Neonatal epilepsy and underlying aetiology: to what extent do seizures and EEG abnormalities influence outcome?

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ABSTRACT – Neonatal seizures constitute the most common and distinctive sign of neurological dysfunction in the first weeks of life and reflect a wide variety of underlying central nervous system disorders. Acute symptomatic seizures occur more often during the neonatal period than at any period of life and are associated with adverse long-term neurodevelopmental sequelae and an increased risk of post-neonatal epilepsy. The improvements of neonatal care in the last decades have changed the spectrum of insults to which the immature brain is exposed and facilitated a decrease in mortality of newborns with seizures. However, the prevalence of long-term morbidity in survivors remains unchanged. Whereas aetiology is presumed to be the main predictor of long-term outcome in neonates with seizures, there is converging evidence that specific electroencephalographic (EEG) abnormalities are related to unfavourable outcomes. Interictal EEG abnormalities, especially concerning background activity patterns, thus constitute a major indicator of disease severity and predictor of outcome, while the added value of sequential EEG assessments is so far controversial. Moreover, experimental as well as clinical studies of hypoxic-ischaemic encephalopathy support the notion that recurrent seizures may amplify injury to the developing brain beyond that associated with the underlying aetiology, thus justifying antiepileptic drug treatment. To date, unresolved issues in seizure detection and classification, in addition to the significant variation in gestational ages and brain insults of neonates, still impede clinical research of neonatal seizures. The wider use of long-term EEG or amplitude integrated EEG monitoring may prove crucial for timely neonatal seizure identification and treatment initiation, and thus ultimately improve outcome.

Key words: neonatal seizure, outcome, prognosis, preterm, term infants

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Epileptic seizures incidence is greatest during the neonatal period compared to any other period of life (Volpe, 2008). The overall incidence of neonatal seizures, as reported in population-based studies conducted between 1985 and 2002, amounts to 1-3 per 1,000 live births

(Lanska *et al.*, 1995; Ronen *et al.*, 1999; Saliba *et al.*, 2001; Glass *et al.*, 2009a), with considerably higher rates in high-risk premature infants (Kohelet *et al.*, 2004). Eighty percent of neonatal seizures occur in the first week of life, constituting the most common and distinctive sign of neurological dysfunction (Volpe, 2008).

The recent technological advances in obstetric and neonatal care have changed the spectrum of insults to which the immature brain is exposed and thus the aetiological profile of neonatal seizures (Arzimanoglou *et al.*, 2004; Mizrahi and Watanabe, 2005; Silverstein and Jensen, 2007). Neonatal seizures are predominantly symptomatic, originating from acute perinatal events such as hypoxic-ischaemic encephalopathy (HIE), metabolic disturbance, intracerebral haemorrhage, central nervous system (CNS) infection, stroke, or inborn errors of metabolism; in order of decreasing frequency (Mizrahi and Watanabe, 2005). Neonatal seizures constitute a grave condition that may lead to neonatal death or dire sequelae including neurological impairment, developmental delay, and post-neonatal epilepsy. With the decrease of mortality rates from 40% to 20% in the last decades, the prevalence of long-term neurodevelopmental sequelae in survivors remains unchanged at 30% (Volpe, 2008).

Several studies have sought to define predictors of long-term outcome in neonates with seizures, most focussing on the underlying aetiology or on specific seizure presentation and electroencephalographic (EEG) abnormalities. However, no clear pattern has emerged so far, possibly due to the variable criteria for neonatal seizure identification and aetiological diagnosis over the years or between different institutions.

Identification of neonatal seizures

The detection and classification of neonatal seizures continues to be challenging, especially when based on clinical observation alone, as is often the case in clinical practice (Murray *et al.*, 2008; Malone *et al.*, 2009). The presentation of neonatal seizures is indeed highly variable and includes subtle, clonic, tonic, and myoclonic events of typically brief and focal nature (Scher, 2002). A seminal study previously postulated that clonic seizures are most typical and characteristic in terms of identification, followed by focal tonic seizures (Mizrahi and Kellaway, 1987). However, detection rate by clinical staff amounted to a mere 9% of electroclinical seizures in a recent study that included 70% clonic seizures (Murray *et al.*, 2008). Similarly, in a study carried out among 137 healthcare professionals, participants correctly identified only half of the clinical seizures in neonates, with detection rates by medical doctors similar to those of other health professionals (Malone *et al.*, 2009).

Since neonatal seizures may present as clinical, electroclinical or electrographic events, the ability to accurately identify them and distinguish them from non-epileptic events is clearly not feasible when based on clinical evaluation alone (Scher, 2002). Encephalopathic neonates can exhibit abnormal motor behaviours, which may not necessarily correlate with ictal EEG patterns and may correspond to "brainstem release" from functional decortication as a result of severe neocortical dysfunction or damage (Mizrahi and Kellaway, 1987). On the other hand, healthy neonates can exhibit non-epileptic movements such as jitteriness, clonus, sleep myoclonus, sucking movements, and repetitive movements during rapid eye movement (REM) sleep that may further hamper detection (Scher, 2002). In addition, the clinical presentation of seizures in affected neonates may be suppressed, despite persisting ictal EEG activity, by the use of medications for ventilatory assistance or seizure control (Boylan *et al.*, 2002).

Therefore, the diagnosis of neonatal seizures based on clinical observation alone inevitably includes "false positives", consisting of neonates with either normal or non-epileptic pathological behavioural patterns. Although amplitude integrated EEG (aEEG) can facilitate diagnosis and treatment monitoring of neonatal seizures to some extent, continuous multichannel video-EEG recording remains the gold standard for their identification and classification (Bednarek, 2001). However, this currently remains largely inaccessible in most neonatal intensive care units (NICUs).

Pathophysiology of neonatal seizures and pharmacotherapeutic effects

The neuronal hyperexcitability of the newborn brain, a key feature for synaptogenesis and neuronal plasticity, may ultimately predispose the developing brain to seizures (Wirrell, 2005). Experimental data from animal models and human tissue studies provide evidence in support of a peak of synaptogenesis from birth through to the first months of life that occurs alongside major developmental changes in the excitatory glutamate receptors and the inhibitory G-aminobutyric acid (GABA) receptors in the central nervous system (Silverstein and Jensen, 2007; Holmes, 2009; Nardou *et al.*, 2013). These developmental mechanisms ultimately enhance synaptic excitation in the neonatal brain, thus increasing its susceptibility to seizures.

In particular, it has been demonstrated that the inhibitory $GABA_A$ network presents delayed matu-

ration, with considerably lower overall receptor expression in the first weeks of life (Sanchez and Jensen, 2001). Furthermore, there is experimental evidence that the subunit composition of GABA$_A$ receptors in early life, particularly when the a4 subunit is over-expressed, renders the receptors less sensitive to GABA agonists (Swann and Moshe, 1997). Finally, GABA receptor activation has been shown to result in depolarisation rather than hyperpolarisation in the immature brain, with this state being critical for normal development (Khazipov et al., 2004). This depolarising effect of GABA in early life is, however, thought to impair the efficacy of GABA$_A$ receptor inhibition by commonly applied anticonvulsants such as phenobarbital and benzodiazepines, with critical consequences for seizure control (Silverstein and Jensen, 2007).

These observations are crucial in understanding the pathophysiology of neonatal seizures as well as the effect of anticonvulsants. It has been further demonstrated that phenobarbital and benzodiazepines may suppress clinical seizures through inhibition exercised on the spinal cord and brainstem and may, at the same time, exacerbate ictal EEG abnormalities through the persistent excitation of cortical neurons (Dzhala et al., 2005). This may be one of the mechanisms that results in "uncoupling" or "electroclinical dissociation", with suppression of clinical seizures coexisting with ongoing ictal EEG patterns in affected neonates (Pinto and Giliberti, 2001; Boylan et al., 2002).

Aetiology and outcome of neonatal seizures

Neonatal seizures occur more often in premature infants, with seizure frequency and neonatal mortality increasing with the degree of prematurity (Bergman et al., 1983; Ronen et al., 2007). However, there is some controversy regarding the incidence of post-neonatal epilepsy and neurodevelopmental disability in relation to gestational age, with recent studies highlighting an increased risk of impairment in preterm compared to term populations (Ronen et al., 2007; Yıldız et al., 2012), contrary to previous reports (Garcias Da Silva et al., 2004). This discrepancy may correspond to a gradual shift from mortality to morbidity in premature neonates with seizures (Ronen et al., 2007). Innovations in neonatal care have contributed to the survival of premature neonates, who have shown an increase in prevalence of intraventricular haemorrhage (IH), and a decrease in the rate of transient metabolic disturbances, such as hypocalcaemia, that are associated with neonatal seizures, with favourable prognosis

(Tekgul et al., 2006). Furthermore, improved maternal and neonatal antimicrobial treatments have led to a marked decrease in seizures resulting from central nervous system infections, compared to earlier cohorts (Bergman et al., 1983; Tekgul et al., 2006).

In a prospective study considering the entire population of live births in Newfoundland, Canada, in 1990-1994, 90 neonates with seizures identified by clinical observation alone were evaluated 10 years later (Ronen et al., 2007). In this population-based study, term neonates had increased chances of favourable outcomes compared to preterm neonates: 84% vs 58% survived the neonatal period and 45% vs 12% had normal outcomes, defined as the absence of neurodevelopmental impairment (table 1). Unfavourable prognosis was further determined by aetiology, including HIE and cortical malformations in term neonates, as well as complicated IH and infections in premature neonates, EEG abnormalities, and poor response to anticonvulsants. It should be noted that HIE constituted the most prevalent seizure aetiology in this population-based study. Seizure semiology predicted long-term prognosis according to gestational age, with clonic seizures in term neonates related to more favourable outcomes, and generalised myoclonic seizures in premature neonates linked to increased mortality. Post-neonatal epilepsy was established in 23% of infants; cerebral palsy and developmental delay developed in 25 and 41%, respectively (Ronen et al., 2007). These observations are in line with a trend in increased rates of neurodevelopmental deficit and decreased mortality of extreme preterm or low-weight infants in developed countries.

In a prospective study considering all term neonates admitted to the NICUs of the Children's Hospital and Brigham and Women's Hospital in Boston, USA, in 1997-2000, 100 infants with seizures, diagnosed on the grounds of clinical observation alone, were evaluated at least 12 months later (Tekgul et al., 2006). In this hospital-based study, mortality was 7%, and 21% presented with post-neonatal epilepsy, 46% cerebral palsy, and 48% developmental delay (table 1). Unfavourable outcome was related to aetiology, especially to the presence of structural lesion on neuroimaging, as well as to abnormal neurological examination and EEG background activity (table 1). Contrary to previous reports (Brunquell et al., 2002), predominant seizure semiology did not relate to long-term outcome. Furthermore, seizure burden influenced developmental and neurological deficit, but not the long-term risk of epilepsy. The authors underlined the role of aetiology, which is increasingly recognised due to novel diagnostic methodology, and EEG background activity in determining long-term outcomes following neonatal seizures (Tekgul et al., 2006).

Table 1. Outcome of neonatal seizures in cohorts of term and/or preterm neonates, as presented in studies published in the last decade in which adequate characterisation of this condition was reported (e.g. aetiology, seizure semiology, EEG findings, seizure duration, response to therapy), with the aim of providing predictive factors.

Authors & year	Recruitment period	Study design	N at inclusion	N at last follow-up visit	Term neonates (%)	Ictal EEG (%)	Seizure duration considered	Mortality (%)	Normal outcome (%)	Post-neonatal epilepsy (%)	Cerebral palsy (%)	Developmental delay (%)	Predictors of poor outcome	Follow-up (m)
Garcias Da Silva et al., 2004	1987-1997	retrospective	158	127	65	7	no	15	48§	34	9	7	Abnormal neurological examination Abnormal polysomnography	NR
Tekgul et al., 2006	1997-2000	retrospective	100	89	100	33	no	7	72$^{#}$	21	46	48	Aetiology (HIE, CNS infection, MCD) Structural lesion on neuroimaging Abnormal EEG background activity	>12
Ronen et al., 2007	1990-1994	prospective	90	88	70	NR	no	24	35*	23	25	41	Prematurity Severe encephalopathy/Sarnat III Aetiology (HIE, CNS infection, MCD) Abnormal EEG findings Drug-resistant seizures Generalised myoclonic seizures (preterms)	>96
Pisani et al., 2007	1999-2004	prospective	106	86	52	100	yes	19	34$^{#}$	26	37	34	Birth weight Abnormal cerebral ultrasound findings Neonatal status epilepticus	24

Table 1. (*Continued*)

Authors & year	Recruitment period	Study design	N at inclusion	N at last follow-up visit	Term neonates (%)	Ictal EEG (%)	Seizure duration considered	Mortality (%)	Normal outcome (%)	Post-neonatal epilepsy (%)	Cerebral palsy (%)	Developmental delay (%)	Predictors of poor outcome	Follow-up (m)
Khan et al., 2008	1987-1997 1999-2003	retrospective	58	50	60	3	no	14	NR	41	NR	60	Sequential EEG background abnormalities	30-40
Pisani et al., 2008	1999-2003	prospective	51	33	0	100	yes	34	20[#]	18	40	36	Apgar score at 1 min Abnormal EEG background activity	58
Glass et al., 2009b	1996-2003	prospective	41(143)	25(77)	100	24	yes	11	-	-	-	56	*Composite score including:* Seizure frequency / Seizure onset in the first 24hrs / Drug-resistant seizures / Abnormal EEG findings	48
Nagarajan et al., 2010	2001-2005	retrospective	52	41	81	83	no	21	37[*]	33	30	63	Abnormal EEG background activity (self-developed numerical score)	>24
Garfinkle and Shevell, 2011	1991-2007	retrospective	120	109	100	NR	no	9	44[#]	27	26	47	Delivery *via* Caesarean section / Aetiology (HIE, CNS infection, MCD) / Abnormal EEG background activity / Seizure onset in the first 24hrs / Seizures other than focal clonic	53

Table 1. (*Continued*)

Authors & year	Recruit-ment period	Study design	N at inclu-sion	N at last follow-up visit	Term neo-nates (%)	Ictal EEG (%)	Seizure duration considered	Mor-tality (%)	Normal outcome (%)	Post-neonatal epilepsy (%)	Cerebral palsy (%)	Develop-mental delay (%)	Predictors of poor outcome	Follow-up (m)
Painter et al., 2012	1990-1995	pros-pective	59	52	NR	100	yes	8	37#	48	NR	51	Seizure severity (duration, EEG channels) Drug-resistant seizures Diffuse severe pathology on neuroimaging	83
Yildiz et al., 2012	2007-2009	retros-pective	112	104	71	NR	yes	7	38*	36	28	63	Aetiology (HIE) Apgar score Need for resus-citation at birth Abnormal EEG background activity Neonatal status epilepticus Abnormal cerebral imaging findings Drug-resistant seizures Duration of anticonvulsant treatment	38
Lai et al., 2013	1999-2009	retros-pective	232	194	100	NR	no	16	60*	23	4	25	Abnormal EEG findings Congenital heart disease Abnormal cerebral ultrasound findings Abnormal anterior cerebral artery RI	>12

Normal outcome is defined as normal neurological development (*) or normal neurological development or mild neurological impairment (#), according to the respective study design, or not defined (§).

NR: not reported; N: number of neonates; HIE: hypoxic ischaemic encephalopathy; CNS: central nervous system; MCD: malformations of cortical development; RI: resistance index; EEG: electroencephalography; m: months.

Numbers in parentheses correspond to the total population of neonates included in each study in which only part of the cohort presented with neonatal seizures.

In a prospective study considering consecutively admitted preterm neonates in a tertiary NICU in Pisa, Italy, in 1999-2003, 51 infants with electro-clinical seizures were included and assessed at age 30-91 months (mean: 58) (Pisani *et al.*, 2008). In this hospital-based study, mortality was 34% and only 20% of preterm neonates had a normal outcome, defined as normal neurological development or mild neurological impairment. Post-neonatal epilepsy was established in 18%, cerebral palsy in 40%, and developmental delay in 36%, in affected infants during long-term follow-up. Abnormal EEG background activity in the first days of life was related to increased mortality, while abnormal EEG background activity and Apgar score at one minute predicted long-term outcome (*table 1*). Gestational age did not influence long-term outcome in this population of extremely premature neonates, in which 51% had HIE and 29% IH. The development of post-neonatal epilepsy was related to abnormal neuroimaging and EEG findings (Pisani *et al.*, 2008).

In a large retrospective study considering consecutively admitted term neonates in a tertiary NICU at the Mackay Memorial Hospital in Taipei, Taiwan, in 1999-2009, 232 infants with seizures diagnosed on the grounds of clinical observation alone were evaluated with a follow-up period of at least 24 months, or at least 12 months if the patient was normal (Lai *et al.*, 2013). In this hospital-based study, mortality was 16% and 60% of term neonates had a normal outcome, defined as normal neurological development or mild neurological impairment (*table 1*). Post-neonatal epilepsy was established in 23%, cerebral palsy in 20%, and developmental delay in 24%, in affected infants during long-term follow-up. The four predictors of poor outcome for term neonates with seizures in this study were abnormal cranial ultrasonography findings, abnormal anterior cerebral artery resistance index, abnormal EEG findings, and presence of congenital heart disease (Lai *et al.*, 2013). In this cohort, abnormal background, especially burst-suppression patterns, and multifocal epileptiform activity were related to adverse outcome.

Overall, current evidence regarding the relation of seizure types to long-term outcome is inconclusive (Brunquell *et al.*, 2002; Pisani *et al.*, 2008; Tekgul *et al.*, 2006). In the largest study to date, it was postulated that neonates with predominantly focal clonic seizures are likely to have focal brain pathology and a more favourable short-term outcome than those presenting with subtle seizures (Mizrahi and Kellaway, 1987). However, in other cohorts, generalised tonic seizures were associated with unfavourable outcomes (Bergman *et al.*, 1983; Brunquell *et al.*, 2002). This discrepancy may be attributed to different underlying pathogenetic mechanisms giving rise to different seizure presentations at different time points during brain maturation, and ultimately influencing outcome (Brunquell *et al.*, 2002; Ronen *et al.*, 2007). Generalised tonic seizures are indeed more common in preterm neonates, in conjunction with structural lesions, such as those resulting from severe IH and are thus associated with unfavourable long-term outcomes.

Seizure-induced injury in the developing brain

The notion that recurrent seizures themselves, regardless of specific semiology, may cause irreversible injury to the developing brain beyond that associated with the underlying aetiology is crucial in terms of neonatal seizure management. However, this issue remains under debate, with experimental evidence from neonatal animal models still awaiting confirmation from clinical evidence in human neonates (Wirrell *et al.*, 2001; Ben-Ari and Holmes, 2006; Painter *et al.*, 2012; Nardou *et al.*, 2013).

In recent years, a growing body of *experimental evidence* has brought to light significant long-term adverse sequelae of prolonged or recurrent seizures in the developing brain. Seizures in early life have been shown to intervene with normal development and eventually result in less efficient cortical networks, even in the absence of cell loss (Holmes, 2005; Ben-Ari and Holmes, 2006). Alterations in neuronal connectivity and receptor expression (Swann and Hablitz, 2000; Brooks-Kayal, 2005) inadvertently lead to permanent impairment in learning, memory, and cognition (Lee *et al.*, 2001; Swann, 2002), as well as to increased susceptibility to seizure-induced brain injury later in life (Jensen *et al.*, 1992). Animal studies have further demonstrated a strong age-dependency of seizure sequelae with alterations in synaptic plasticity (Stafstrom *et al.*, 2006) and signal cascades (Sanchez *et al.*, 2005), affecting exclusively the immature brain (Nardou *et al.*, 2013). Interestingly, prolonged seizures or status epilepticus in animal models have been shown to result in brain injury only when superimposed onto pre-existing insults, such as those associated with HIE (Wirrell *et al.*, 2001).

In line with these findings, there is *clinical evidence* from magnetic resonance spectroscopy studies in term neonates with HIE corroborating a further compromise of brain metabolism by clinical seizures. In this context, the severity of neonatal seizures, rather than the severity of HIE, has been linked to adverse neurodevelopmental outcomes (Miller *et al.*, 2002; Glass *et al.*, 2009b). However, it is difficult to distinguish between aetiology-specific and seizure-induced effects in a clinical setting, since the severity of seizures may indicate a more grave brain injury

or independently cause and/or exacerbate neurological damage. Furthermore, the critical seizure burden necessary for aggravation of brain damage remains unknown. Interestingly, a recent study of 56 term neonates with status epilepticus demonstrated a correlation between longer seizure duration and adverse neurodevelopmental outcomes, specifically in a subgroup of 48 HIE neonates (van Rooij et al., 2007). In another study from the same year, neonatal status epilepticus correlated with adverse outcomes for term neonates with a higher risk of post-neonatal epilepsy in early preterm, as well as term, neonates (Pisani et al., 2007).

The importance of timing, in addition to severity, of brain injury for long-term outcomes in neonates has been further underlined in a third population-based study (Ronen et al., 2007). In this study, premature neonates with seizures were at higher risk of mortality as well as dire neurodevelopmental sequelae than term neonates. This clinical observation suggests that the effect of brain injury is linked to a specific stage in brain development, with damage expected to be more severe in mid, rather than late, gestation, in line with animal studies (Rees and Inder, 2005).

Finally, it should be taken into consideration that the developmental differences across species may contribute to a disparity in seizure outcomes and predictive factors between animal and human data. Thus, caution is needed when attempting to transfer observations from animal models to the NICU. On the other hand, clinical studies may not be as well controlled as animal studies, for a variety of reasons.

These observations add to the ongoing discussion as to whether all neonatal seizures, both clinical (identified solely by clinical observation) and electroclinical or electrograhic, (diagnosed by ictal EEG recordings) justify antiepileptic drug (AED) treatment. This is crucial, since current therapeutic options for the treatment of neonatal seizures are not only largely ineffective, but also contribute to the inaccurate estimation of seizure load and drug-induced injury to the developing brain (Boylan et al., 2002; Ikonomidou and Turski, 2010).

EEG patterns as biomarkers in neonates with seizures

EEG abnormalities in neonates with seizures have been associated with a poor prognosis in numerous studies (Rowe et al., 1985; Holmes and Lombroso, 1993; Laroia et al., 1998; Tekgul et al., 2006; Pisani et al., 2008; Yıldız et al., 2012; Lai et al., 2013). Interictal EEG abnormalities remain the major indicator for disease severity and predictor for outcome, due to the limited availability of ictal EEG recordings. Identification of severe interictal EEG abnormalities, although not specific to particular aetiologies or to the timing of brain injury, may even predict seizure occurrence based on subsequent EEG records (Laroia et al., 1998). Abnormal EEG background patterns were found to be more significant than interictal epileptic discharges (Laroia et al., 1998; Rowe et al., 1985; Tekgul et al., 2006; Pisani et al., 2008; Nagarajan et al., 2010; Garfinkle and Shevell, 2011). Furthermore, ictal discharges, regardless of their clinical correlates, have been associated with an unfavourable outcome (Legido et al., 1991; Rowe et al., 1985).

The correlation between EEG findings during the neonatal period and long-term outcomes was retrospectively studied in 118 term neonates, assessed in the British Columbia Children's Hospital, Vancouver, British Columbia, Canada, in 1992-2009, with at least one EEG recording in the first month of life and at least one clinical evaluation 4-16 years later (Almubarak and Wong, 2011). The authors concluded that generalised EEG low-voltage background activity was highly correlated to unfavourable outcome, including post-neonatal epilepsy and neurological deficit at follow-up. The overall sensitivity was 94% and specificity was 42%. Interestingly, the underlying aetiology did not significantly correlate with outcome in this cohort.

Performing sequential EEG assessments in neonates was shown to enhance the prognostic value with persisting EEG abnormalities highly related to long-term outcomes (Holmes and Lombroso, 1993; Khan et al., 2008). In particular, the persistence of EEG pathology beyond the first week of life has been linked to unfavourable outcomes, even if clinical abnormalities resolved. In a recent study, two historical cohorts of newborns with seizures, from 1987-1997 and 1999-2003 that were admitted to the NICU of University Hospital São Lucas, in Porto Alegre, Brazil, were combined and pairs of sequential EEGs of 58 newborns were classified into four groups: normal-normal, abnormal-normal, abnormal-abnormal, and normal-abnormal. The presence of an abnormal background activity in both the first and second EEG was associated with an increase in the risk of epilepsy and developmental delay, while abnormal background only in the second EEG was associated with an increase in the risk of developmental delay alone (Khan et al., 2008). Conversely, in a recent study, it was postulated that there was no added value in considering sequential EEG studies in term neonates with seizures due to HIE (Tekgul et al., 2006).

Finally, paroxysmal fast activity based on scalp EEGs of neonates with seizures has been recently assessed as a possible network marker and its correlation with long-term outcomes has been analysed (Nagarajan

et al., 2011). The EEG recordings of 42 neonates with seizures from the NICU of the Princess Margaret Hospital for Children, Perth, Australia, were retrospectively studied. Ictal fast activity indeed correlated with the occurrence of clinical features during an EEG seizure, but not with neuroimaging abnormalities, neurodevelopmental impairment or post-neonatal epilepsy.

Discussion

In spite of groundbreaking improvements in neonatal care in the past decade leading to a promising decrease in the mortality of neonates with seizures, the long-term neurodevelopmental morbidity in survivors remains substantial and unchanged compared to earlier studies (Arzimanoglou et al., 2004; Silverstein and Jensen, 2007; Volpe, 2008).

Unresolved issues in seizure detection and classification, as well as the relationship with underlying brain pathology and EEG abnormalities, still impede clinical research of neonatal seizures. Previous studies show some converging evidence towards EEG abnormalities and aetiology as predictors of unfavourable outcome. However, it is not feasible to draw definitive conclusions due to the variation of gestational age and brain insults of neonates populating current NICUs, as well as the fact that hospital-based studies include cases of high-risk delivery and population-based studies include cases in which neonates are less affected. Therefore, predictive factors of neonatal seizure outcome still remain to be validated on larger, representative contemporary cohorts.

Future approaches will inevitably be enhanced by the use of aEEG and increased availability of continuous video-EEG and/or aEEG monitoring in the diagnosis and treatment evaluation of neonatal seizures. Furthermore, biomarkers which have been established for a long time, such as seizure semiology and EEG findings, are expected to play a new role in the context of genetic disease. In addition to the resolution of diagnostic issues, novel therapies (Fürwentsches et al., 2010; Ramantani et al., 2011), deriving from laboratory research which aim to minimise damage to the immature brain (Galanopoulou, 2007; Ikonomidou and Turski, 2010), may influence EEG findings and seizure presentation, as well as long-term outcome. These challenges call for a consensus on classification and treatment, a close collaboration between clinicians and researchers, and ultimately randomised, placebo-controlled, ethically-acceptable trials of anticonvulsant efficacy and safety for the treatment of neonatal seizures.

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