

Postneonatal Epilepsy Following Amplitude-Integrated EEG-Detected Neonatal Seizures

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To assess the incidence of postneonatal epilepsy in term infants treated with antiepileptic drugs for neonatal seizure discharges that were detected with amplitude-integrated electroencephalography (aEEG), 206 term infants were monitored using this modality. They received anti-epileptic drugs for clinical as well as subclinical neonatal seizures. Follow-up data were analyzed for the development of postneonatal epilepsy and for their neurodevelopmental outcome, assessed at 3, 9, 18 months, and 3 and 5 years of age. A total of 169 (82%) neonates received two or more antiepileptic drugs. Overall mortality was 39% (n = 80). Forty-one of the 126 survivors (33%) were abnormal at follow-up, and 12 of them developed postneonatal epilepsy (9.4%). Eighty-four children survived after hypoxic-ischemic encephalopathy grade II (n = 92), and 6 (7%) developed postneonatal epilepsy. In this subgroup, no postneonatal epilepsy was observed if seizures were controlled within 48 hours after birth and when not more than two antiepileptic drugs were required. Twenty-four children survived after an intracranial hemorrhage (n = 28), and only 1 (4%) developed postneonatal epilepsy. Eleven children survived after perinatal arterial stroke (n = 13), and 2 (18%) developed postneonatal epilepsy. In conclusion, the incidence of postneonatal epilepsy after treatment of clinical and subclinical neonatal seizures detected with continuous amplitude-integrated electroencephalography was 9.4%; This figure is lower than previously reported in children who only received treatment for clinical seizures. © 2005 by Elsevier Inc. All rights reserved.

Toet M, Groenendaal F, Osredkar D, vanHuffelen A, deVries L. Postneonatal Epilepsy Following Amplitude-Integrated EEG-Detected Neonatal Seizures. *Pediatr Neurol* 2005;32: 241-247.

Introduction

The incidence of neonatal seizures is 3.5/1000 live births [1]. Hypoxic-ischemic brain injury is the most common cause of seizures in the neonatal period. Clinical manifestations of neonatal convulsions are diverse and not always easy to recognize, especially when they are subtle. Continuous electroencephalographic monitoring often reveals electroclinical dissociation (seizure discharges without clinical manifestations), especially after initiation of therapy for clinical seizures [2,3]. Without the use of continuous monitoring, subclinical seizure discharges will not be detected. Thus far there is no agreement whether these subclinical seizure discharges should be treated, although some studies suggest an adverse effect on neurodevelopmental outcome [4,5]. Recent findings in animal studies indicate adverse effect of neonatal seizures as well as antiepileptic drugs on the brain [6-10].

The incidence of postneonatal epilepsy after neonatal seizures reported in the literature is approximately 20-50% [11]. These data are either based on overt clinical seizures subsequently confirmed by electroencephalography, or more often on the clinical diagnosis of seizures. Brunquell et al. [12] reported 21% postneonatal epilepsy among 77 survivors with a significantly higher prevalence of postneonatal epilepsy in those with subtle and generalized tonic seizures. In another study using continuous amplitude-integrated electroencephalography (aEEG) monitoring, both clinical and subclinical neonatal seizure discharges were treated. In that study, subsequent postneonatal epilepsy was present in only 8.3% of the children [13]. This cohort consisted of both preterm and term infants. The incidence of postneonatal epilepsy will depend both on the maturity of the infant and on the underlying etiology.

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Received August 4, 2004; accepted November 8, 2004.

Single-channel aEEG is increasingly being used in neonatal intensive care units, and it has been demonstrated that aEEG has a high concordance with multichannel standard electroencephalography [14].

The aim of this study was to determine the occurrence of postneonatal epilepsy in a group of term infants with neonatal seizures and to assess whether postneonatal epilepsy was related to the duration of seizures, number of antiepileptic drugs, and adverse outcome. We hypothesized that continuous aEEG monitoring and early treatment of clinical and subclinical seizures would reduce the occurrence of postneonatal epilepsy.

Patients and Methods

Between June 1992 and December 2002, all newborn infants who were admitted to our regional tertiary neonatal intensive care unit because of suspected seizures or moderate to severe hypoxic-ischemic encephalopathy were monitored using aEEG as part of routine care. Neonatal aEEG recordings and follow-up data of all infants with a gestational age of ≥ 37 weeks, who developed seizure discharges, were analyzed in this retrospective study. Neonates with infections of the central nervous system, congenital abnormalities, chromosomal disorders, or longstanding hypoglycemia were excluded. Informed parental consent for the study was obtained in all infants.

Immediately after admission, aEEG recording was initiated by the attending neonatologist. The aEEG recording was continued for a minimum duration of 48 hours or longer until normalization of the background pattern was observed and until antiepileptic drug therapy was discontinued, usually after 3 to 5 days. A standard 16-channel neonatal electroencephalogram was obtained during office hours as soon as possible after admission. If clinical seizures were observed or seizure discharges were recognized on the aEEG recording, antiepileptic drugs were administered. Thus both clinical and subclinical seizures were treated. Before 1998, a regimen of phenobarbital, phenytoin, clonazepam, and lidocaine (as a rescue drug) was used. After 1998 this regimen was changed into phenobarbital, lidocaine, and/or midazolam, and sometimes clonazepam as a fourth-line antiepileptic drug.

Hypoxic-ischemic encephalopathy was classified as mild (grade I), moderate (grade II), and severe (grade III) according to the criteria of Sarnat and Sarnat [15].

Amplitude-Integrated Electroencephalography

For aEEG recording, the Cerebral Function Monitor (CFM 4640, Lectromed Devices Ltd, UK) was used. The aEEG recorded a single-channel electroencephalogram from two parietal needle electrodes (P3-P4, ground Fz). A second tracing continuously recorded the electrode impedance. The filtered signal was rectified, smoothed, and amplitude-integrated before it was written out at slow speed (6 cm/hour) [16-18]. The aEEG signal thus gave a continuous, on-line, trend recording of cerebral electric activity at the cot side. Background activity and seizure activity could be easily identified. The aEEG traces were assessed visually and classified into different categories for both background as well as seizure discharges as previously described [14,16-21].

aEEG appeared to be a reliable tool for monitoring both background pattern (especially normal and extremely abnormal) and ictal activity. Because of the long periods of registration, the aEEG was especially useful to evaluate changes in background pattern over time and to detect the occurrence of ictal discharges [14].

Epileptiform activity (characteristic pattern, with increased amplitude during epileptic seizure activity and lower voltage in the postictal period) was classified as:

Single seizure;

Repetitive seizures: ≥ 3 discharges during a 30-minute period;

Status epilepticus: "saw-tooth pattern".

Examples of aEEG seizure patterns are given in Figure 1.

We looked at the duration of seizure activity after birth in epochs of 12 hours up to 72 hours of age.

Assessment of Neurodevelopmental Outcome

The survivors were examined in the follow-up clinic at 3, 9, and 18 months, 3 and 5 years. Assessment of outcome was performed using the Griffiths Mental Developmental Scale and items from Amiel-Tison and Grenier and Touwen [22-24]. The Alberta Infant Motor Scale (AIMS) was used during the first 18 months of age and the Movement ABC at 5 years of age to further assess motor function [25].

A full neurologic assessment was performed at each visit to the follow-up clinic, and cerebral palsy was classified according to the criteria of Hagberg et al. [26]. This disorder could either be a dyskinetic form of cerebral palsy, a diplegia, quadriplegia, or hemiplegia. Global delay was considered if there was a developmental quotient (DQ) < 85 , obtained at 18-24 months of age, using the Griffiths Mental Developmental Scale.

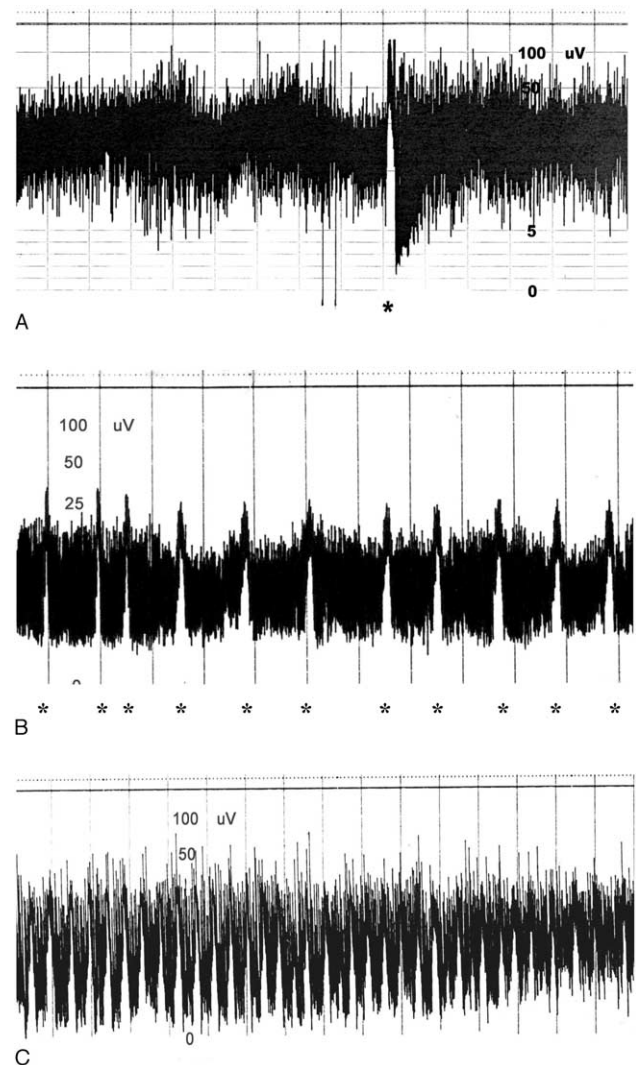


Figure 1. Seizures can be identified on the aEEG trace as a sudden rise of the lower margin of the trace. Three aEEG traces disclose (a) a single seizure (*), (b) repetitive seizures (seizures are marked with *), and (c) a status epilepticus (saw-tooth pattern).

Table 1. Neurodevelopmental outcome in relation to underlying etiology (n = 206)

Total	n 206	Died 80	Normal Outcome 85	Abnormal Outcome 41		
				GD (n = 16)	CP* (n = 25)	Abnormal Outcome and PNE (n = 12)
HIE	165					
Grade II	92	8	58 [†]	10	16	6
Grade III	68	66	—	1	1	2
Muscle paralysis	5	—	3	2	—	1
Intracranial hemorrhage	28					
Subdural/Subarachnoid	4	—	4	—	—	—
Intraventricular	6	1	5	—	—	—
Posterior fossa	6	1	3	1 [‡]	1 [‡]	—
Parenchymal	10	2	6	1	1 [‡]	—
Posterior fossa/Intraventricular	2	0	1	1	—	1
Perinatal arterial stroke	13	2	5		6	2

* Dyskinetic form of CP: 10; quadriplegia: 4; hemiplegia: 11.

[†] 7 infants; follow-up <12 months.

[‡] Also perinatal asphyxia.

Abbreviations:

CP = Cerebral palsy

GD = Global delay: DQ < 85, without CP

HIE = Hypoxic-ischemic encephalopathy

PNE = Postneonatal epilepsy

Statistical Analysis

For statistical analysis of the data, chi-square tests were used. For comparing the data of abnormal and normal outcome in relation to time of control of neonatal seizures, logistic regression analysis was used.

Results

Two hundred six infants were enrolled in the study; 80 (39%) of them died in the neonatal period. Forty-one (33%) of the 126 survivors were abnormal at follow-up. Twelve of these abnormal infants developed postneonatal epilepsy (9.5% of the survivors) (Table 1). One hundred sixty-five patients had perinatal asphyxia (68 patients had hypoxic-ischemic encephalopathy grade III; 92 patients had hypoxic-ischemic encephalopathy grade II; and in five patients, the severity of the hypoxic-ischemic encephalopathy could not be determined owing to muscle paralysis). Twenty-eight infants had an intracranial hemorrhage, and 13 infants had a perinatal arterial stroke. Thirty-seven patients received only one antiepileptic drug. One hundred sixty-nine neonates received two or more antiepileptic drugs.

Development of Postneonatal Epilepsy in Relation to Neonatal Problems

Onset of Postneonatal Epilepsy. The 12 patients who developed postneonatal epilepsy are listed in Table 2. Seven infants developed postneonatal epilepsy during the first year of life, and in four of them a diagnosis of infantile spasms was established. In the other five children, postneonatal epilepsy developed between the age of 18 months and 7 years.

Number of Antiepileptic Drugs. All but one of the infants who developed postneonatal epilepsy required three or more antiepileptic drugs in the neonatal period. In Patient 3, seizure activity was difficult to control despite antiepileptic drug use. Patient 6 produced a repetitive seizure pattern on aEEG at admission, which discontinued immediately after administration of clonazepam. In Patient 9, who was paralyzed on the ventilator, aEEG monitoring was initiated 41 hours after birth and revealed a status epilepticus pattern. Patient 12 received three antiepileptic drugs in another hospital because of a status epilepticus (confirmed with electroencephalogram) before he was admitted to our unit 48 hours after birth. On admission, epileptic activity could no longer be identified on aEEG.

Duration of Seizure Activity. All but two of the infants with postneonatal epilepsy had neonatal seizures lasting for at least 48 hours after birth. In four infants, seizures persisted beyond the first 72 hours after birth.

Associated Imaging Findings. Severe lesions were observed using neuroimaging techniques (ultrasound day 1, 2, 3, 5, and 7 and magnetic resonance imaging days 4-7) in all. The thalami and basal ganglia were involved in seven infants; two developed subcortical cystic leukomalacia, associated with basal ganglia lesions in one; two developed a middle cerebral artery infarct; and one had an intraventricular hemorrhage and blood in the posterior fossa.

Hypoxic-Ischemic Encephalopathy

Nine infants of the 91 survivors with hypoxic-ischemic encephalopathy developed postneonatal epilepsy (10%).

Table 2. Infants with PNE in relation to etiology and seizure duration

	Neonatal Diagnosis/Type of Lesion	Follow-up	Age at Last follow-up	Age PNE	Number of AED	Start aEEG*	Duration of Seizures
1	HIE grade III: SCL	Microcephaly/Retardation/Deafness	4 yr	2 yr	4	8 hr	32 hr
2	HIE grade III: BGT	CP/Retardation	3 yr	3 mo	4	4 hr	40 hr
3	HIE grade II-III: BGT	CP	13 mo	3 mo	3	3 hr	>72 hr
4	HIE grade II: BGT and SCL	Microcephaly/Retardation/CVI	18 mo	1 yr	4	27 hr	>72 hr
5	HIE grade II: BGT	CP/Microcephaly/Retardation	14 mo	3 mo	3	48 hr	>72 hr
6	HIE grade II: BGT	CP/Retardation/CVI	6 yr	9 mo	3	46 hr	48 hr
7	HIE grade II: BGT	Ataxia/Global delay	4.5 yr	4.5 yr	4	6 hr	48 hr
8	HIE grade II: SCL	Global delay	4 yr	4 yr	4	48 hr	72 hr
9	HIE (Paralysis): BGT	CP	19 mo	6 mo	2	41 hr	72 hr
10	IVH/posterior fossa hemorrhage	Global delay	6 yr	1.5 yr	4	24 hr	72 hr
11	HIE/MCA Rt	Hemiplegia/Hearing loss	7 yr	7 yr	4	90 hr	>72 hr
12	MCA Lt	Hemiplegia/Global delay	3.5 yr	3 mo	3	48 hr	—†

* Clinical seizures before start aEEG.

† Evident clinical seizures and status epilepticus in another hospital for which he received phenobarbitone, phenytoin, and clonazepam; no clinical seizures and seizure activity on aEEG after admission.

Abbreviations:

AED = Antiepileptic drugs	IVH = Intraventricular hemorrhage
aEEG = Amplitude-integrated electroencephalography	Lt = Left
BGT = Basal ganglia thalami	MCA = Middle cerebral artery infarct
CP = Cerebral palsy	PNE = Postneonatal epilepsy
CVI = Cerebral visual impairment	Rt = Right
HIE = Hypoxic ischemic encephalopathy grade II-III	SCL = Subcortical cystic leukomalacia

Only 2 of the 68 patients with a grade III encephalopathy survived. Both developed postneonatal epilepsy (Tables 1 and 2). One patient developed mental retardation, microcephaly, and sensorineural deafness (Patient 1), and the other infant developed a dyskinetic form of cerebral palsy and mental retardation (Patient 2).

Eighty-four of the 92 patients with a grade II encephalopathy (Tables 1 and 3) survived. Seven patients had a follow-up shorter than 12 months and appear to be normal so far. Of the remaining 77 patients, 51 patients were normal at follow-up. Six infants (7% of the survivors) with hypoxic-ischemic encephalopathy grade II developed postneonatal epilepsy. Twenty-six children were abnormal at follow-up (30%): nine children developed dyskinetic cerebral palsy, and two of them developed postneonatal epilepsy; three children developed a hemiplegia; four children developed quadriplegia; four children manifested microcephaly with learning disabilities, and two of them

developed postneonatal epilepsy; six children manifested a global delay, and two of these developed postneonatal epilepsy.

Of these 84 infants with hypoxic-ischemic encephalopathy grade II, control of seizures was achieved significantly later in those patients with an abnormal outcome compared with the ones with a normal outcome ($P < 0.003$). In 76 infants, the time of control of seizures could be determined. In nine infants, seizure control occurred within 12 hours of age, in 13 infants within 24 hours, in 11 infants within 36 hours, in 19 infants within 48 hours, in six infants within 60 hours, in four infants within 72 hours. In 14 infants seizures persisted beyond 72 hours after birth. None of these infants whose seizures were controlled within 48 hours developed postneonatal epilepsy, whereas in those who did develop postneonatal epilepsy seizures continued for more than 72 hours in four of the six infants. When seizures were controlled with only one or two antiepileptic drugs, none of the infants developed postneonatal epilepsy but 9.5% and 18% respectively had an abnormal outcome. When more antiepileptic drugs were required, the incidence of abnormal outcome rose to 39% and 55% with three and four antiepileptic drugs, respectively. Six of these 52 patients (11%) who received three or four antiepileptic drugs developed postneonatal epilepsy (Table 3).

Table 3. HIE II survivors and number of AED in relation to outcome

	1 AED	2 AED	3 AED	4 AED
HIE II Survivors (84)	21	11	41	11
Abnormal	2	2	16	6
Abnormal %	9.5%	18%	39%	55%
PNE			4	2

Abbreviations:

AED = Antiepileptic drugs
HIE = Hypoxic-ischemic encephalopathy grade II
PNE = Postneonatal epilepsy

Intracranial Hemorrhage

Twenty-eight infants had an intracranial haemorrhage (Table 1). Eight of these infants manifested mild to

moderate perinatal asphyxia as well. Five infants died. Five of the survivors (22%) had an abnormal outcome. Three of these infants had associated perinatal asphyxia, two of them developed cerebral palsy, and three infants developed global delay. One of the 23 survivors who also had a global delay developed postneonatal epilepsy (4,3%).

Perinatal Arterial Stroke

Twelve infants had a perinatal arterial stroke: nine infants had a middle cerebral artery infarct, one a posterior cerebral artery infarct, one an anterior cerebral artery infarct, and one a combined anterior and middle cerebral artery infarction. One infant died, six of the survivors developed a hemiplegia, and two of these developed postneonatal epilepsy. One developed infantile spasms at 3 months of age, and one developed multifocal seizures at the age of 7 years. Two of the 11 survivors developed postneonatal epilepsy (18%). One further infant with sinovenous thrombosis died in the neonatal period.

Development of Postneonatal Epilepsy in Relation to Neurodevelopmental Outcome

Looking at the complete cohort, only infants with an abnormal outcome developed postneonatal epilepsy. Seven of the 25 (28%) infants with cerebral palsy, compared with 5 of the 101 (5%) infants without cerebral palsy developed postneonatal epilepsy ($P = 0.001$). In the group with a DQ < 85, with or without microcephaly, 5 of the 16 infants (31%) developed postneonatal epilepsy, compared with 7 of the 110 (6%) infants without global delay ($P < 0.01$).

Discussion

A strikingly lower incidence of postneonatal epilepsy (9.4%) was observed in the term infants in the present study, who received treatment for both clinical and subclinical seizures, compared with 20-50% reported in previous studies only treating clinical seizures [11,12]. A similar incidence of 8.3% was reported by one other group, who also has the policy of treating both clinical and subclinical seizures, using continuous aEEG [13].

The lower incidence of postneonatal epilepsy could not be explained by a higher mortality rate, as the mortality rate of 39% in the present study was comparable to that reported by other groups (30-36%) [11-13]. Our study group consisted of term infants, whereas previous groups studied a mixture of term and preterm infants [11-13].

In a subgroup of hypoxic-ischemic encephalopathy only, we found an incidence of postneonatal epilepsy of 10% among all survivors and 7% among the survivors with grade II encephalopathy. To keep the hypoxic-ischemic encephalopathy group as homogeneous as possible, the infants with hypoxic-ischemic encephalopathy

and an intracranial hemorrhage were classified separately. The highest incidence of postneonatal epilepsy (18%) was found in the subgroup with perinatal arterial stroke, which is in agreement with the literature [27]. The lowest incidence of 4.2% was observed in the subgroup with an intracranial hemorrhage.

A third of the survivors in the present study with a follow-up of at least 12 months had an abnormal outcome, and a strong relationship was observed between an abnormal outcome, consisting of cerebral palsy or global delay, and the occurrence of postneonatal epilepsy, as has previously been demonstrated by others. Clancy and Legido [11] reported that postneonatal epilepsy was significantly related to cerebral palsy, mental retardation, and more than 10 electrographic seizures per hour, detected in the neonatal electroencephalogram recorded at random. Menache et al. [28] found in their retrospective study that an infant whose neonatal electroencephalogram contains a predominant interburst interval duration of more than 30 seconds has a 100% probability of experiencing severe neurologic disabilities or death and an 86% chance of developing postneonatal epilepsy. Because the conventional analogue aEEG monitor was used for this study, we were unable to investigate this in more detail. In their study, refractory seizures were strongly associated with an unfavorable outcome but not with later occurrence of epilepsy.

In the present study, two regimens of antiepileptic drugs were used in the neonatal period. Before 1998, a regimen of phenobarbital, phenytoin, and clonazepam was used. Lidocaine was sometimes used when seizure activity persisted despite these drugs. After 1998 this regimen was changed to phenobarbital, lidocaine, and/or midazolam, and sometimes clonazepam as a fourth-line antiepileptic drug. The reason for this change was that we did not find phenytoin to be effective in the treatment of neonatal seizures, which was in agreement with the literature [29]. Because of the experience of others and our own experience, we changed the regimen to lidocaine and midazolam as second- or third-line antiepileptic drug [30-36].

Apart from the multifactorial etiology of neonatal seizures, the number of antiepileptic drugs needed to control the neonatal seizures was associated with the risk of developing postneonatal epilepsy. All but one of the children who developed postneonatal epilepsy in the present study received three or more antiepileptic drugs in the neonatal period. None of the infants who needed only one antiepileptic drug and none of the infants with hypoxic-ischemic encephalopathy grade II who needed one or two antiepileptic drugs developed postneonatal epilepsy.

Seven of the 12 infants developed postneonatal epilepsy during the first year of life, and a diagnosis of infantile spasms was made in four of them. Intracranial lesions detected with neuroimaging techniques were observed in all children who developed postneonatal epilepsy. Involvement of the central gray nuclei was most common and was observed in 7 of the 12 children.

It is not clear from other studies how many antiepileptic drugs were administered or how effective they were in controlling (sub)clinical seizures. As they did not monitor electroencephalography or aEEG continuously, no information is available about the frequency of subclinical seizures, which appeared to be high in our study group, especially after initiation of treatment with antiepileptic drugs. This phenomenon has also been reported by others, both in newborn infants as well as in adults [2,3,37-40]. Bye and Flanagan [38] reported reduced clinical features after administration of antiepileptic drugs. Using prolonged video-electroencephalographic monitoring, they found that 85% of all seizures were not associated with clinical manifestations. This phenomenon, which is called electroclinical dissociation or "uncoupling," was recently also addressed by Sher et al. [3]. They found that 58% of the infants with seizures persisting after treatment with phenobarbital or phenytoin manifested uncoupling of electrical and clinical seizures [3,29]. Boylan et al. [2] also reported that electrographic seizures were common in infants with severe hypoxic-ischemic encephalopathy after initial treatment with phenobarbital.

Duration of seizure activity also appeared to be of importance as only two of the infants in the present study developed postneonatal epilepsy after seizure control within 48 hours after birth.

There is no agreement in the literature whether neonatal seizures themselves can lead to damage of the immature neonatal brain. Electroclinical and electrographic neonatal seizures produce an increase in cerebral blood flow velocity [41]. It is suggested that electrographic seizures are associated with disturbed cerebral metabolism and that treatment of neonatal seizures until electrographic seizure activity is abolished may improve outcome. A case report of a newborn infant with hemiconvulsions occurring during phosphorus magnetic resonance spectroscopy examination documented depletion of phosphocreatine and adenosine triphosphate in the affected hemisphere as well as an increase in inorganic phosphate indicating a loss of high phosphates during seizures [42]. Other studies in humans reported that the severity of seizures in newborns with perinatal asphyxia is independently associated with brain injury [4,5,43].

Recent findings in animal studies demonstrate that neonatal seizures can permanently disrupt neuronal development, induce synaptic reorganization, alter plasticity, and "prime" the brain to increased damage from seizures later in life [6-8,44]. Seizures superimposed on hypoxic ischemia in rat pups were observed to significantly exacerbate brain injury [9]. On the other hand, Bittigau et al. reported that antiepileptic drugs may cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans [10].

The main difference in treatment of neonatal seizures between the present study and other studies (looking at outcome and postneonatal epilepsy) is that we used continuous monitoring and did not restrict antiepileptic ther-

apy to clinical seizures, but also treated subclinical seizures during the neonatal period. This difference might be the explanation for our lower incidence of postneonatal epilepsy. This hypothesis is supported by the similar incidence of postneonatal epilepsy in the cohort studied by Hellström-Westas et al. [13], who also used aEEG and had a similar treatment policy. Their group was, however, less homogeneous as they also included premature infants. In the study of McBride et al. [5], an association was documented between the amount of electrographic seizure activity and subsequent mortality and morbidity. To be able to calculate this, continuous monitoring of neonatal seizures is required. With the new generation of digital aEEG monitoring devices, where the raw electroencephalographic signal is displayed as well, this might be easier to accomplish.

To ascertain whether more effective treatment of seizures as well as treatment of subclinical seizures will reduce the occurrence of postneonatal epilepsy and improve long-term outcome, a multicenter randomized study, Treatment Versus Non-treatment of Subclinical Neonatal Convulsions, is now in progress with participation of seven neonatal intensive care units in the Netherlands and three centers in Belgium.

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