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Treatment of neonatal seizures

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SUMMARY

Seizures occur more often during the neonatal period than at any other period of life. Precise incidence is difficult to delineate and depends on study population and criteria used for diagnosis of seizures. Controversy exists as to whether neonatal seizures themselves cause damage to the developing brain, or if the damage is primarily due to the underlying cause of the seizures. As a result of this controversy there is an ongoing discussion as to whether all seizures (both clinical and subclinical) should be treated. When (sub)clinical seizures are treated, there is no consensus about the most appropriate treatment for neonatal seizures and how to assess the efficacy of treatment. Current therapeutic options to treat neonatal seizures (i.e. primarily first generation antiepileptics) are relatively ineffective. There is an urgent need for prospective, randomized, controlled trials for efficacy and safety of these second-generation antiepileptic drugs in neonates. The aim of this review is to survey current knowledge regarding treatment of neonatal seizures in both term and preterm infants.

1. Introduction

Seizures occur more often during the neonatal period than at any other time during life.[1] The most common aetiology of neonatal seizures is hypoxic–ischemic encephalopathy (HIE) due to perinatal asphyxia. In a population-based study by Ronen et al.,[2] 42% of neonatal seizures were seen following HIE. Other important causes of seizures include intracranial haemorrhage and stroke, infections of the central nervous system, congenital malformations, inborn errors of metabolism, transient metabolic disturbances, maternal drug abuse and rare neonatal epilepsy syndromes (benign familial neonatal–infantile seizures or fifth-day seizures).[1,2] When seizures persist in spite of administration of different antiepileptic drugs (AEDs) one should always consider pyridoxine-dependent epilepsy (PDE) or pyridoxine phosphate oxidase deficiency (PNPO) as possible causes, and a therapeutic trial with oral pyridoxal 5′-phosphate in addition to pyridoxine should be given.[3,4]

1.1. Incidence

The precise incidence of neonatal seizures is difficult to delineate and depends on the population studied and criteria used for diagnosis of seizures. In studies from the USA, an incidence of 0.15–3.5 per 1000 live births has been reported, with higher rates in preterm infants.[2,5,6] Clinical recognition of seizures in newborns is not always straightforward because of a highly variable clinical expression and the prevalence will consequently be highest in populations including infants monitored with continuous electroencephalogram (EEG) or amplitude-integrated (a)EEG.[1,7,8]

The use of continuous aEEG with limited-channel EEG (aEEG/EEG) and EEG monitoring in the neonatal intensive care unit (NICU) is increasing worldwide. This was recently evaluated by Boylan et al. analysing 210 surveys (124 from Europe, 54 from the USA and the remainder were from Australia, New Zealand, Africa and the United Arab Emirates).[9] They showed that 90% of the respondents had access either to EEG or to aEEG/EEG monitoring, and 51% used both aEEG/EEG and EEG. The EEG was mainly interpreted by neurophysiologists (72%), whereas aEEG/EEG was usually interpreted by neonatologists (80%). However, as many as 31% of the respondents reported that they did not feel confident in their ability to interpret the aEEG/EEG, pointing out the needs for continuing education and close collaboration with neurologists and neurophysiologists. Shellhaas et al. investigated the clinical consequences of using aEEG monitoring in infants with suspected seizures.[10] In the group of infants where aEEG was used, the time to seizure diagnosis was significantly reduced and the rate of infants with a seizure diagnosis without electrographic confirmation of seizures was also significantly reduced, but there was no difference in the number of AEDs used or number of neuroimaging studies.

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1.2. Diagnosis

In the past few decades the technology to diagnose neonatal seizures has greatly improved. Advanced techniques with continuous (video) EEG and simplified technique with aEEG allows clinicians to detect more seizures at the bedside. As a result of the improvement in monitoring, it is known that a substantial part of electrographic neonatal seizure patterns are not accompanied by clinical signs (subclinical) especially following administration of AEDs.[7,8,11,12] This so-called 'uncoupling' or 'electroclinical dissociation' has recently been reported by several groups and was found in 50–60% of the children studied.[8,11] The accuracy of seizure detection is of great importance as more evidence has become available from animal studies that seizures may impair brain development and lead to long-term deficits in learning, memory and behaviour.[13] Although data in humans are scarce, recent studies suggest an adverse effect of both clinical and subclinical neonatal seizures on neurodevelopmental outcome. Neonatal seizures have been reported to predispose to later problems with regard to cognition, behaviour and development of postneonatal epilepsy (PNE).[14,15] Observational and randomized studies suggest that rapid, protocol-driven treatment leads to a reduction in seizure burden.[16–18]

Hypothermia has recently become a standard treatment for full-term infants with moderate–severe HIE and has been shown to improve outcome.[19,20] However, data regarding seizure occurrence during therapeutic hypothermia are still limited. Wusthoff et al. reported an incidence of 65%, with 46% of the infants having subclinical seizures.[21] They also found that the range of time to seizure onset was wide. A recent study by Glass et al.[22] reported an incidence of 30% and several AEDs were required to control the seizures. Low et al. reported a decreased seizure burden in neonates with moderate HIE who received hypothermia treatment [non-cooled: 162 (97–262) vs cooled: 49 (26–89) min; $P = 0.02$].[23]

All these factors have contributed to an increasing interest in the management and treatment of neonatal seizures. In the literature there is no consensus on whether all seizures (both clinical and subclinical) should be treated. And when (sub)clinical seizures are treated, there is no consensus about the most appropriate treatment for neonatal seizures and how to best assess the efficacy of treatment.

This review focuses on treatment of neonatal seizures in both term and preterm infants with the most frequently used AEDs (phenobarbital, midazolam, lorazepam, clonazepam, phenytoin and lidocaine).

2. Treatment of neonatal seizures

As a consequence of the growing body of evidence that neonatal seizures per se contribute to adverse neurodevelopmental outcome, clinicians are more focused on the diagnosis and treatment of neonatal seizures.[24] However, the most important questions that still need to be answered are the following: which drugs should we use and how aggressively and for how long should we treat neonatal seizures?

Unfortunately, data from randomized controlled trials to support the choice of AEDs are limited, and no definite recommendations based on available data can be made.[25] A 2004 Cochrane report concluded that there was little evidence to support the use of any AED currently used in the neonatal period.[26] First-generation AEDs, such as phenobarbital and phenytoin, are still the drugs of first (and second/third) choice because of extensive clinical experience, despite their limited clinical effectiveness and potential neurotoxicity.[27,28] Table 1 outlines the commonly used drugs for the treatment of neonatal seizures.

Table 1
Frequently used drugs for treatment of neonatal seizures.

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	0.1–0.5 mg/kg per 24 h
Phenytoin/ phosphenytoin	20 mg/kg in 30 min i.v.	5 mg/kg/day (target level: 10–20 μg/mL)

i.v., intravenous.

Traditional mechanisms of first-generation AEDs comprise an inhibitory effect on the glutamatergic pathway, enhanced gamma-aminobutyric acid (GABA) inhibition or an influence on neuronal ion homeostasis. However, in the developing brain neuronal apoptosis can be triggered by blockade of *N*-methyl-D-aspartate receptors or (excessive) activation of $GABA_A$-receptors. First generation AEDs, such as phenobarbital and benzodiazepines, exert their effect by stimulation of GABA. Bittigau et al. showed that these AEDs may cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans.[27,29,30]

2.1. Phenobarbital

In practice phenobarbital remains the drug of first choice for confirmed or suspected seizures.[31–33] The choice of phenobarbital can be explained by its safety profile, although there is evidence that phenobarbital itself may impair neurodevelopmental outcome and increase neuronal apoptosis.[27,34] Nevertheless, there are limited studies that demonstrate good efficacy of phenobarbital. Seizure response rates after a loading dose of 15–20 mg/kg are reported to range from 33% to 40%. With rapid sequential loading doses, up to a total dose of 40 mg/kg, the responsiveness could be improved to 77%.[35–37]

Painter et al. reported the effect of phenobarbital compared to phenytoin in a randomized crossover study.[28] In 43% of the phenobarbital-treated group, seizures were controlled compared to 45% in the phenytoin-treated group. Addition of the other drug, when seizures were not controlled with the first drug, did not significantly improve seizure control. A non-randomized study by Castro Conde et al.[38] showed that, of 45 neonates with aEEG-confirmed seizures, seizures persisted in 53% of the neonates who received phenobarbital/phenytoin. In a small randomized controlled study by Boylan et al.,[39] 11 of 22 neonates responded to phenobarbital in a dose of 40 mg/kg as a first-line AED.

It has been suggested that early posthypoxia–ischemia administration of phenobarbital may augment the neuroprotective efficacy of therapeutic hypothermia in a neonatal rodent model.[40] Studies in newborn infants are scarce. Van den Broek et al.[41] studied the pharmacokinetics and pharmacodynamics of phenobarbital during hypothermia. The observed responsiveness was 66%, and, as the plasma concentrations were <20 mg/L in 69% of the infants, they recommended the administration of an additional dose after the first 20 mg/kg before switching to a second AED. Based on their pharmacokinetic/dynamic model, administration of phenobarbital under hypothermia seems to reduce the transition rate from a continuous normal voltage (CNV) pattern to discontinuous normal voltage aEEG background level in hypothermic asphyxiated newborns, which may be attributed to an additional neuroprotective effect of phenobarbital in infants with a CNV pattern. A retrospective analysis by Meyn et al.[42] showed no reduction in neurodevelopmental impairment in the group of infants who

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received prophylactic phenobarbital (40 mg/kg) at the time when cooling was initiated. In the cooled infants who received prophylactic phenobarbital fewer clinical seizures were seen.

Sarkar et al.[43] found that phenobarbital treatment (prophylactically or for clinical seizures) before the start of hypothermia treatment, did not improve composite outcome of neonatal death or the presence of abnormalities on a neonatal magnetic resonance imaging (MRI). Long-term outcomes of this group have not yet been evaluated.

2.2. Midazolam

Midazolam has also been used for (phenobarbital) refractory seizures with an efficacy reported from zero to 100% with two studies reporting responses of respectively 67% and 80%.[38,39,44–46]

In a non-randomized study by Castro et al.,[38] all seizures were rapidly controlled with midazolam in 13 non-responders to phenobarbital/phenytoin. In the three other studies midazolam was compared to lidocaine as a second-line anticonvulsive drug. In a small randomized trial Boylan et al.[39] showed that none of the six neonates treated with midazolam as a second-line drug responded. In a study by Shany et al.[44] four of the eight neonates treated with midazolam showed a partial response. Sirsi et al.[46] reported three neonates with a status epilepticus due to different aetiologies. Seizures in all three neonates did not respond to phenobarbital and phenytoin but responded to a midazolam infusion. The dosing regimen of midazolam is a loading dose of 0.05 mg/kg for 10 min followed by a maintenance dose of 0.15–0.5 mg/kg/h with increased dosing in steps of 0.05 mg/kg/h.

2.3. Lidocaine

Although not widely used, several (small) studies indicate that lidocaine is an effective drug for refractory seizures as second- or third-line treatment (Fig. 1). The response rate varies from 70% to 92%.[39,44,45,47–50] In a small RCT by Boylan et al. three of five infants

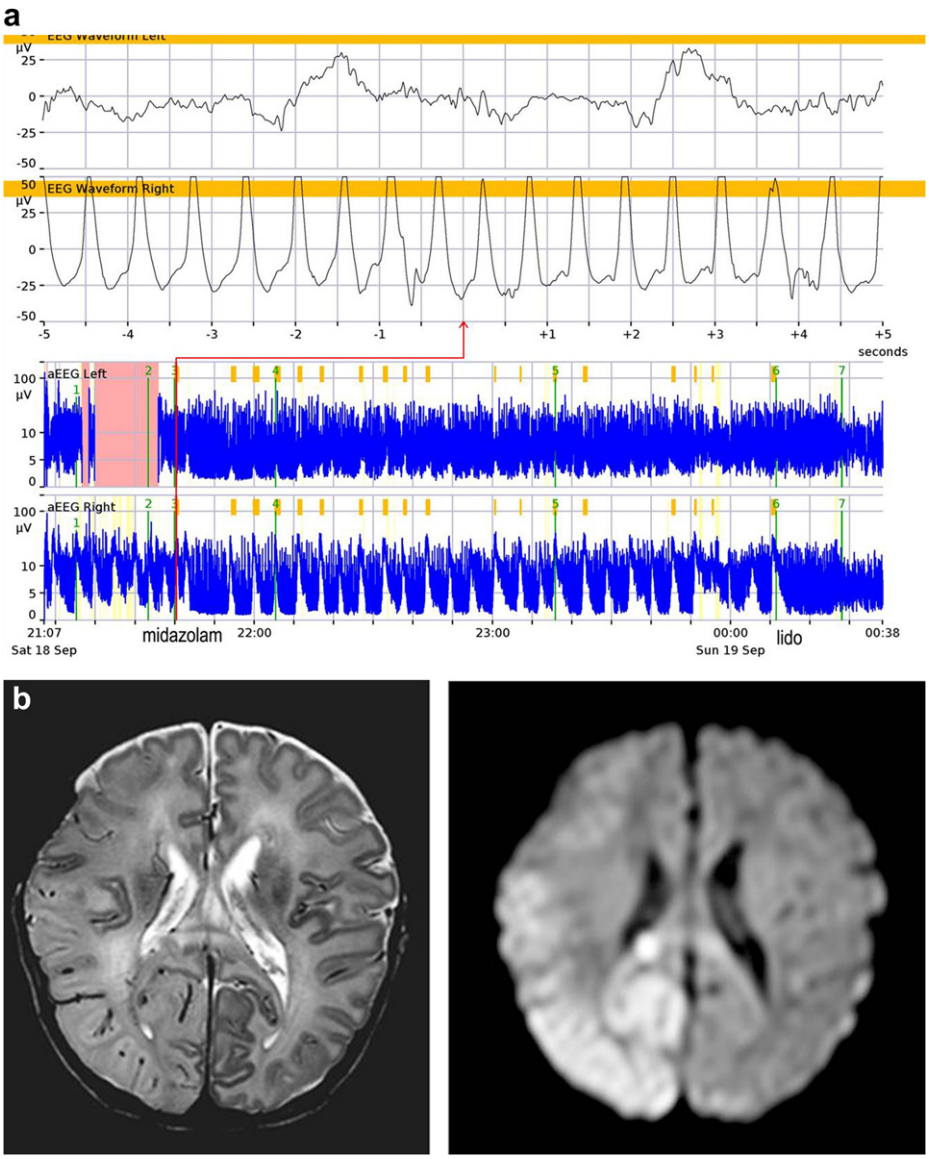

Fig. 1. (a) Full-term patient with hemiconvulsions. On amplitude-integrated electroencephalogram right-sided seizures were seen. Phenobarbitone was already given in the referral hospital. Midazolam was not effective and after administration of lidocaine seizure discharges stopped. (b) Magnetic resonance imaging on day 5 shows a predominant posterior stroke associated with more extensive diffusion changes of the cortex in the right hemisphere.

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responded to lidocaine as a second line drug after phenobarbital.[39] The study by Shany et al.[44] reported a good or partial response to lidocaine in seventeen (77%) of the 22 infants who received lidocaine after phenobarbital.

Concerns about cardiac toxicity of lidocaine have limited the widespread use of this agent.[51] In the past we found an incidence of 4.8% of cardiac arrhythmias during continuous lidocaine infusion.[52] The introduction of a new dosing regimen and the recommendation to give lidocaine only in a NICU setting under continuous cardiac monitoring should reduce this potential risk. Lidocaine should be discontinued immediately when an arrhythmia occurs and lidocaine should preferably not be given to neonates with congenital heart disease nor to infants who have already received phenytoin.[48,53]

Lidocaine dosing should also be adjusted during therapeutic hypothermia. Lowered body temperature may alter pharmacokinetic and pharmacodynamic profiles may increase the risk of (cardiac) toxicity due to decreased lidocaine clearance.[54] Table 2 gives the advised dosing regimen for lidocaine.

Unfortunately first-generation AEDs (or a combination thereof) are not always effective enough for seizure control in neonates with repetitive seizures. A recent survey among 55 pediatric neurologists in the USA found that 73% (40/55) recommended treatment of neonatal seizures with one or both of levetiracetam and topiramate; 47% (26/55) recommended levetiracetam; and 55% (30/55) recommended topiramate, despite an absence of data on neonatal pharmacokinetics of either drug.[13]

Recent non-randomized studies have reported levetiracetam to be an effective and well-tolerated adjunctive antiepileptic agent for seizure control in neonates and infants.[55–57]

Besides the discussion about which AEDs to use in neonates, it is also important to question how aggressively we should treat neonatal seizures, i.e. should we try to eradicate all electrographic seizures or can we allow some seizure activity to persist? Although no study has been able to prove that aggressive therapy for neonatal seizures will improve outcome, there are several studies suggesting that ongoing seizures may exacerbate brain injury, especially in hypoxic–ischemic encephalopathy.[15,58–60] Previous studies have shown that infants treated for clinical and subclinical seizures have a lower incidence of post-neonatal epilepsy compared to those who underwent treatment only for EEG-confirmed clinical seizures.[58,61–64]

In a study by Miller et al.[15] of term newborns with HIE, brain injury was independently associated with the severity of seizures. They performed MRI and proton magnetic resonance spectroscopy in 90 full-term infants. Thirty-three infants (37%) developed EEG-confirmed seizures, and these seizures were scored according to frequency and severity, EEG findings and AED use. Multivariate linear regression tested the independent association of seizure severity with impaired cerebral metabolism measured by lactate/choline and compromised neuronal integrity measured by *N*-acetylaspartate/choline in the basal nuclei and the intervascular boundary zones. Seizure severity was associated with increased lactate/choline in both the intervascular boundary zone ($P < 0.001$) and the basal nuclei ($P < 0.011$) when controlling for potential confounders of MRI abnormalities and amount of resuscitation at birth. Seizure severity was independently associated with diminished *N*-acetylaspartate/choline in the intervascular boundary zone ($P < 0.034$).

The same group was recently able to show an independent effect of clinical neonatal seizures and their treatment on neurodevelopment in 77 children who were born at term and were at risk for hypoxic–ischemic brain injury, and who all had brain MRI in the newborn period.[65] About one-third of the children (25/77) had clinically detected neonatal seizures. Neonatal MRIs were classified for anatomic distribution and severity of acute injury. The severity of brain injury was assessed using high-resolution newborn MRI and outcome was assessed at age 4 years, using the Full-Scale Intelligence Quotient (FSIQ) of the Wechsler Preschool and Primary Scale of Intelligence—Revised as well as a neuromotor score. After controlling for severity of injury on MRI, the children with neonatal seizures had worse motor and cognitive outcomes compared with those without seizures. The children with severe seizures had a lower FSIQ than those with mild–moderate seizures ($P < 0.0001$). The major limitation of these two important studies is the reliance on clinical evaluation for seizure diagnosis and severity.

A pilot study by Lawrence et al.[16] also showed that continuous monitoring for seizures and treatment of electrographic seizures was associated with a trend toward reduced seizure burden.

In a unique randomized controlled trial of seizure treatment in term infants with moderate–severe HIE, a trend was found for shorter duration of seizure discharges in the group of infants treated for both clinical and subclinical seizures seen on aEEG, compared with the group of infants where only clinical seizures were treated.[18] This difference was not significant, most likely due to the small number of infants in both study arms (19 vs 14 infants). In this study a significant correlation was found between the duration of seizure patterns and the severity of brain injury in the whole group and in the group of infants only treated for clinical seizures. No significant differences were noted in the number of infants who died (6/19 vs 7/18). The number of infants who survived and were assessed with the Bayley Scales of Infant Development (BSID-II) at 2 years of age was small. In the group where both clinical and subclinical seizures were treated, more infants survived with severe disability or post neonatal epilepsy. There was also a trend in longer duration of seizure discharges in the infants with an unfavourable outcome. It was of interest that three of the four infants with PNE had extended duration of seizure discharges, and, although they were in the arm for treating clinical and subclinical seizures, treatment in these infants was not appropriate and

Table 2
Lidocaine dosing regime for preterm and term infants.

Lidocaine (i.v.)	Body weight	Initial bolus	Infusion	First dose reduction	Second dose reduction
During normothermia (ref.)	0.8–2.0 kg	2 mg/kg in 10 min	5 mg/kg/h during 4 h	2.5 mg/kg/h (4–10 h)	1.25 mg/kg/h (10–22 h)
	2.0–2.5 kg	2 mg/kg in 10 min	6 mg/kg/h during 4 h	3.0 mg/kg/h (4–16 h)	1.50 mg/kg/h (16–28 h)
	2.6–4.5 kg	2 mg/kg in 10 min	7 mg/kg/h during 4 h	3.5 mg/kg/h (4–16 h)	1.75 mg/kg/h (16–28 h)
During therapeutic hypothermia (ref.)	2.0–2.5 kg	2 mg/kg in 10 min	6 mg/kg/h during 3.5 h	3 mg/kg/h (3.5–15.5 h)	1.5 mg/kg/h (15.5–27.5 h)
	2.5–4.5 kg	2 mg/kg in 10 min	7 mg/kg/h during 3.5 h	3.5 mg/kg/h (3.5–15.5 h)	1.75 mg/kg/h (15.5–27.5 h)

Source: Van den Broek MP, Rademaker CM, van Straaten HL, et al. Anticonvulsant treatment of asphyxiated newborns under hypothermia with lidocaine: efficacy, safety and dosing. *Arch Dis Child Fetal Neonatal Ed* (in press).

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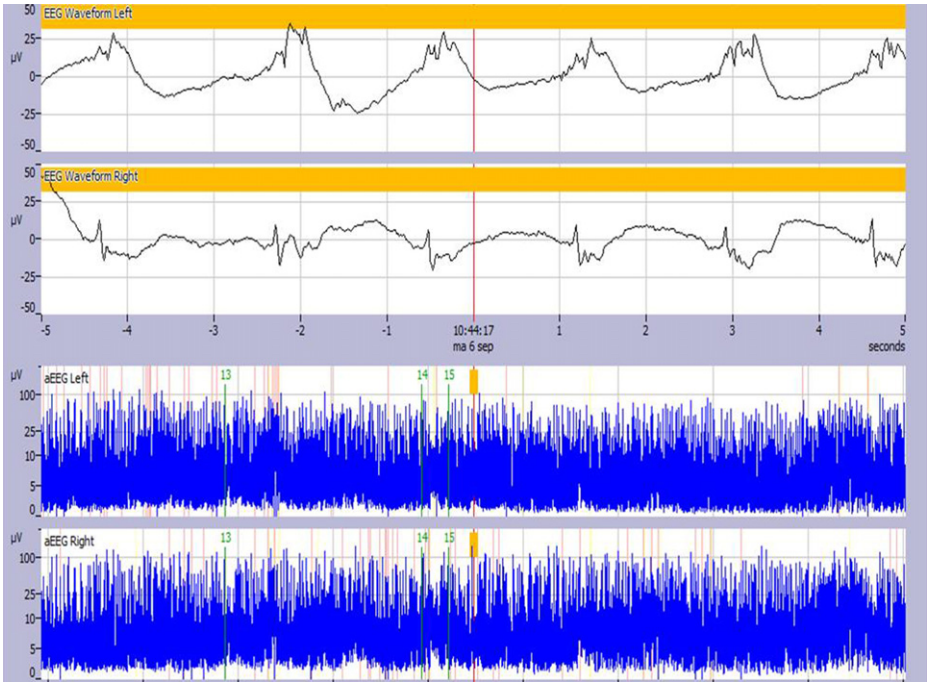

Fig. 2. Gestational age 24 weeks. On ultrasound a small intraventricular haemorrhage was seen. Seizure detection was seen (orange marker). On amplitude-integrated electroencephalogram (aEEG) no clear seizures were seen, but the raw EEG shows seizure discharges.

subclinical seizures were not treated within the proposed 2 h window. (unpublished data). A similar randomized controlled trial is enrolling newborn infants in Australia at present [Neonatal ECMO Study of Temperature (NEST)].

Another important question is for how long should neonatal seizures be treated and is treatment after the neonatal period warranted? No randomized controlled trials addressing this subject have been performed, so no evidence-based recommendation can be made. Several surveys have tried to find out what is common practice.[24,51,66,67] It is of interest that there is a striking difference between neonatologists and neurologists. Fewer neurologists recommended continuous monitoring. Neurologists tend to recommended longer treatment for seizures following perinatal asphyxia or haemorrhage. Furthermore there are some differences in the choice of AEDs, with more off-label drugs used by neurologists. Changes of attitude regarding the duration of seizure treatment have become evident. Regarding the potentially toxic effect of AEDs on brain development and the knowledge that neonatal seizures are often controlled within a few days after start of medication warrant a shorter duration of treatment.

2.4. Treatment of neonatal seizures in the preterm infant

Seizures are more common in preterm infants; the incidence increases with decreasing gestational age.[2] The proportion of preterm infants with EEG-verified seizures is probably lower than in term infants, although there are few data to support this assumption. It was recently shown that clinical events that were diagnosed as seizures were independently associated with a worse neurodevelopmental outcome in a large cohort of very low birth weight infants.[68] In this study, only 22% of the infants had EEG-confirmed seizures. Epileptic seizure activity in preterm infants can be identified in a similar way to full-term infants, i.e. by conventional EEG, by aEEG/EEG or by (video) EEG monitoring. Epileptic seizure activity, often without clinical symptoms, is very frequent in the aEEG/EEG of preterm infants during development of intracerebral haemorrhages.[2,69–71]

Identifying seizure activity in the aEEG/EEG in infants with a discontinuous background pattern can be a challenge. Furthermore, seizures in extremely preterm infants may be of very low frequency. Since the aEEG method filters out most of the slow activity (<2 Hz) in the EEG, these seizures may be missed in the aEEG trend. Consequently, access to and evaluation of the raw EEG trace on the digital aEEG devices, as well as a seizure detection algorithm, are often required to recognize these seizures (Fig. 2).

Treatment of seizures in preterm infants poses special considerations, not least since these infants may be more sensitive to side-effects of AEDs, e.g. hypotension and sedation. To the best of our knowledge, there are no randomized controlled studies investigating antiepileptic treatments specifically in preterm infants neither with regard to efficacy of the drugs nor with regard to treatment in relation to long-term outcomes. In a recent international survey, a majority of the respondents would administer phenobarbital as the first drug of choice, i.e. the same first-line drug as in full-term infants.[24] It is well known that early in development the GABA-receptor may be excitatory, and myoclonic events have been described after administration of, for example, midazolam in preterm infants. However, whether the myoclonus represented electrographic seizure activity, or not, is unknown.

3. Conclusion

Neonatal seizures in the neonatal period are a widespread problem. During the last decade a lot of attention has been given to improve recognition of neonatal seizures. Continuous monitoring with two-channel rather than single-channel aEEG and also continuous (video) EEG are increasingly being used as standard of care in infants at risk of developing seizures. Regarding treatment of neonatal seizures, there are many questions remaining unanswered. As there are no evidence-based answers for any of these questions, it is not possible to produce an

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evidence-based protocol on which AEDs neonatal seizures should be treated, nor how aggressively or for how long to treat. One can recognize changes in attitude regarding treatment of both clinical and subclinical seizures, as well as shorter duration of AED use. Furthermore some AEDs with a wide acceptance in adult and paediatric neurology practice are being used to treat neonatal seizures. New randomized controlled trials are needed to establish protocols for: diagnosis of neonatal seizures, efficacy and safety of new generation AEDs and to determine optimal duration of drug administration.

Practice points

- Neonatal seizures are a common problem in the neonatal period.
- Recognition of neonatal seizures has improved during the last decade.
- There are no evidence-based guidelines regarding treatment of neonatal seizures.

Research directions

- To study the efficacy and safety of new generation AEDs.
- To determine optimal duration of drug administration for neonatal seizures.

Conflict of interest statement

None declared.

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