or frequent seizures that are often poorly controlled with antiepileptic drugs (AEDs), or with encephalopathy resembling HIE. In some, onset may be later in life.

There may be partial or temporary response to AEDs. Once suspected, the diagnosis can be confirmed by response to pyridoxine or pyridoxal phosphate (PLP) in PDE and only to PLP in PNPO deficiency. For this reason, Wang and Kuo suggest that PLP should be used preferentially. There is a clinical response to intravenous (IV) administration within 15 minutes in most[45]. In suspected cases not showing an immediate response, oral treatment should be continued for one to three weeks, an approach for which there is no clear evidence. Doses are empirical. If seizures remit with treatment, then stopping pyridoxine (or PLP) will result in recurrence, and reinstitution will cause cessation. This therapeutic trial supports the clinical suspicion; testing for α-amino-adipic semialdehyde (elevated) in blood, urine or cerebrospinal fluid (CSF) confirms the diagnosis of PDE. PNPO deficiency may be associated with abnormal levels of catecholamines, indoleamine, glycine, threonine etc. Low or absent levels of serum alkaline phosphatase are diagnostic of perinatal hypophosphatasia. Demonstration of the specific gene defect is definitive, and is advised when there has been a therapeutic response to pyridoxine or PLP. Abnormalities of brain development (cortical dysplasia, agenesis of corpus collosum), abnormalities of the white matter and enlarged ventricles may be found on MRI.

Folinic-acid responsive seizures

Affected subjects often present early in the neonatal period with epileptic seizures, apnea and irritability.

Folinic acid-responsive seizures are now considered to be identical to PDE, laboratory findings being similar[46]. Gallagher et al[46] stress the importance of pyridoxine in treatment of suspected cases: (i) IV pyridoxine 100 mg, followed by (ii) pyridoxine daily 30 mg/kg for three to seven days, (iii) "optionally" combined with folinic acid daily 3 to 5 mg/kg, together with a (iv) lysine-restricted diet.

Glucose transporter-1 (GLUT1) deficiency syndrome[47]

Seizures, often multiple types, usually start in the neonatal period, although diagnosis is frequently delayed. Dyskinesias may occur. The condition should be considered in any neonate with poorly controlled seizures. Biochemically, CSF glucose is < 2.5 mmol/L (controls: 2.5-3.7 mmol/L), the CSF: blood glucose ratio <0.5 (controls: 0.5-0.8) and CSF lactate concentrations slightly low < 1.5 mmol/L (controls: 1.3-1.9 mmol/L). The majority have mutations in the SLC2A1 gene. Most respond to the ketogenic diet.

Familial neonatal epilepsy syndromes[48-54]

Chromosomal and molecular genetics are identifying an increasing number of familial neonatal epilepsy syndromes. These neonates are often normal. Seizures usually start around 3 days of age or later. Seizures are generalized, focal or both, rarely tonic. EEGs are non-specific. The majority remit within the first year. However, 10%-15% can develop epilepsy later; others may associate with 'febrile seizures plus' and some may have intractable epilepsy and cognitive dysfunction. Association with prolonged QT syndrome has been reported. Hence, not all have a benign prognosis. Presently, mutations, deletions and duplications involving the KCNQ2 and KCNQ3 genes are considered responsible for most cases; inheritance is autosomal dominant, although denovo mutations may occur. Mutations may differ between families.

Benign neonatal convulsions[10]

These appear around the fifth day of life (hence, termed fifth day fits), in an otherwise normal neonate. Seizures are typically clonic and may be apneic. SE can occur. The condition usually remits within the first month; neurodevelopmental outcome is normal. Some cases may have molecular genetic defects.

Early infantile epileptic encephalopathy (EIEE; Ohtahara's syndrome) and early myoclonic epilepsy (EME)

These epileptic syndromes have a characteristic clinical presentation and EEG findings, burst suppression being common. Tonic seizures occur in EIEE, and myoclonic seizures in EME. They are often symptomatic to inborn errors of metabolism and/or abnormalities of brain development[37]. Seizures are usually intractable, severe neurodevelopmental dysfunction common and the prognosis poor.

Stroke and neonatal seizures

With the use of computed tomographic (CT) scanning, and magnetic resonance imaging (MRI), venous and arterial strokes are being recognized as relatively frequent causes of neonatal seizures[55-57]. The underlying mechanisms are often multi-factorial or unknown.

Clinical clues to etiology

General Neonatal seizures due to a symptomatic cause are associated with other features, which can be clues to etiology: fever or temperature instability (infective cause), systemic derangement, including metabolic, renal and hepatic (HIE, but also some inborn errors of metabolism including pyridoxine related), dysmorphic features (abnormalities of brain development; inborn errors of metabolism; chromosomal disorder), cutaneous lesions (neurocutaneous syndromes), encephalopathy (HIE, infection, and inborn errors of metabolism); focal signs such as hemiparesis (stroke; herpes simplex encephalitis, although encephalitis in the neonate is usually associated with diffuse signs; hemi-megalencephaly). Cerebral venous thrombosis often presents with generalized motor dysfunction and impaired consciousness, and the examination may be normal in arterial stroke.

Seizures that occur in a "normal neonate" should suggest the possibility of primary hypocalcemia/hypomagnesemia or a familial neonatal epilepsy syndrome; non-epileptic phenomena must be excluded. If the mother is known to have an infection [acquired-immune deficiency syndrome (AIDS), toxoplasmosis, cytomegalovirus, herpes simplex types I & II], one should an-

ticipate that the fetus may be affected. Seizures in infants of a diabetic mother and those with intrauterine growth restriction are often hypoglycaemic in origin.

Specific seizure type (*Table* 2) Consistently focal seizures suggest a localized brain lesion such as stroke, infection or focal dysplasia. Epileptic apnea may be associated with focal temporal lobe lesions[58] or benign neonatal convulsions. Multifocal clonic or myoclonic seizures generally suggest diffuse structural disturbance or metabolic cause.

Timing of seizure and etiology The timing may provide a clue, but there is considerable overlap. See Table 3[10,20,21,59,60].

Clinical status epilepticus (SE)[61]

SE is rare in neonates, serial seizures being more common. Both may occur with any of the causes of neonatal seizures (Table 3). Metabolic causes must always be considered and excluded. HIE and intracranial hemorrhage accounted for 66% of 106 cases in a report from Italy; transient metabolic disorders, inherited metabolic disorders and cerebral malformations were responsible for 6% each[62]. In our experience, abnormalities of brain development (example, lissencephaly and hemi-megalencephaly) and inborn errors of metabolism (example, non-ketotic hyperglycinemia) have been the commonest causes of poorly controlled seizures, serial seizures and SE in neonates.

Benign neonatal sleep myoclonus, which occurs in an otherwise normal neonate during sleep, can last 30 minutes or more, mimicking SE[17]. This can be excluded by waking the neonate with a painful stimulus.

History and physical examination

The history and examination should be standardized for each neonatal unit, ideally regionally, to minimize inter- and intra-observer variability. The general and specific neurological examinations of neonates have been detailed in several references[10,63,64].

Maternal (and family) history

General health; illnesses (example diabetes); prenatal care; sexually transmitted diseases (behaviours that render mother at high risk example sex-trade worker; multiple partners); medications; substance use/abuse; history and testing for toxoplasmosis, rubella, cytomegalovirus, herpes simplex; consanguinity; ethnic background of parents; neurological and systemic disorders in family, including neonatal seizures/adverse events; fetal movements (normal or abnormal).

Labor/delivery

Gestational age of baby at time; adverse events; duration and mode; trauma; need for resuscitation; Apgar scores; blood gases at birth.

Neonatal information

(i) Gestational age; (ii) Head circumference, weight and length; may need to compare head circumference of baby with that of parents; note that head moulding and caput may give erroneous head circumference. (iii) Blood pressure, respiration, pulsations; (iv) Dysmorphic features; (v) Cutaneous abnormalities; (vi) Evidence of trauma; (vii) Fontanelle, skull sutures; (viii) Assessment of chest (respiratory, cardiovascular systems) and abdomen; (ix) Standard neonatal neurological examination, including state and level of consciousness, age appropriate behaviours, cranial nerve, motor system and reflex testing. Determine if asymmetries, focal or generalized weakness, abnormal posturing, and normality of movements and posture for gestational age.

Events of concern

(i) Ideal to video, and even better to do standard video-electroencephalogram during events; (ii) Describe events, and if they recur note if they are stereotypical i. e., do they always have the same pattern; (iii) any provoking stimuli, such as touch, handling, suctioning, light, sound etc; (iv) Duration and frequency; (v) Do they happen awake or asleep i. e., state of neonate when they occur; (vi) how do they respond to firm pressure, touch, arousal with painful stimulus?; (vii) associated changes in pupils, heart rate, blood pressure, respiration.

Investigations (Table 4)

These should be based on the clinical diagnostic

possibilities of the case. Some of the tests will be detailed below.

CSF examination

CSF examination is essential when infectious or inherited metabolic disorders are suspected. The characteristics of the fluid can differentiate between viral and bacterial infection. Gram stain, culture, and special tests (such as polymerase chain reactions etc) may help identify the infective agent.

Table 4 Investigations

Investigation	Clinical situation
Hematologic	
Complete blood count	All
Tests for acquired or inborn errors of coagulation	As clinically suspected or if ultrasound of the head /MRI scan show venous or arterial stroke
"Simple biochemical" (blood) *	All
Urinalysis	All
Blood gases	Routine in critically ill neonate or to assess acid-base status as clue to some inborn errors of metabolism
Urine/blood culture, CSF culture/viral studies	When infection suspected
Tests for specific infections (HIV; TB;malaria etc)	Based on clinical suspicion
CSF examination (cell, protein, glucose, culture) **	Suspected infection
CSF/blood glucose ratio **	Bacterial meningitis; glucose transporter deficiency
CSF/blood/urine examinations: lactate; special metabolic studies	Certain inborn errors of metabolism
Aminoacids and organic acids in blood and urine	These may be routine for all newborns in several countries; otherwise if clinical suspicion
Toxicology screen (infant and mother),blood and urine	If maternal substance abuse is suspected
Screen/test mother for infection (viral, HIV etc) ***	If suspected in neonate
Chromosomal studies (including for microdeletions)	Based on clinical suspicion
Electroencephalogram (ideally, Video-EEG)	Essential in all neonates suspected of having neonatal seizures
Continuous Video-EEG	Suspect serial seizures or status epilepticus or when high doses of depressant drugs are being given
Amplitude integrated EEG (1-2 Channels)	See text
Radiologic	
Plain xrays skull	If skull fracture suspected
Ultrasound	Excellent screen test
CT Scan	Excellent for identifying blood and skull fractures (bone windows);however, radiation dose high for developing brain; hence use with caution and do not repeat unless there is no alternative
MRI Scan	Ideal test to assess all aspects of brain anatomy
MRI brain with MRA and MRV	When vascular suspected (include if cause of neonatal seizures not obvious)
MRS (brain, muscle, blood, CSF)	Especially for certain inborn errors of metabolism
Skin, liver biopsies	For certain inborn errors of metabolism

Note: * "Simple biochemical": Blood glucose; serum calcium, magnesium, phosphate, and sodium; blood urea, creatinine, lactate,serum alkaline phosphatase; ** Blood glucose must be done near simultaneously with collection of CSF so the blood/CSF glucose can be calculated. CSF Pressure may need to be measured if raised intracranial pressure is suspected; *** includes testing for syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex.

In suspected metabolic disorders, blood for glucose, lactate and plasma amino acids, and urine for amino acids and organic acids should be obtained. Tests on a CSF sample can be diagnostic in a number of inherited metabolic disorders; CSF samples should be obtained for glucose, lactate, amino acid analysis, and special studies such as quantifying neurotransmitter metabolites; a sample should also be stored for future analyses. Blood glucose (lactate and aminoacids) should be checked at the time of lumbar puncture, so that the

CSF/blood glucose ratio can be determined. In the absence of infection, a ratio of < 0.5 strongly favours GLUT1 deficiency. In the absence of meningitis, an elevated CSF lactate suggests a mitochondrial disorder. Elevated glycine in the CSF is diagnostic of non-ketotic hyperglycinemia.

Neuroimaging

An ultra-sound is a simple yet informative cost-effective bedside test that can be done at the bedside. MRI is the investigation of choice if HIE, stroke, inborn error of metabolism, neurocutaneous syndrome or abnormalities of brain development are suspected. MR angiography and venography should be done if a vascular cause is suspected. MR spectroscopy of the brain, muscle etc., can help diagnose inborn errors of metabolism. Discussion with the pediatric neuroradiologist is mandatory so that the appropriate techniques for the clinical situation are used. Plain X-rays of the skull and CT scans are useful if skull fracture, intracranial calcification, craniosynostosis or intracranial haemorrhage are suspected. They should be performed only if necessary because of exposure to radiation; radiation dose, especially cumulative, can be minimized without compromising image quality[65-67].

Electroencephalography (EEG)

Conventional EEG The fundamentals of neonatal EEG including technical aspects, recognition of normal and abnormal patterns (in the preterm and term infant), and interpretation have been discussed in two monographs[68-69]. The recording should be polygraphic i.e., electroculogram, electromyogram, electrocardiogram, respiration (nasal and abdominal) must always be included; one or more mid-line electrodes (Cz mainly; Pz and Fz optionally) must be placed; a full array of electrode placements is recommended; however, if it is not possible to use a full array, then a reduced montage using nine electrodes has > 80% sensitivity and specificity for detecting electrographic seizures and background abnormalities[70]; the recording should be done through an entire sleep-wake cycle (typically 1 hour); reaction to sound, light and painful stimuli should be noted, as should changes in behaviour, posture, clinical state. Video-EEG has become the gold standard when neonatal seizures are suspected[69,71]. Cherian et al[72] have recently discussed standards for recording and interpreting neonatal EEGs.

Continuous polygraphic EEG (ideally video-EEG) monitoring is essential when: (i) neonates are comatose, (ii) treated with neuromuscular blocking agents or (iii) during neurointensive treatment of intractable/refractory seizures.

EEG patterns can be diagnostic of etiology and in prognostication, serial EEGs being especially helpful.

Amplitude integrated EEG (aEEG) Conventional EEG requires technical and neurophysiologic expertise, which is not usually available 24/7. Therefore, aEEG (also called cerebral function monitor: CFM) is being used increasingly in many neonatal intensive care units (NICUs)[72]. In an European survey, all respondents "routinely used aEEG"[73].

aEEG is very helpful for assessing background activity and trends over time. However, because the recording is limited to one or two channels, asymmetries and electrographic seizures can be missed, and contamination by artefact can confound interpretation[72]. In one study, one or two channel aEEG alone had low sensitivity and low inter-observer agreement[74]. aEEG may be useful for assessing and following generalized abnormalities of the background, especially when high doses of depressant drugs are used. One or two channel aEEG is inadequate for detecting all (electrographic) seizures, since the coverage is limited[75-76]. A conventional EEG should always be performed if the findings are likely to affect therapeutic decisions[72,76]. Freeman has cautioned against the uncritical use of aEEG[77]. Automated methods to reliably detect electrographic seizures on aEEG are being explored[71].

Electrographic seizures The increasing use of aEEG has led to a renewed interest in neonatal electrographic seizures. Most of the information is from cases with HIE. Electrographic seizures, typically have an abrupt onset and offset, and consist of a repetitive sequence of waveforms which evolve in frequency, amplitude, electrical field, and morphology, lasting 10 seconds or more[78]. These often include delta, theta, alpha and beta rhythms.

In one study, 80% of electrographic seizures were not associated with clinical correlates[79]. Electro-

graphic seizures occurred in 1% of 1200 neonates considered high risk for seizures[80]. These often last < 9 minutes but recur serially, although electrographic SE may occur[78,80]. Fifty-six (48 with HIE) of 311 neonates monitored with aEEG had SE; of these, 28 (50%) were electrographic alone[81]. The onset of clinical and electrographic seizures with HIE depends upon the timing of the insult but generally occurs < 24 hours of age; electrographic seizures in those with HIE almost always stop by 72 hours of age[80]. Clinical and electrographic seizures can be associated with increased cerebral blood flow[82-83].

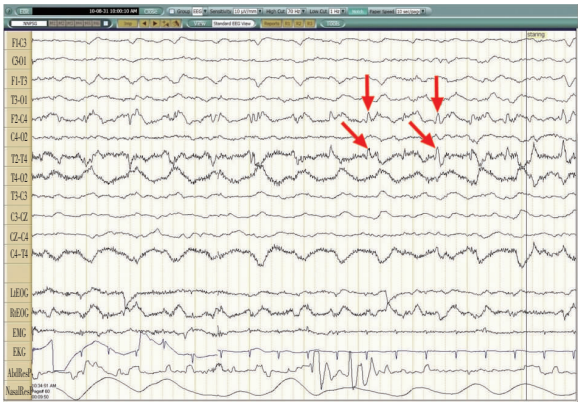

Figure 1 Clinical and EEG seizure Rhythmic spikes (arrows) at 1 Hz (C4,T4) associated with eye opening and staring.

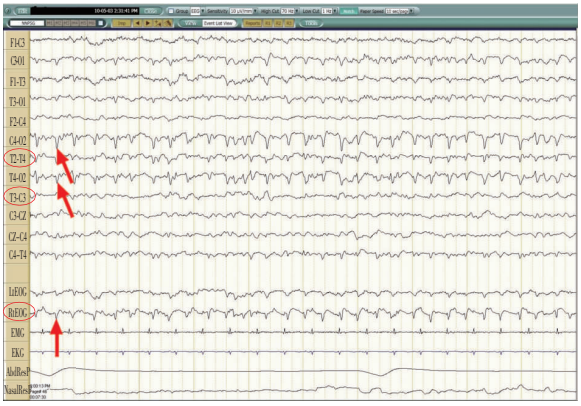

Figure 2 Electrographic seizure Rhythmic spikes (arrows and in the entire channel) at 3 Hz (C4,T4, R EOG) No clinical change seen on simultaneous video EEG recording. REOG: Right electro-oculogram.

The term 'electroclinical dissociation' has been used when clinical and electrographic events occur synchronously on some occasions but are dissociated at other times[84]. 'Uncoupling', or 'decoupling' describes the situation, often after administration of an AED, when the clinical component of an epileptic seizure stops but the electrographic one persists[3,7].

Examples of an epileptic (i.e., clinical and electrographic) seizure and electrographic seizure alone are shown in EEG figures 1 and 2 respectively.

Outcomes

Some research has shown that etiology is the major determinant of outcome[19,21,85]. There is conflicting evidence regarding the role of seizures influencing the outcome of neonates with HIE[86-87]. The relationship between electrographic seizures alone and outcome is also controversial[19,77,80,88-90]. The duration of electrographic SE did not correlate with outcome in neonates with HIE[81].

Readers are referred to the papers by Jensen and Lombroso for details[2,19,91]. Experimental studies suggest the following: seizures have lasting effects on future seizure susceptibility and outcome; the occurrence of seizures or hyperthermia on a compromised neonatal brain contributes to brain injury, and normalizing temperature is protective[92-96]. These animal data have been used to argue for aggressive pharmacological management of electrographic seizures.

On the other hand, phenobarbital, diazepam, phenytoin, and valproic acid, have deleterious effects on brains of experimental immature animals[2]. Hence, caution should be exercised in attempting to abolish electrographic seizures in neonates, until risk-benefits have been evaluated. The newer AEDs have not been studied adequately.

Treatment

See Figure 3. Our philosophy is similar to that outlined recently by Sankar et al[97]. Antenatal preventive measures include management of maternal high risk factors for neonatal seizures. Peri- and post-natally, common and treatable causes must always be anticipated and excluded; if there is any doubt to their presence, then appropriate treatment should be started un-

til the diagnosis is confirmed or excluded. This applies to conditions like hypoglycaemia, bacterial meningitis, herpes simplex encephalitis, and certain inborn errors of metabolism, where failure to institute treatment early can result in morbidity and mortality. It is standard Canadian practice to strongly recommend administration of Vitamin K (intramuscularly 1 mg for those >1500 g and 0.5 mg for <1500 g) within 6 hours of birth, to prevent hemorrhagic disease of the newborn. The stepwise approach summarized in the flow diagram is in keeping with current information summarized below.

There are no randomized controlled trials[98]. There is variation between pediatric neurologists and neonatologists and among themselves, even in our centres, on various facets of treatment, including choice of AEDs and duration of prophylaxis[99-102].

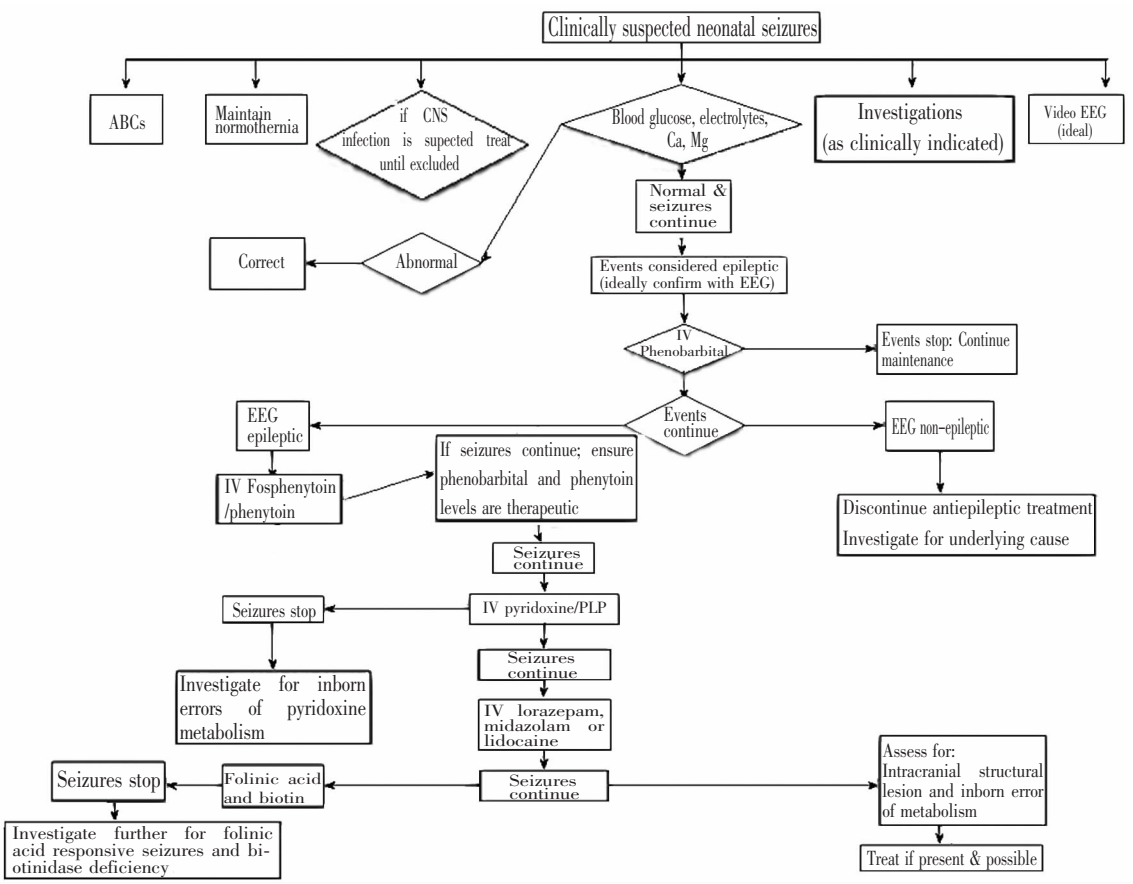

Figure 3 Management of clinically suspected neonatal seizures Treatment for bacterial infection, herpes simplex encephalitis, inborn errors of metabolism should be instituted at the outset if these are suspected, in addition to treating seizures symptomatically. At every step, It is crucial to ensure that events are epileptic (with an EEG); EEG confirmation is absolutely necessary before proceeding to treatment with midazolam or lidocaine infusions; these should be done under EEG monitoring. ABC: attention should constantly be paid to ensuring adequate Airway, Breathing (normal blood gases), Circulation (blood pressure and perfusion pressure) and homeostasis in general ie normal electrolytes etc. Note that global or regional (head) hypothermia is currently advised for those with hypoxic-ischemic encephalopathy. PLP: Pyridoxal phosphate.

Hepatic and renal dysfunction will decrease the clearance of most AEDs. Hence, doses have to be reduced in these situations and drug levels monitored to guide therapy. Thus, Gal et al[103] found that asphyxiated neonates required about half the maintenance dose of phenobarbital when compared to non-asphyxiated neonates, to achieve similar plasma levels. The half-life of phenobarbital is 1 day-3 days even in healthy neonates and longer in those with hepatic/renal dysfunction. Therefore, levels done within the first few days of administration may not reflect steady-state.

Initial approach

Among the AEDs, despite concerns about its adverse effects on the developing brain, phenobarbital is still the first choice of over 80% world-

wide[6,10,60,97,101,104-107]. Most centres use a loading dose of 20 mg/kg IV. If seizures persist, then additional doses (typically, maximum total of 40 mg/kg, lower in severely asphyxiated neonates) can be given to achieve phenobarbital levels of 40 to 50 μg/mL. Although levels of 60 μg/mL may be tolerated by an individual neonate, the maximum benefit seems to peak at levels of 40-45 μg/mL[108-109], and significant side-effects are likely at higher levels[10].

What if phenobarbital (serum level 40-45 μg/mL) is ineffective?

Phenobarbital alone is ineffective in about 15%-50% cases[108-111], depending upon level achieved, etiology and definition of seizures. It is essential to confirm that the events are epileptic and exclude metabolic causes before adding another AED. Choices, depending on the clinical situation, include phenytoin (fosphenytoin is ideal in neonates because of its lower side-effect profile; however, it is more expensive, but is our preferred option), lorazepam, midazolam, lidocaine, topiramate, and leviteracetam, most of them off-label use[112-116]. The order in which these are tried currently varies between individuals and centres. In Europe, the first choice is phenobarbital; the second add-on is either midazolam or clonazepam, and if seizures are still refractory then lidocaine, all given IV[73].

Co et al[60] advocated phenytoin as the second choice, and diazepam or lorazepam as additional options. The Indian Academy of Pediatrics also suggested phenytoin as the 2nd choice, followed by lorazepam or diazepam, and then midazolam as infusion, with a trial of pyridoxine to follow, presumably if seizures continued[6]. Because of its unique pharmacokinetics, phenytoin (fosphenytoin) is recommended only for acute treatment and generally not for long term maintenance. The cardio-toxicity of phenytoin may be increased with cooling; hence, phenytoin should not be given when hypothermia is used in management (Guidelines: NICU, Children's Hospital, Winnipeg). Caution should be exercised in the dosing of all AEDs during cooling because of altered pharmacokinetics.

Beware of the toxicity of excipients in drugs!

Excipients are substances that are added to an active drug for a variety of reasons. Many IV medicines, benzodiazepines included, contain potentially toxic excipients like benzyl alcohol, propylene glycol and hydrochloric acid. The actual excipient in a medication can vary from country to country. Physicians should be familiar with the excipients in the drugs they use. Neonates, especially critically ill ones, can be exposed to toxic amounts of excipients through continuous infusions. In one study, neonates received 21 and 180 times the acceptable daily doses of benzyl alcohol and propylene glycol respectively; midazolam and lorazepam were involved in over 66% of such exposures[117]. Neonatal deaths from benzyl alcohol have been reported[118]. Deleterious 'refractory' metabolic acidosis, attributed to hydrochloric acid, has been associated with midazolam infusion[119].

Which benzodiazepine is the preferred one?

Cost, availability and individual clinical situations determine choice. Lorazepam has a longer half life than diazepam or midazolam. Hence, administration is less frequent and dosing is intermittent. Therefore, cumulative exposure to toxic excipients is minimized. It may be the preferred benzodiapine in most cases.

Diazepam may be the cheapest of the benzodiazepines but has a short half life, very narrow therapeutic/toxicity window and potentially greater depressant effects, especially when higher than recommended doses are given or phenobarbital also used[10,120]; cardiorespiratory arrest may be precipitated. We no longer use diazepam in our nurseries. Volpe and Sankar et al also recommend its avoidance[10,97].

One of us (KS) also advises against the use of midazolam as it has often to be given as an infusion, exposing neonates to potentially toxic levels of excipients.

Other options

In one review, the combination of phenobarbital (maximum 40 mg/kg) and drugs such as midazolam, clonazepam, lorazepam, phenytoin or lidocaine, for the treatment of EEG proven seizures, achieved seizure control in 43%-100%[121].

It is unclear at what stage topiramate and leviteracetam should be used (i.e., 2nd line, 3rd line or 4th line); precise dosing for them is also uncertain. Topiramate has to be given orally as does leviteracetam (in countries where the IV formula is not available), a

limitation in critically ill neonates in whom absorption of orally administered drugs may be compromised. Leviteracetam has been used orally and IV in a limited number of neonates with seizures; doses have ranged from daily 10mg to 115 mg/kg[112-114,122-123]. The use of leviteracetam and topiramate in the neonate needs systematic study, and dosing based on pharmacokinetic principles firmly established. Additionally, information on one web-site suggested that keppra (one brand of leviteracetam) concentrate for infusion contained potentially toxic excipients like sodium acetate and glacial acetic acid.

Valproic acid is an effective AED for recurrent seizures and SE. However, it should be used with extreme caution because of the relatively high risk of fatal hepatotoxicity in neonates (as in children < 10 years of age), especially with polytherapy and if there is an underlying inborn error of metabolism.

The agents commonly used for neonatal seizures are listed in Table 5. Pharmacogenetic factors (genetic makeup that determines beneficial and adverse effects of drugs on an individual), and systemic derangements influence dosing. Therapeutic drug level monitoring, including determination of free levels should guide administration. Hence, treatment should be individualized for each neonate. Bumetanide is being evaluated in animal models but caution is advised in applying the limited information to humans[124].

Management of intractable epileptic seizures or SE

When epileptic seizures (clinical with electrographic correlate) fail to respond to adequate doses (and levels) of two AEDs, then they can be termed refractory or intractable. Further management, requires a high level of medical and neuro-critical care support. AEDs become less effective the longer a seizure lasts, benzodiazepines being the best studied[61].

It is important to ensure that the events are epileptic. In this situation, EEG confirmation is mandatory. Additionally, a metabolic cause, both simple mineral and inherited disorders such as pyridoxine related, should be excluded. An MRI should be obtained (if not done so earlier) to determine if there is evidence of abnormality of brain development or an inborn error of metabolism. The presence of the former does not exclude the latter. Any suspicion of an inborn error of metabolism requires the stepwise approach proposed by Prasad and Hoffman[37]. EEG patterns can be diagnostic in a number of disorders, including non-ketotic hyperglycinemia and GLUT1 deficiency.

Table 5 Agents used in the treatment of neonatal seizures*

Agent	Loading dose	Maintenance/information
Phenobarbital	20 mg/kg; further loads to a maximum of 40 mg/kg	Based on level and need
Phenytoin	20 mg/kg	Based on level and need
Fosphenytoin	20 mg/kg phenytoin equivalent	Based on level and need
Diazepam	0.25 mg/kg	Rapid clearance; short lasting effect; depressant especially with phenobarbital; may provoke cardio-respiratory arrest. Use only if no alternative. Only single dose.
Lorazepam	0.05 to 0.1 mg/kg	8 hourly if needed
Midazolam	0.2 mg/kg	0.1 to 0.4 mg/kg/hr
Lidocaine	2 mg/kg	2-6 mg/kg/hr
Topiramate	Insufficient information to make recommendations	
Leviteracetam	Insufficient information to make recommendations	
Pyridoxine	100 mg	Daily 30 mg/kg
Pyridoxal phosphate	10 mg/kg	Daily 10 mg/kg
Folinic acid	3-5 mg/kg/day p. o.	Same
Biotin	5-10 mg p. o	Same daily

Note: Doses are guidelines. Pharmacogenetic considerations and systemic derangements (example, renal, hepatic) will influence individual dosing. Consult current pediatric/neonatal drug dosage handbooks for dosing. Therapeutic drug level monitoring should be done wherever possible; free levels to be monitored for drugs that are highly protein bound. Unless otherwise stated, administration is intravenous. p. o: oral administration. Please see text for details.

A therapeutic trial of pyridoxine (ideally PLP) should be done before adding a 3rd AED. If seizures are refractory to three AEDs then one may need to consider infusions of midazolam or lidocaine. If they are still refractory then a more prolonged trial of pyridoxine or PLP, folinic acid and biotin should be tried if the etiology is undetermined. Lidocaine is contraindicated in those with congenital heart disease, cardiac arythmias and if phenytoin has been given earlier[116]. It is essential to have continuous EEG monitoring in this sit-

uation. We do not advocate midazolam or lidocaine infusions for clinical events that do not have an electrographic correlate.

Neonates in whom seizures relapse once neuro-intensive care is withdrawn, or whose clinical epileptic seizures remain refractory despite adequate treatment with two AEDs and trials of pyridoxine/PLP, folinic acid and biotin, should be evaluated for surgical treatment, provided an inborn error of metabolism has been conclusively eliminated.

Management of electrographic seizures without clinical expression

Glass & Wirrell[9] suggest that "aggressive treatment" of electrographic seizures "will be proven to be warranted". However, the notion that electrographic seizures in the human contribute to brain damage is disputed[77]. There is no consensus or evidenced-based management on this issue. Most observations have been in neonates with HIE. Electrographic seizures in this situation generally resolve within 72 hours making it difficult to judge effect of treatment.

Standard doses of phenobarbital, phenytoin or both abolished or reduced electrographic seizures by 80% in 66%-80% of cases[80,111,125]. Therefore, some experts use a combination of these drugs for seventy-two hours if electrographic seizures are detected in those with HIE. In a small sample of neonates with HIE, there was no significant reduction in electrographic seizure duration using a stepwise treatment protocol that included phenobarbital, lidocaine or midazolam, clonazepam and pyridoxine[126]. AEDs have adverse effects on the developing brain. Therefore, randomized controlled trials are needed, especially in the setting of HIE to determine if abolishing electrographic seizures results in improved outcome. Pentobarbital is often effective in suppressing electrographic seizures in infants and children[61]; we are not aware of data in neonates. Such treatment is often associated with systemic and hemodynamic side-effects.

Temperature control and hyperthermia

Hyperthermia is deleterious. Hence, a target abdominal skin temperature of 36.5℃ should be maintained. Whole body or regional (head) induced therapeutic hypothermia can improve the outcome in selected cases of HIE[127-128].

Evolution and follow up

Neonatal seizures in those with HIE and intracranial infection (i.e. acute symptomatic), self-limit within a few days. In this situation, AEDs should be discontinued shortly after such remission, often prior to discharge[129]. AEDs may have to be continued longer in those with abnormalities of brain development, as the risk of seizure relapse is high. In cases with benign familial epilepsy syndromes, an attempt could be made to withdraw treatment after 3 seizure free months; some suggest that treatment should be continued as long as the EEG shows epileptiform abnormality. There is no evidence for either approach. Neonates with seizures should be followed up into childhood.

Conclusions

The challenges of differentiating epileptic from non-epileptic (especially motor) behaviours continue to confound clinical practice, especially since both often co-occur. Careful clinical assessment must guide management. Conventional EEG, especially video-EEG, is an essential tool for best management practice. Each geographic region must develop its own data base of causes for neonatal seizures so that preventative strategies and uniform approach to management can be adopted.

CAUTION! Drug information changes rapidly. Hence, readers are advised to check the current information about the drugs mentioned in this paper relevant to their patient population for contra-indications, drug-interactions, doses, side-effects etc.

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(The main part of this article is smmarized and translated into Chinese as following.)

"Neonatal seizures: diagnosis and management"**中文摘译:**

新生儿惊厥的诊断与处理

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[**摘要**] 新生儿会发生各种形式的发作性运动,其中有些是癫痫性的惊厥,有些则不是。如何去识别是件困难的事。目前尚缺乏新生儿惊厥诊断与处理的全球性指南。该讲座在全面复习新生儿惊厥的文献并结合作者丰富的临床经验的基础上提出一个处理新生儿惊厥的方案。新生儿惊厥病因很多,缺氧-缺血性脑病和感染是最常见的原因,新生儿中风、遗传代谢病也逐渐被认识。病因是新生儿惊厥结局好坏的主要决定因素。视频-EEG 是鉴别癫痫性惊厥与非癫痫惊厥的金标准。苯巴比妥依然是新生儿惊厥的首选药。足量苯巴比妥治疗无效时可考虑使用苯妥英、咪达唑仑或氯硝安定等。顽固性的惊厥,早期可试用吡哆醇、磷酸吡哆醛、叶酸和生物素治疗。对没有惊厥表现的脑电图发作的是否需要治疗有待于进一步的研究。

[**关键词**] 惊厥; 新生儿

新生儿癫痫性惊厥是指由于大脑皮质或丘脑的神经元异常"超同步"放电而引起的一种异常、反复发作的临床症状,常常突然发生并且有自限性(即发作性)。来源于其他部位(如基底神经节、脑干、小脑)的异常放电不属于癫痫性惊厥。癫痫性惊厥的诊断只有在临床发作时有典型的脑电图(EEG)改变才能明确,视频-EEG 通常被认为是鉴别癫痫性惊厥与非癫痫发作的金标准。缺乏脑电图改变的临床发作可能不是癫痫,但并不绝对。当临床医生无法确定是否癫痫性惊厥时,最好诊断为"惊厥待查"。

癫痫性惊厥与非癫痫发作的临床鉴别

易被误认为癫痫性惊厥的非癫痫活动见表 1。包括颤动、惊跳、良性睡眠性肌阵挛、惊骇(hyperekplexia)、良性婴儿肌阵挛等。颤动和惊跳可因轻压而停止。新生儿良性睡眠性肌阵挛是在瞌睡或睡眠时发生的肌肉抽动,当被唤醒时抽动会立即停止。呼吸暂停,尤其是早产儿呼吸暂停,是癫痫性惊厥的可能性不大。但是,如果呼吸暂停对疼痛刺激无反应,或伴有眼球颤动、眼球偏斜、眨眼或瞳孔改变时就要想到癫痫性呼吸暂停的可能。

分类

伴有和不伴有 EEG 改变的发作可以发生在同一新生儿身上,同一新生儿也可能发生一种类型以上的癫痫发作。强直姿势,尤其是全身强直, 不太可能是癫痫。但大田原综合征的强直性发作例外。鉴别阵挛性和肌阵挛性惊厥比较困难,前者的频率要比后者慢。典型的多灶性新生儿阵挛性和肌阵挛性发作是从身体的一部分到另一部分,通常是无序的。各种自动症,特别是嘴和舌的运动常发生于弥漫性脑损伤,如缺氧缺血性脑病(HIE)的新生儿。全身强直-阵挛发作和杰克逊发作不会发生在新生儿。

病因

引起新生儿惊厥的原因很多(见表 3),在不同的国家和地区之间有差异,并随年代而变化。由于及时的维生素 K1 的补充,新生儿出血症引起的颅内出血在西方已很罕见。矿物质(钙、镁、磷)代谢紊乱、低血糖、低钠和高钠血症诱发的惊厥主要发生在发展中国家,特别是农村地区。新生儿患先天性甲状腺功能低下也可以出现惊厥。HIE 是新生儿惊厥最常见的病因,占 35% ~70%。无论在发达国家还是发展中国家感染(败血症和脑膜炎)都是常见的重要病因,病原体因国家和地区而异。本文作者在以前的研究中发现 HIE 和低血糖症是中国新生儿惊厥的最常见的两大原因。

神经皮肤综合征如结节状硬化症、Sturge-Weber 综合征和色素失禁症可能会引起新生儿惊厥。颅内肿瘤和血管畸形是罕见原因 。脑发育异常特别是皮层/大脑半球异常(如灰质异位,巨脑回)均可导致新生儿惊厥。脑发育异常,特别是灰质异位和胼胝体的异常可能有遗传代谢疾病或染色体病。关于新生儿惊厥的病因还有大量的新知识,下面将予详谈。

影响神经系统的遗传代谢病(包括线粒体脑肌病)

遗传代谢病在新生儿惊厥中虽不多见但十分重要。因为早期诊断和治疗可能使患儿恢复正常;通过遗传咨询和产前诊断可指导下次妊娠;可能纠正了 HIE 的误诊 。参考文献 36、37 是两篇很好的综述,有关诊断和处理的详情可供读者参考。

维生素 B6 (吡哆醇)相关性癫痫

四种先天性代谢缺陷可减少脑中维生素 B6 浓度,包括 2 型高脯氨酸血症、吡哆醇依赖性癫痫(PDE)、吡哆醇磷酸氧化酶(PNPO)缺乏和围产期磷酸酶过少症(芳香族氨基酸脱羧酶缺乏)。患儿可以在围产和新生儿期就表现为癫痫持续状态 (SE) 或频繁发作难以用抗癫痫药物(AEDs)控制,或具有与 HIE 类似的脑病表现。也可以在新生儿期以后发病。PDE 和 PNPO 缺乏患儿的母亲可以感觉到胎儿在宫内发生的惊厥,生后惊厥一般发生在 48 h 内。表现为肌阵挛性抽搐和强直,眼运动异常,做鬼脸,打嗝和易激惹。这些发作不完全与 EEG 一致,因此,这些发作不一定都是癫痫性惊厥。

一旦怀疑该病,可以通过试验性治疗确诊,即 PDE 缺乏对吡哆醇(维生素 B6)或磷酸吡哆醛(PLP)治疗都有反应,而 PNPO 缺乏只对 PLP 有反应 。因此,怀疑此类疾病时建议优先使用 PLP 而不是吡哆醇。多数病例在静脉用药 15 min 内就会有临床效果 。如果用药后抽搐缓解,停药后复发,再用药又会终止发作者临床诊断即可成立。检测到血、尿和脑脊液(CSF)中 α - 氨基己二酸半醛水平升高可确定 PDE 诊断。PNPO 缺乏可能与儿茶酚胺、吲哚胺、甘氨酸和苏氨酸等水平异常有关。明确特异性基因缺陷有确诊意义,当患儿对吡哆醇或 PLP 治疗有反应时建议做基因检测。头部 MRI 可以有脑发育异常,如脑皮质发育不良、胼胝体发育不全、脑白质异常和脑室扩张。

亚叶酸反应性惊厥

新生儿期表现为癫痫发作、呼吸暂停和易激惹。目前认为该病与 PDE 相同,实验室结果类似。Gallagher 等强调用吡哆醇治疗可疑病例:(i) 吡哆醇 100 mg,IV;(ii)继以每天 30 mg/kg,3 ~7 d;(iii) "选择性"联用亚叶酸每天 3 ~5 mg/kg;(iv)同时给以限赖氨酸饮食。

葡萄糖运载蛋白 - 1(GLUT - 1)缺陷综合征

通常新生儿期就开始发生多种类型的惊厥,但诊断常常延迟。可能发生运动失调。新生儿出现难以控制的惊厥时都应考虑本病。生化方面,CSF 葡萄糖 <2.5 mmol/L (正常:2.5 ~3.7 mmol/L), CSF: 血糖比值 <0.5 (正常: 0.5 ~0.8),CSF 乳酸 < 1.5 mmol/L (正常: 1.3 ~ 1.9 mmol/L)。大部分有 *SLC2A1* 基因突变,大部分对生酮饮食有反应。

家族性新生儿癫痫综合征

新生儿出生时正常,一般生后 3 d 左右出现惊厥,但也可能在 3 d 以后起病。惊厥可以是全身性或局限性或两者都有,很少是强直性的,EEG 无特异性。大部分病人会在第 1 年内缓解,但有 10% ~15% 的病人会发展成癫痫;有些可能并发热性惊厥,而有些可能出现顽固性癫痫和认知障碍。有出现长 QT 综合征的报道,所以不是所有的病例都结局良好。大部分病例与 *KCNQ2* 和 *KCNQ3* 基因的突变、缺失和复制有关;为常染色体显性遗传,常有新的突变发现,不同家系突变也各不相同。

良性新生儿惊厥

生后 5 d 左右发病(故又称 5 日风),其他方面正常。为典型阵挛性发作,有时伴发呼吸暂停,或出现癫痫持续状态(SE)。惊厥在生后 1 个月内停止,神经发育正常。部分病例有遗传缺陷。

早期婴儿型癫痫性脑病 (EIEE; 大田原综合征)和早期肌阵挛癫痫(EME)

这些癫痫综合征具有特征性的临床表现和 EEG 发现(爆发抑制波形)。EIEE 常见强直惊厥,而 EME 常见肌阵挛发作。常伴有先天性代谢缺陷和或脑发育异常的症状,惊厥难以控制,常见严重的神经发育功能异常,预后差。

中风和新生儿惊厥

随着 CT 特别是 MRI 的出现,动静脉中风作为新生儿惊厥相对频发的原因逐渐得到认识。机制尚不清楚。

惊厥病因的临床线索

新生儿惊厥常伴发其他临床特征,可作为探索病因的线索:发热或体温不稳定(感染);全身功能紊乱,包括代谢、肾、肝功能(HIE、先天性代谢异常如维生素 B6 缺乏);异常形态(脑发育异常、先天性代谢异常、染色体疾病);皮肤损害(神经皮肤综合征);脑病 (HIE、感染、先天性代谢异常);局部体

征如偏瘫(中风、单纯疱疹病毒脑炎、巨脑回)。脑静脉血栓形成常常表现为全身性的运动失调和意识障碍,动脉中风时可能正常。

其他方面表现正常的新生儿出现惊厥时应该想到低钙血症/低镁血症或家族性新生儿惊厥综合征的可能,但必须排除非癎性惊厥。如果已知母亲感染(艾滋病、弓形虫病、巨细胞病毒或单纯疱疹病毒 1 型、11 型感染),就应该想到累及胎儿的可能。小于胎龄儿或糖尿病母亲婴儿以及宫内发育受限的新生儿惊厥常因低血糖引起。

惊厥持续状态(SE)

SE 在新生儿很少见,而连续的惊厥更常见,两者都可见于惊厥的任何一种病因 。一定要想到代谢原因并予排除。意大利报道 106 例 SE 中,HIE 和颅内出血占 66%,暂时性代谢紊乱、遗传代谢病、脑畸形各占约 6%。据我们的经验,脑发育异常(如无脑回畸形和一侧巨脑畸形)和代谢异常(如非酮症高氨酸血症)是新生儿难治性惊厥、连续性惊厥和 SE 的最常见原因。

检查

脑脊液(CSF)

当怀疑感染或遗传代谢紊乱时需要检查 CSF。革兰氏染色、培养和特殊检测(如 PCR)有助于明确特异性感染原。如果考虑代谢紊乱,腰穿的同时应该抽血化验血糖、乳酸和氨基酸,并留尿检查氨基酸和有机酸。留 CSF 做糖、乳酸测定;氨基酸分析。甚至可以做神经递质的测定。计算 CSF 糖/血糖比值,无感染时,如比值 <0.5 则强烈提示 GLUT1 缺陷。没有脑膜炎时,CSF 中乳酸升高提示线粒体异常。CSF 中甘氨酸水平升高可诊断非酮症高氨酸血症。

神经影像学检查

头颅超声作为一个简单却有信息价值和成本效益的筛查方法可以床边操作。如果怀疑 HIE、中风、先天性代谢异常、神经皮肤综合征或脑发育异常,可选择 MRI。怀疑血管原因应做 MR 血管造影术和静脉造影术。脑、肌肉等的 MR 光谱学有助于先天性代谢异常的诊断 。如果考虑有颅骨骨折、颅内钙化、颅缝早闭或颅内出血,那么颅骨平片或 CT 扫描是有帮助的。

EEG

常规 EEG

EEG 应为多图记录,即必须包括眼电图、肌电图、心电图和呼吸图(鼻腔和腹部);必须放置一个或多个中线电极(主要是 Cz;可选择 Pz 和 Fz);建议放置一整排电极;应包含完整的睡眠 - 觉醒周期(典型为 1 小时),记录对声、光和疼痛刺激的反应以及行为、姿势和临床状态的变化等;怀疑惊厥时,视频 - EEG 已经成为诊断的金标准。

下列情况需要连续监测多道 EEG(最好是视频-EEG):(i)昏迷;(ii)应用神经肌肉阻滞剂;或(iii)难治/顽固性惊厥。

EEG 模式有病因诊断和判断预后的意义,连续 EEG 尤其有用。

振幅整合 EEG(aEEG)

常规 EEG 需要技术支持和神经生理学专家,常常很难做到。所以许多 NICU 越来越多地应用 aEEG 。aEEG 曾局限于一个导联,典型的记录来自于顶骨区域(P3 和 P4);现在也可使用 2 导联了。aEEG 对于评估背景活动和趋势非常有用。可是因为记录只局限于一或两个导联,不对称的脑电图发作可能被错过。因为覆盖率低,一或两导联 aEEG 对于探测所有的(脑电图)发作是不充分的。如果结果可能影响治疗抉择,那么应该行常规 EEG 检查。

随着 aEEG 应用的增加,新生儿脑电图惊厥又受到重视,其大部分知识来源于 HIE 病例。典型的脑电图惊厥突然发作,突然终止,由重复序列的波形(包括 δ、θ、α、β 波)组成,波形的频率、幅度、电场和形态会演变,持续 10 s 或更长。研究表明,80% 的 EEG 惊厥没有相应临床发作。在 1200 个有惊厥高危因素的新生儿 EEG 惊厥发生率为 1%,大部分电惊厥持续 <9 min,但经常复发,电惊厥持续状态也有发生。另一研究中,311 例监测 aEEG 的新生儿中 56 例(48 例 HIE)有惊厥持续状态;其中 28(50%)例只有 EEG 惊厥而没有临床发作。HIE 患儿临床和电惊厥的时间多发生于生后24 h 内。其 EEG 惊厥几乎都在生后 72 h 内终止。临床和电惊厥可能与脑血流增加有关。“脑电临床分离”曾被用来描述临床和 EEG 惊厥有时同时发生而有时又无关联的情形。

图 1 示临床和 EEG 惊厥同时发作,图 2 示只有 EEG 惊厥。

病因是结局好坏的主要决定因素。惊厥是否影响 HIE 新生儿预后以及单独 EEG 发作与预后的关系均有争议。

治疗

缺乏临床对照研究。关于治疗的各个方面包括对顽固性惊厥 AEDs 选择和预防用药的时间,儿科神经学医生和新生儿科医生之间以及各自内部的意见都没有统一,每个 NICU 内也是如此。肝肾功能损害会降低对大部分 AEDs 的清除,这种情况下剂量要减少并且检测血药浓度以指导治疗。

初始治疗

全世界 80% 以上的国家中,苯巴比妥依然是第一选择。大部分中心应用负荷量 20 mg/kg IV,如果惊厥持续,可以再给药至总量达到 40 mg/kg(严重窒息者降低)。使血药水平维持在 40 ~ 50 μg /mL,尽管个别新生儿能耐受 60 μg /mL,但在 40 ~ 45 μg/mL时效果最好。副作用一般发生于血药浓度较高时。

苯巴比妥治疗无效怎么办?

15% ~50% 的病例苯巴比妥治疗无效,此时,必须确定是否癫癎并排除代谢原因,然后可选择其他药物包括苯妥英

(新生儿用磷苯妥英比较理想,副作用少,但价格贵)、氯羟去甲安定、咪达唑仑、利多卡因、托吡酯和左乙拉西坦。在欧洲,第一选择是苯巴比妥,其次是咪达唑仑或氯硝安定,如果惊厥依然难治,再用利多卡因,均为静脉给药。

Co 等提倡把苯妥英作为第二选择,然后再选安定或氯羟去甲安定。印度儿科学会也建议苯妥英为第二选择,随后是氯羟安定或安定,然后输入咪达唑仑,惊厥仍不能控制,再用吡哆醇。因其独特的药物动力学,建议苯妥英只用于急性期治疗,一般不用来长期维持。低温时苯妥英对心脏的毒性会增加,所以低温治疗时不能用苯妥英。因为低温时药物动力学会改变,应注意所有 AEDs 的剂量。

警惕药物辅料的毒性!

辅料是因各种原因添加于活性药物中的物质。包括苯二氮卓类的许多静脉药物含有潜在毒性的辅料成分如苯甲醇、丙二醇和盐酸。新生儿,尤其是病情严重的新生儿可能通过持续静脉输入而暴露于大剂量辅料中。在一项研究中,新生儿接受的苯甲醇和丙二醇分别达到可接受每日剂量的 21 和 180 倍;其中 66% 与咪达唑仑和氯羟安定使用有关。曾有新生儿死于苯甲醇毒性的报道。也曾有由于使用咪达唑仑,赋形剂盐酸输入过多导致顽固性代谢性酸中毒的报道。药物中的实际赋形剂每个国家可能不同,所以临床医生应该熟悉所使用的药物赋形剂。

哪种苯二氮卓类药物比较好?

氯羟去甲安定(劳拉西泮)半衰期比安定和咪达唑仑长,不用频繁给药,辅料的累积少,所以可能是最好的苯二氮卓类药。安定最便宜,但半衰期短,治疗/毒性窗较窄,并且有潜在的抑制效应,特别是应用较大剂量或同时使用苯巴比妥时。我们不用安定。也有人建议不用咪达唑仑,因为它常用来静脉输入,使新生儿可能暴露于潜在毒性水平的赋形剂中。

其他选择

联合应用苯巴比妥(最大剂量 40 mg/kg)和其他药物如咪达唑仑、氯硝安定、氯羟去甲安定、苯妥英或利多卡因对于治疗 EEG 证实的惊厥,完全控制率为 43% ~100% 。

尚不清楚应该在什么阶段使用托吡酯和左乙拉西坦(即第 2,3 线还是第 4 线),精确剂量也不明确。托吡酯和左乙拉西坦(无静脉制剂的国家)需口服,病情严重新生儿口服吸收效果可能受影响。新生儿应用托吡酯和左乙拉西坦需要系统研究,剂量应以药物动力学为基础。丙戊酸治疗复发性惊厥和 SE 很有效,可是因对新生儿有致命性肝毒性的风险,所以使用时应极其小心(<10 岁儿童也一样),特别是当多次使用或有潜在先天性代谢紊乱时。

顽固性惊厥或 SE 的处理

当惊厥发作(有脑电图放电的临床发作)对 2 种足量 AEDs 无反应时,可定义为顽固性或难治性惊厥。进一步的处理需要高水平的药物和神经重症护理支持。惊厥持续时间越长,AEDs 效果就越差,苯二氮卓类研究最多。

确定惊厥是否癫痫性的非常重要,因此必须用 EEG 证实。另外,如前所述,还应排除代谢原因包括简单的电解质紊乱和遗传性代谢紊乱。需要做 MRI 以明确是否有脑发育异常或先天性代谢异常,而有前者并不排除后者的存在 。EEG 对很多紊乱包括非酮症高甘氨酸血症和 GLUT1 缺陷有诊断意义。

在加用第 3 种 AED 之前应该试用吡哆醇(最好是 PLP)。如果用了第 3 种 AEDs,惊厥依然顽固就应考虑输入咪达唑仑或利多卡因;如果依然顽固而病因不明,再用亚叶酸和生物素。先天性心脏病、心律不齐新生儿如果之前用了苯妥英,则禁忌使用利多卡因。在这种情况下连续监测 EEG 很有必要。对于有临床表现而无相关 EEG 异常的,我们不推荐使用咪达唑仑或利多卡因输入。

对那些停止神经重症监护惊厥复发的新生儿,或即使给予充分 2 剂 AEDs 并试用吡哆醇/PLP、亚叶酸和生物素后临床惊厥依然顽固的新生儿,假如确定排除了先天性代谢异常,那么应该考虑是否需要进行外科治疗。

没有临床表现的 EEG 发作的处理

EEG 发作是否对大脑有害尚有争议,关于这个问题仍缺乏共识。大部分观察是以新生儿 HIE 为研究对象的,而 HIE 的脑电图发作通常 72 h 内消失,从而难以判断治疗效果。

温度控制和体温过高

体温过高非常有害。目标腹部皮温应维持在 36.5 ℃ 。全身或局部(头部)低温治疗可能改善 HIE 患儿的预后。

后续治疗

典型 HIE 和颅内感染的惊厥几天内自动消失,症状缓解后,通常在出院前,即可停用 AEDs。对那些脑发育异常者因为复发的风险大,用药时间可以持续长些。对良性家族性癫痫综合征者,可以在 3 个月无惊厥发作后试停药;有些专家建议只要 EEG 提示癫痫样异常活动就应该继续治疗,两种意见均为经验性的。新生儿惊厥应该随访至儿童时期。

结语

鉴别癫痫与非癫痫性发作的困难使新生儿惊厥的临床处理复杂化,特别是当两种形式的发作同时存在时。必须用仔细的临床评估来指导治疗。常规 EEG,特别是视频 EEG 是处理新生儿惊厥的必要工具 。每个地区须根据新生惊厥的病因开发自己的资料库,从而制定预防策略和统一的处理方法。

(本文编辑:邓芳明)