Neonatal Seizures

Lena K. Hellström-Westas and Malcolm Levene

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Abstract

Neonatal seizures affect 1–3 infants per 1000 newborns in the general population. The incidence of neonatal seizures is higher in preterm infants than in term infants. The most common etiologies of neonatal seizures are perinatal hypoxic-ischemic and hemorrhagic insults, resulting in hypoxic-ischemic encephalopathy, stroke, and intracranial hemorrhages. Since most neonatal seizures occur as a result of perinatal insults, a majority of neonatal seizures emerge during the first 3 days of life. Infants with suspected seizures should be evaluated immediately. EEG and aEEG/EEG should be recorded early since several studies have shown that clinical recognition of neonatal seizures is not reliable. The prognosis is usually dependent on the underlying condition; the overall mortality is 10–30%, and 30–40% of survivors develop neurodevelopmental sequels with less than 20% developing postnatal epilepsy.

L. K. Hellström-Westas (✉)
Department of Women's and Children's Health, Uppsala University and University Hospital, Uppsala, Sweden
e-mail: lena.westas@kbh.uu.se

M. Levene
Academic Unit of Paediatrics and Child Health, University of Leeds, Leeds, UK

Department of Neonatal Medicine, Leeds Teaching Hospitals Trust, Leeds, UK

131.1 Salient Points

- Neonatal seizures are mainly due to previous hypoxic-ischemic, hemorrhagic, or metabolic insults, while seizures due to epileptic

syndromes and congenital conditions are rare in newborns.

- The most common causes of neonatal seizures are hypoxic-ischemic brain injury, intracranial hemorrhages, and stroke.
- Clinical recognition of neonatal seizures is unreliable since a majority of neonatal seizures are subclinical, or have only subtle clinical expression, and also since clinically observed seizure-suspected motor activity may not have an epileptic origin.
- EEG or aEEG/EEG is necessary for correct identification of neonatal seizures and is associated with earlier detection of seizures, more precise treatment of seizures, and less use of antiepileptic medications.
- Clinically important questions that need to be addressed include: Do all neonatal seizures require antiepileptic treatment? Is antiepileptic treatment associated with less brain injury and better outcome? Which medications should be used? For how long should antiepileptic treatment be administered?

131.2 Incidence

Neonatal seizures affect 1–3 infants per 1000 newborns in the general population (Ronen et al. 1999; Sheth et al. 1999). The incidence in different populations varies according to differences in diagnostic criteria (clinical seizures or EEG required for diagnosis) and the studied time period, but may also be associated with differences in maternal characteristics (parity, smoking, obesity), living conditions, and standard of perinatal care. The incidence of neonatal seizures is higher in preterm infants than in term infants (Ronen et al. 1999; Sheth et al. 1999; Scher et al. 1993). Seizures are more prevalent in high-risk populations such as infants requiring neonatal intensive care (NICU); older studies indicate that 3–5% of infants may be affected but the exact numbers are difficult to establish (Scher et al. 1993; Hellström-Westas et al. 1995). Recent studies indicate that the seizure incidence may be quite high in extremely preterm infants and associated with intraventricular

hemorrhages and mortality (Vesoulis et al. 2014). A majority of these seizures are brief and subclinical and only possible to detect with EEG or aEEG/EEG.

The most common etiologies of neonatal seizures are perinatal hypoxic-ischemic and hemorrhagic insults, resulting in hypoxic-ischemic encephalopathy, stroke, and intracranial hemorrhages (Scher et al. 1993; Weeke et al. 2015; Glass et al. 2016). Other relatively common causes of seizures include infections and metabolic disturbances such as hypoglycemia and metabolic diseases. Seizures are prevalent in metabolic diseases, and intense seizures (mainly subclinical) can be seen in infants with disorders of energy metabolism, hyperammonemia, peroxisomal disorders, and organic/amino acidopathies (Olischar et al. 2012). Pyridoxine (vitamin B6) dependent seizures are rare but should always be considered in infants with therapy-resistant seizures. Hereditary familial seizures are caused by various mutations, including genes coding for voltage-gated sodium and potassium channels. They usually have a variable clinical course and outcome. So-called fifth day fits were previously described as being relatively prevalent but they are now rarely seen. Othahara syndrome, or early infantile epileptic encephalopathy (EIEE), and early myoclonic epileptic encephalopathy (EMEE) are severe conditions caused by a variety of disorders including cerebral malformations and various mutations. They are characterized by burst-suppression pattern in the EEG (constant in EIEE and during sleep in EMEE) and severe outcomes (Hart et al. 2015) (Table 1).

Since most neonatal seizures occur as a result of perinatal insults, a majority of neonatal seizures emerge during the first 3 days of life. This is a strong argument for using routine aEEG/EEG or EEG monitoring of high-risk infants during the first 3 days of life in order to enhance epileptic seizure detection and cerebral compromise in these infants. Only in moderately preterm infants, the peak of incidence is somewhat later, because seizures in these

Table 1 Etiologies of neonatal seizures (Ronen et al. 1999; Weeke et al. 2015; Glass et al. 2016; Tekgul et al. 2006; Yildiz et al. 2012)

Etiology	Prevalence (%)
Hypoxic-ischemic encephalopathy	29–46
Intracranial hemorrhage	12–18
Perinatal stroke	13–18
Infections, including sepsis	7–20
Metabolic, including hypoglycemia	9–19
Cerebral dysgenesis	3–5
Epileptic syndromes, other	1–2

infants are more often caused by infections (Sheth et al. 1999).

131.3 Diagnosing Seizures

Observation of clinically suspected seizures in newborn infants is the most common way of diagnosing neonatal seizures. Suspected clinical seizures in a newborn infant in the NICU, maternity unit, or at home, if the baby was already discharged from the hospital, should be given prompt attention. These infants should immediately be examined clinically: blood glucose should be checked, a decision should be taken whether antiepileptic treatment should be administered, and the baby should be referred to a NICU for further observation and evaluation (Table 2).

The first strategy should be to identify the potential etiology and to rule out disorders that could be treatable with a timely intervention, e.g., hypoglycemia, infection, and intracranial hemorrhages requiring surgery.

Clinical description of suspected neonatal seizures can give important clues to the etiology. Clinical seizures are clinically observed events suspected of being electroclinical seizures. Electroclinical seizures are clinical seizures with simultaneous epileptic activity in the EEG, while electrographical seizures denote presence of epileptic seizure activity in the EEG but no clinical symptoms (often called subclinical seizures).

Clinical seizures were traditionally classified by Volpe as subtle, clonic (focal or multifocal), tonic (focal or generalized), or myoclonic (focal,

Table 2 Suggested initial management of infants with suspected seizures

Prompt clinical evaluation should include perinatal medical history and physical examination.
Blood glucose should be checked immediately since hypoglycemia is a treatable condition.
A decision should be taken regarding administration of antiepileptic treatment.
Further observation and evaluation in a NICU should include a standard EEG or video EEG, continuous monitoring with aEEG/EEG, and cranial ultrasound.
Biochemical evaluation should include hemoglobin, blood gas, glucose, lactate, electrolytes (Na, K, Mg, Ca), bilirubin, CRP, white blood cell count, and platelets.
Decision should be taken on further investigations, e.g., lumbar puncture, MRI, other biochemical tests.

multifocal, or generalized) (Volpe 1989). More recently, Nagarajan et al. classified clinical features of electroclinical seizures (seizure semiology) with brief and for neonatologist's clinically very useful definitions as: (1) clonic (repetitive clonic jerking of the limbs, head, or trunk), (2) tonic (stiffening of limbs or trunk), (3) myoclonic (single jerk or slow serial jerking of the limbs, head, or trunk), (4) ocular (features around eyes, e. g., blinking, wide opening, eye deviation, nystagmus), (5) orolingual (mouthing/chewing type movements, tongue thrusting/ movements, crying/grimacing type of movements, noises/ vocalizations, dry retching), (6) autonomic (color change, change in breathing pattern, oxygen desaturation, apneas, blood pressure changes, changes in heart rate), (7) hypomotor (obvious decrease or cessation of behavioral activity, staring), and (8) other (Nagarajan et al. 2012).

Several studies have shown that clinical recognition of neonatal seizures is not reliable and that many clinically suspected seizures do not have corresponding EEG seizure activity. Furthermore, a majority of neonatal seizures are actually subclinical. Mizrahi and Kellaway demonstrated that some clinical seizure types are more closely associated with EEG seizures: focal clonic, generalized myoclonic, and focal tonic seizures, including tonic eye deviation. Other clinical seizures types were more inconsistently associated with electrographic seizure activity, including

generalized tonic and myoclonic seizures, motor automatisms including oral-buccal and ocular movements, progression movements including pedaling, stepping and rotatory arm movements (Mizrahi and Kellaway 1987). Term and preterm infant seem to exhibit similar types of clinical seizures, although subclinical seizures are more prevalent in preterm infants (Scher et al. 1993). In a video-EEG study of term asphyxiated infants less than 10% of all seizures were correctly identified by clinical observation in the NICU due to the fact that a majority of seizures were subclinical and many clinically suspected events could not be confirmed as seizures in the EEG (Murray et al. 2008).

Although some clinical manifestations of seizures are very typical for specific etiologies, e.g., unilateral clonic seizures in babies with stroke, many electroclinical seizures contain different clinical seizure types. Orolingual and autonomic symptoms are common at the onset of seizures, while ocular events more often appear during seizures (Nagarajan et al. 2012).

It has been suggested that clinical differentiation between epileptic and nonepileptic movements could be enhanced by applying mild restraint to the active limb or part of the body since nonepileptic movements are expected to stop. However, it may still be difficult to differentiate epileptic from nonepileptic movements clinically, and recording of EEG or aEEG/EEG is best way to increase the certainty of the epileptic nature of such movements.

In spite of the nonconsistent association between clinically suspected seizures and epileptic activity in the EEG, abnormal movements suspected to be clinical seizures are still conditions associated with increased risk for adverse outcome both in term and preterm infants (Davis et al. 2010; Glass et al. 2009). Seizure-suspected movements may be caused by immaturity, jitteriness, tremors, or other abnormal movements in compromised infants (Facini et al. 2016). Some of these infants (usually with severe cerebral compromise) may also display subcortical epileptic seizures that are not possible to recognize in the EEG or aEEG/EEG.

131.4 Treatment of Neonatal Seizures

Treatment of neonatal seizures is very much based on traditions and old studies assessing efficacy on clinical seizures. However, newer data demonstrates how administration of antiepileptic medications can abolish clinical seizures while electrographical (subclinical) seizures persist or even increase (Boylan et al. 2002). There is a lack of evidence as regards best treatment of neonatal studies, since only a few randomized studies compared antiepileptic medications while assessing electrographical seizures with EEG and none included structured follow-up and long-term outcome. Two small randomized studies evaluated whether the use of aEEG/EEG monitoring was associated with decreased seizure burden. In both studies, there was a decrease in seizure burden when using aEEG/EEG, but the differences were only border-line significant (Lawrence et al. 2009; van Rooij et al. 2010). One interesting observation in one of the studies was that there was a correlation between seizure burden and the severity of brain injury (scored by MRI); higher seizure burden was associated with more severe brain injury. This correlation was, however, not present in the group allocated to aEEG/EEG with the option of treating also electrographical seizures. The results indicate that treatment of subclinical seizures can limit brain injury in newborns. Other studies have demonstrated that use of EEG monitoring or aEEG/EEG is associated with more precise management, i.e., earlier identification of seizures which is associated with similar number or fewer administered antiepileptic drugs (Shellhaas and Barks 2012; Wietstock et al. 2015). Consequently, EEG monitoring or aEEG/EEG should be standard of care for infants with neonatal seizures. The benefits and limitations of aEEG/EEG as compared to standard EEG are discussed in ▶ Chap. 121, "Neonatal Electroencephalography".

Phenobarbital (or phenobarbitone) is the first drug of choice in many centers and countries, and bensodiazepines (diazepam, midazolam, clonazepam) are also commonly used. Lidocaine (or lignocaine) is frequently used in northern Europe, while phenytoin or fosphenytoin is

more commonly used in southern Europe, in the UK, and the USA as presented in a number of surveys on treatment strategies. Phenobarbital and fenytoin seem to be equally efficient as first-line medications and abolish seizures in around 45% of term infants receiving these drugs, when adding the two drugs efficacy is seen in around 60% of infants (Painter et al. 1999). There are only observational studies regarding the efficacy of bensodiazepines (e.g., diazepam, lidocaine, clonazepam). Care should be taken when administering bensodiazepines to preterm infants, since these drugs may cause arterial hypotension. The GABA receptor is excitatory in early life and seizure-like events have been observed after midazolam although even more worrying is recent data indicating abnormal hippocampal growth and neurodevelopmental outcome in preterm infants related to midazolam (Duerden et al. 2016).

Lidocaine was previously considered an efficient second-line medication after phenobarbital (lidocaine should not be combined with phenytoin or fosphenytoin), but a large evaluation demonstrated that it was actually only efficient as a third-line drug after administration of phenobarbital and bensodiazepines (Weeke et al. 2016). Levetiracetam is a drug that has gained increased use in many countries, but so far there are no randomized trials published on this drug. Topiramate is another promising drug that has been used off-label, but so far no controlled neonatal studies have been conducted (Glass et al. 2011). When neonatal seizures become difficult to treat, it is usually advisable to consult with neurologists, both for evaluation of the potential etiology of the seizures and for more effective management. The possibility of pyridoxine-dependent seizures should always be considered. Administration of pyridoxine should be done when the infant is monitored with EEG or aEEG/EEG and when the infant is in the NICU, since hypotone reactions with EEG depression and apnea have occurred in pyridoxine-dependent infants after administration of pyridoxine (Hellström-Westas et al. 2002). Table 3

Table 3 Commonly used antiepileptic medications

Drug	Loading dose	Maintenance
Phenobarbital	20–40 mg/kg in 20 min i.v.	5 mg/kg/day (target level: 40–60 µg/mL)
Midazolam	0.05 mg/kg in 10 min i.v.	0.15 mg/kg/h (max. dose: 0.5 mg/kg/h)
Lorazepam	0.05–0.1 mg/kg i.v.	
Clonazepam	0.01 mg/kg i.v.	0.1–0.5 mg/kg per 24 h
Phenytoin/fosphenytoin	20 mg/kg in 30 min i.v.	5 mg/kg/day (target level: 10–20 µg/mL)
Lidocaine[a]	2 mg/kg in 10 min i.v.	Body weight 2.5–4.5 kg: 7 mg/kg/h for 4 h (3.5 h during hypothermia) 3.5 mg/kg/h for 12 h 1.75 mg/kg/h for 12 h
Pyridoxine	100 mg i.v.	

[a]Lidocaine should not be combined with phenytoin/fosphenytoin. Please note that lidocaine metabolism is affected by hypothermia treatment and that the initial dosage reduction should be faster than in non-cooled babies. For dosage recommendations of infants below 2.5 kg, please see van Rooij et al. (2013)

summarizes suggested doses of some commonly used antiepileptic medications (van Rooij et al. 2013; Painter et al. 1999).

131.5 Prophylactic Treatment

Prophylactic long-term antiepileptic treatment is frequently administered to infants with neonatal seizures. A recent meta-analysis included data from more than 4538 children in 44 studies and demonstrated that the average risk of epilepsy after neonatal seizures was 17.9% (Pisani et al. 2015). Of the children developing epilepsy, 68.5% had seizure recurrence during the first year of life and 80.7% had neurological impairments (Pisani et al. 2015). There is little data to guide which infants could benefit from prophylactic treatment. In a NICU cohort of infants, in which aEEG/EEG and EEG was used for diagnosis and treatment of neonatal seizures, antiepileptic treatment was discontinued after a

median of 4.5 days. Recurrence rate during the first year of life was 8.3% and two of the three children developing epilepsy were already receiving prophylactic phenobarbital due to recurring neonatal seizures and persisting abnormalities in the EEG (Hellström-Westas et al. 1995).

131.6 Prognosis

The overall mortality in infants with neonatal seizures is around 10–30%, but the prognosis is usually dependent on the underlying condition (Ronen et al. 1999; Sheth et al. 1999; Scher et al. 1993; Weeke et al. 2015; Glass et al. 2016; Tekgul et al. 2006; Yildiz et al. 2012; van Rooij et al. 2013). Neurodevelopmental sequels develop in 30–40% of survivors, while less than 20% develop postnatal epilepsy.

131.7 Conclusion

There are many unsolved question as regards optimal management of neonatal seizures. Clinically important questions that need to be addressed in the future include: Do all neonatal seizures require antiepileptic treatment? Is antiepileptic treatment associated with less brain injury and better outcome? Which medications should be used? For how long should antiepileptic treatment be administered?

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