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A review of long-term EEG monitoring in critically ill children with hypoxic-ischemic encephalopathy, congenital heart disease, ECMO, and stroke

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Introduction

Conventional continuous EEG (cEEG) monitoring is currently being utilized with increasing frequency in critically ill children, but in a non-standardized fashion (Abend, et al. 2010, Sanchez, et al. In press.). The most common cEEG indication is concern regarding identification of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) which are known to occur in critically ill children with a variety of acute encephalopathies (Abend, et al. 2011, Hyllienmark and Amark 2007, Hosain, et al. 2005, Jette, et al. 2006, Abend, et al. 2009, Abend and Dlugos 2007, Saengpatrachai, et al. 2006, Alehan, et al. 2001, Tay, et al. 2006, Williams, et al. 2011, McCoy, et al. 2011, Kirkham, et al. 2012, Greiner, et al. 2012, Shahwan, et al. 2010). cEEG findings may lead to changes in clinical management since if NCS or NCSE are confirmed or disproven then anticonvulsants can be initiated, increased or discontinued (Abend, et al. 2011). In addition to NCS identification, cEEG monitoring may aid in outcome predictions in children with critical illnesses such as hypoxic ischemic encephalopathy (HIE). However, unanswered questions have led to substantial variability in practice across centers (Abend, Dlugos, Hahn, et al. 2010). These questions include which patients should undergo cEEG monitoring, what is the appropriate duration of monitoring, and do management changes made as a result of cEEG monitoring findings improve outcome. This review discusses the available data regarding cEEG use in critically ill children with special attention to HIE, congenital heart disease, and acute stroke.

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Hypoxic-Ischemic Encephalopathy

Non-convulsive Seizure Occurrence and Risk Factors

HIE is a term generally applied to a variety of acute conditions which feature both *diffuse* hypoxia and ischemia. Examples include birth asphyxia, cardiac arrest and near-drowning. A recent survey of primarily large academic pediatric neurology institutions in the United States and Canada found that 68% of institutions performed cEEG monitoring in children resuscitated from cardiac arrest (Sanchez, Carpenter, Chapman, et al. In press.). Retrospective series of acutely ill children with NCS and NCSE have reported HIE as a common etiology (Hyllienmark and Amark 2007, Jette, Claassen, Emerson, et al. 2006, Abend and Dlugos 2007, Tay, Hirsch, Leary, et al. 2006), including the most common etiology in one retrospective series of children with NCSE (26% of 19) (Tay, Hirsch, Leary, et al. 2006). Similarly, a prospective series of children who underwent cEEG due to altered mental status and acute encephalopathy identified NCS in 39% of 31 children with acute HIE (Abend, Gutierrez-Colina, Topjian, et al. 2011). A retrospective study of critically ill children reported that seizures occurred in 33% of 9 with hypoxia-ischemia as an etiology and 17% of 30 with cardiac arrest as an etiology (Williams, Jarrar and Buchhalter 2011). However, these studies may be limited by the fact that not all children with HIE underwent cEEG and that cEEG may not have continued for a long duration. One prospective study enrolled 19 consecutive children with a median age of 11 months undergoing therapeutic hypothermia after cardiac arrest who underwent cEEG for a mean duration of 68 hours as part of the clinical therapeutic hypothermia pathway (Abend, Topjian, Ichord, et al. 2009). Electrographic seizures occurred in 47% and of those with seizures. Two-thirds of children had NCSE and one-third had only electrographic seizures without any electroclinical seizures. Seizures began during the first half of hypothermia in one, the second half of hypothermia in four and during re-warming in four patients (Figure 1) (Abend, Topjian, Ichord, et al. 2009). While this study utilized prospective enrollment of consecutive patients, these children were all considered to have experienced sufficient injury to warrant management with therapeutic hypothermia and thus may represent a more severely injured cohort of children with HIE. However, it is also possible that hypothermia may have prevented NCS in the same patients. Prior reports have also described the occurrence of electrographic and clinical seizures after discontinuation of therapeutic hypothermia in adults (Legriel, et al. 2006, Hovland, et al. 2006) and neonates (Battin, et al. 2004), and studies continuing cEEG during rewarming have reported higher seizure occurrence than when cEEG was performed only during the hypothermic period (Abend, Topjian, Ichord, et al. 2009, Williams, Jarrar and Buchhalter 2011). Therapeutic hypothermia may induce a delay in brain injury evolution, leading to deferred seizure occurrence. Alternatively, therapeutic hypothermia itself could act as a seizure suppressing therapy such that seizures are postponed until re-warming. An animal model of status epilepticus demonstrated that hypothermia reduced seizure frequency and intensity (Schmitt, et al. 2006). A case series of three children reported control of refractory status epilepticus reported with a combination of hypothermia to 30-31°C and thiopental (Orlowski, et al. 1984).

There are few data available to predict which children with HIE will have seizures. In the prospective series of children undergoing therapeutic hypothermia described above, seizures occurred in all eight patients with a severely abnormal EEG background and in only one patient with a mildly/moderately abnormal EEG background. Background assessment was made in the first 30 minutes of the EEG tracing. Severe background abnormalities included excessive discontinuity, burst suppression, or highly attenuated-featureless tracings (Abend, Topjian, Ichord, et al. 2009). If these data are confirmed, then initial EEG findings might help direct limited cEEG monitoring resources to children with more severely abnormal initial tracings. Studies addressing cEEG in heterogeneous samples of critically ill children and not just HIE have reported risk factors for seizure occurrence include younger age

(Abend, Topjian, Ichord, et al. 2009, Williams, Jarrar and Buchhalter 2011), in-hospital clinical seizures (Jette, Claassen, Emerson, et al. 2006), and epileptiform discharges (Jette, Claassen, Emerson, et al. 2006, Williams, Jarrar and Buchhalter 2011).

EEG Features and Prognosis

Beyond seizure identification, cEEG may also be useful for categorizing the degree of brain injury in children with HIE. This could provide prognostic information to families and care teams, and it might assist risk stratification in neuroprotection studies, such as the selective head cooling trial for neonatal HIE (Gluckman, et al. 2005). While individual clinical, laboratory, imaging, and neurophysiologic features may be useful in outcome prediction, none has perfect predictive value (Abend and Licht 2008). Utilization of EEG data is appealing since it can be acquired non-invasively at the bedside and provides semi-objective data when clinical history and resuscitation details are unknown. Unfortunately, an important limitation of EEG-based prognosis is the unclear reproducibility of EEG interpretation in critically ill patients (Husain 2006, Gerber, et al. 2008, Hirsch, et al. 2005, Ronner, et al. 2009). Nevertheless, several EEG classification systems that group EEG features into predictive categories have been developed in adults (Roest, et al. 2009, Synek 1988, Young, et al. 1997) and children (Nishisaki, et al. 2007, Kessler, et al. 2011), although recent studies suggest these categories may not be as sensitive for outcome prediction as when component features are utilized (Thenayan, et al. 2010).

Certain EEG background features are known to have prognostic significance in adults (Wijdicks, et al. 2006, Young 2000) and children (Nishisaki, Sullivan, Steger, et al. 2007, Pampiglione and Harden 1968, Tasker, et al. 1988, Cheliout-Heraut, et al. 1991, Ramachandrannair, et al. 2005, Mandel, et al. 2002, Pampiglione, et al. 1978, Evans and Bartlett 1995). Patients with more severely abnormal EEG backgrounds tend to have a worse short-term outcome than patients with only mild/moderate background abnormalities. Pediatric studies have reported that burst suppression (Pampiglione and Harden 1968), excessive discontinuity (Mandel, Martinot, Delepouille, et al. 2002), severe attenuation (Tasker, Boyd, Harden, et al. 1988), lack of reactivity (Ramachandrannair, Sharma, Weiss, et al. 2005, Mandel, Martinot, Delepouille, et al. 2002), and generalized epileptiform discharges (Mandel, Martinot, Delepouille, et al. 2002) are associated with unfavorable prognosis. Conversely, rapid EEG improvement (Pampiglione, Chaloner, Harden, et al. 1978), reactivity (Cheliout-Heraut, Sale-Franque, Hubert, et al. 1991) and normal sleep patterns (Cheliout-Heraut, Sale-Franque, Hubert, et al. 1991, Evans and Bartlett 1995) are associated with good prognosis. While alpha coma is often considered in relation to anoxic encephalopathy and unfavorable prognosis, it is a non-specific pattern that can occur with a wide variety of etiologies and outcome is probably mostly dependent on etiology. Alpha coma that is reactive to stimulation may indicate a more favorable prognosis (RamachandranNair, et al. 2005, Kaplan, et al. 1999). Together, these studies demonstrate that mild slowing and rapid improvement of the EEG are associated with good outcome, while burst suppression, severe attenuation, and lack of reactivity are associated with poor outcome. Knowledge of the patient's clinical status is essential to ensure that EEG changes are not pharmacologically induced or compromised by scalp edema or extra-axial fluid collections.

EEG Features and Prognosis in the Context of Therapeutic Hypothermia

Therapeutic hypothermia has been shown to improve outcome after cardiac arrest in adults (Bernard, et al. 2002) and HIE in neonates (Gluckman, Wyatt, Azzopardi, et al. 2005, Shankaran, et al. 2005, Azzopardi, et al. 2009, Simbruner, et al. 2010) and despite the current lack of efficacy data (Fink, et al. 2009, Doherty, et al. 2009), therapeutic hypothermia is sometimes employed as a neuroprotective strategy in children after cardiac

arrest (Topjian, et al. 2011, Fink, et al. 2010). At extremely low temperatures, as used in deep hypothermic circulatory arrest, the EEG may develop a discontinuous and then isoelectric pattern (Levy 1984, Stecker, et al. 2001, Rodichok, et al. 1994). While these severe EEG abnormalities are not seen with the moderate hypothermia temperatures used for therapeutic hypothermia in adults (Stecker, Cheung, Pochettino, et al. 2001, Kochs 1995) or neonates (Horan, et al. 2007), EEG patterns have been shown to evolve during the course of therapeutic hypothermia (Abend, Topjian, Ichord, et al. 2009, Rundgren, et al. 2006). This evolution may result from evolving brain injury, temperature modulation, sedative medication adjustments, or all three. In children undergoing deep hypothermia during cardiac surgery, slowing and then attenuation occurred during the procedure but by the end of the procedure activity returned to normal in most children (Rodichok, Winters, Myers, et al. 1994), suggesting hypothermia does not have a persisting impact on EEG features in most children once they return to normothermia.

It is unclear whether the EEG features that predicted outcome prior to utilization of therapeutic hypothermia retain their predictive value when therapeutic hypothermia is utilized. One study enrolled 35 children after cardiac arrest managed with a standard clinical therapeutic hypothermia algorithm. Thirty minute EEG segments obtained during therapeutic hypothermia and during the first 30 minutes of normothermia were scored in a standardized manner and categorized by three pediatric encephalographers. The three EEG categories were: (1) continuous and reactive tracings, (2) continuous but unreactive tracings, and (3) any degree of discontinuity, burst suppression, or lack of cerebral activity. The primary outcome was unfavorable short-term outcome defined as Pediatric Cerebral Performance Category score of 4-6 (severe disability, vegetative, death) at hospital discharge. For tracings obtained during hypothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcome than those in category 1 (OR 10.7, $P = 0.023$ and OR 35, $P = 0.004$, respectively). Similarly, for tracings obtained during normothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcomes than those in category 1 (OR 27, $P = 0.006$ and OR 18, $P = 0.02$, respectively). These data suggest that even when therapeutic hypothermia is utilized, lack of reactivity and discontinuity are associated with unfavorable outcome. However, these features did not have 100% predictive value, and thus cannot be used in isolation for prognostication (Kessler, Topjian, Gutierrez-Colina, et al. 2011).

More data are available regarding the prognostic value of EEG in adults after cardiac arrest. A study of comatose adults after CA using amplitude integrated EEG reported that 54% of 24 patients with initially flat amplitude integrated EEGs developed continuous tracings by normothermia and that all of the patients with improving tracings regained consciousness. Thus, early amplitude integrated EEG even when flat did not reliably predict outcome. However, once normothermic a continuous amplitude integrated EEG was predictive of recovery of consciousness and good neurologic outcome while a flat, burst suppression, or status epilepticus pattern was a strong predictor of poor outcome (Rundgren, Rosen and Friberg 2006). Other studies in adults treated with therapeutic hypothermia after cardiac arrest have also reported that an unreactive EEG (Thenayan, Savard, Sharpe, et al. 2010, Rossetti, et al. 2010) (Rossetti, et al. 2012), suppression (Thenayan, Savard, Sharpe, et al. 2010, Rundgren, Rosen and Friberg 2006) or generalized epileptiform discharges (Thenayan, Savard, Sharpe, et al. 2010) predict unfavorable outcome. A prospective study of 61 adults treated with therapeutic hypothermia after resuscitation from cardiac arrest reported a correlation between serum neuron specific enolase and EEG findings, suggesting that early EEG abnormalities reflect permanent neuronal damage. Median neuron specific enolase levels were higher in patients with unreactive and discontinuous EEGs (Rossetti, Carrera and Oddo 2012). One study of comatose adults treated with therapeutic hypothermia after cardiac arrest reported that all with status epilepticus died (Legriel, et al. 2009).

However, another case series of adults with post-anoxic status epilepticus reported that if they had preserved brainstem reactions, somatosensory evoked potentials, and EEG reactivity a favorable outcome was possible (Rossetti, et al. 2009). Quantitative features during the initial 24 hours after cardiac arrest including the burst-suppression ratio, response entropy, and state entropy may differentiate between patients with good and poor outcome (Wennervirta, et al. 2009). The use of quantitative features may allow standardized interpretation that is not confounded by inter-rater agreement problems inherent in conventional EEG interpretation.

Congenital Heart Disease

Seizure Occurrence and Risk Factors

Neonates and infants undergoing surgery for congenital heart disease often have clinically evident seizures in the post-operative period. A study of risk factors for clinical seizures in infants who survived newborn cardiac surgery requiring deep hypothermic circulatory arrest for defects other than hypoplastic left heart syndrome reported seizures in 18% of 164 infants, with most seizures occurring within two days of surgery (Clancy, et al. 2003). Similarly, a study of infants undergoing repair of D-transposition of the great arteries reported convulsions in 6% of 171 infants during the initial two days (Helmers, et al. 1997).

NCS may be even more common than convulsions in patients with congenital heart disease (Helmers, Wypij, Constantinou, et al. 1997, Gaynor, et al. 2005, Clancy, et al. 2005, Chock, et al. 2006, Schmitt, et al. 2005, Gunn, et al. 2012). In the D-transposition of the great arteries study mentioned above, 136 of 171 infants underwent cEEG for 48 hours, and electrographic seizures occurred in 20%. Most seizures had no clinical correlate and most occurred 13 to 36 hours after surgery (Helmers, Wypij, Constantinou, et al. 1997). Similarly in a second study, NCS occurred in 12% of 183 children who underwent 48 hours of cEEG after cardiac surgery. None had a clinical correlate, and the median seizure onset time was 21 hours (Clancy, Sharif, Ichord, et al. 2005). A retrospective study of infants with congenital heart disease reported electrographic seizures in 6% of 93, and all occurred within one week of surgery (Chock, Reddy, Bernstein, et al. 2006). A study of children who underwent cardiac surgery with cardiopulmonary bypass and underwent EEG from intubation until 22-96 hours after bypass reported electrographic seizures in 8% of 36 (Schmitt, Finckh, Christen, et al. 2005). Finally, a study of 39 infants undergoing Norwood-type operations and continuous amplitude integrated EEG identified intraoperative seizures in 23% and postoperative seizures in 18% (Gunn, Beca, Penny, et al. 2012).

Risk factors for seizures have been identified. In one study, variables associated with an increased risk of clinical seizures included co-existing genetic defects, aortic arch obstruction, and deep hypothermic circulatory arrest duration greater than 60 minutes (Clancy, McGaurn, Wernovsky, et al. 2003). In another congenital heart disease population, electrographic seizures occurred in 24% of 58 children with deep hypothermic circulatory arrest duration 40 minutes or longer, 7% of 59 when duration was less than 40 minutes, and only 3% of 61 who did not undergo deep hypothermic circulatory arrest. Electrographic seizures occurred in 14% of the neonates but only 7% of the older infants (Gaynor, Nicolson, Jarvik, et al. 2005). In the Boston circulatory arrest trial of infants with transposition of the great arteries, risk factors associated with electrographic seizures included treatment with deep hypothermic circulatory arrest rather than continuous cardiopulmonary bypass, longer duration of deep hypothermic circulatory arrest, and the presence of a ventricular septal defect (Helmers, Wypij, Constantinou, et al. 1997).

Multiple etiologies may explain the high incidence of electrographic seizures in neonates and infants undergoing repair of congenital heart disease. Hypoxic-ischemic injury and

systemic inflammatory response may arise during the pre-operative, operative, and post-operative periods. Periventricular leukomalacia was identified by *preoperative* MRI in 16% of 24 neonates (Mahle, et al. 2002). New lesions or worsening of preoperative lesions occurred in 67% of those subjects, including new infarcts in 19% and new parenchymal hemorrhages in 33% (Mahle, Tavani, Zimmerman, et al. 2002). In another neuroimaging study, post-operative MRIs showed periventricular leukomalacia in 54% of 82 neonates and 4% of 23 older infants (Galli, et al. 2004). Stroke is reported in 10% of 122 children with congenital heart disease, and half of these occurred pre-operatively (Chen, et al. 2009). Delayed brain maturation is reported in children with congenital heart disease (Licht, et al. 2009), and this may associated with increased excitatory mechanisms predisposing to electrographic seizures.

The impact of these electrographic seizures remains unclear. In the Boston circulatory arrest study, early post-operative electrographic seizures were associated with an 11.2 point reduction in the psychomotor development index of the Bayley scales of infant development at one year follow-up, and also with a significantly higher risk of possibly or definite MRI abnormalities (Bellinger, et al. 1995). A study of 171 children with D-transposition of the great arteries who underwent neurodevelopmental assessment at 1 and 2.5 years of age reported that children with postoperative clinical and electrographic seizures had significantly lower psychomotor development scores than those without seizures (12.9 mean difference for clinical seizures and 13.3 mean difference for electrographic seizures). Children with seizures were also significantly more likely to have an abnormal neurologic examination and abnormal MRI (Rappaport, et al. 1998). Similarly, a study of 158 infants undergoing repair of D-transposition of the great arteries who underwent neurodevelopmental testing at four years reported that clinical or electrographic seizures in the perioperative period were associated with significantly lower mean intelligence quotient scores and increased risk of neurological abnormalities (Bellinger, et al. 1999). A study of 139 adolescents who had undergone repair of D-transposition of the great arteries as infants reported that postoperative seizures were the medical variable most consistently associated with worse outcome (Bellinger, et al. 2011). A study of 164 infants with congenital heart disease participating in an APOE polymorphisms study (Clancy, et al. 2005) reported that at one year follow-up, abnormal or suspect neurological examination results were found in 41 of 99 (41%) patients without seizures and 11 of 15 (73%) patients with postoperative seizures. Seizure occurrence was not associated with significantly lower scores on Bayley Scales of Infant Development, except for frontal-onset seizures which were associated with significantly lower Mental Development Index scores compared with non-frontal-onset seizures (Gaynor, et al. 2006). In a study of amplitude integrated EEG in infants undergoing Norwood-type procedures seizures were associated with higher mortality when they occurred during the intraoperative period (63% versus 7%) or post-operative period (44% versus 13%). However, among survivors, seizures were not associated with neurodevelopmental impairment (Gunn, Beca, Penny, et al. 2012). Further study is needed to better determine the impact of clinical and electrographic seizures on neurodevelopmental outcome, and establish whether identifying and managing electrographic seizures is associated with improved neurodevelopmental outcome.

In addition to the problem of seizures during the acute period of congenital heart disease repair, a history of congenital heart disease is common in children with NCSE identified later in life. Retrospective studies of children with NCS and NCSE have reported that 8-25% of children have a history of cardiac disease (Abend and Dlugos 2007, Saengpatrachai, Sharma, Hunjan, et al. 2006). As described above, congenital heart disease may be associated with multiple forms of brain injury which later result in remote symptomatic seizures.

EEG Background and prognosis after surgery for congenital heart defects

EEG findings other than seizures may have predictive value. A study of 60 children (36 newborns and 24 infants) who underwent congenital heart disease repair and perioperative EEGs reported that moderate or severe EEG abnormalities were associated with abnormal acute neurological examinations (93%). Further, outcome at one year could be predicted by postoperative EEG findings; children with normal EEGs had favorable neurologic outcome, and all with severely abnormal EEGs died or had severe disability (Limperopoulos, et al. 2001). In contrast, a prospective study of 66 infants (70% neonates) undergoing congenital heart disease repair with deep hypothermic circulatory arrest did not identify any association between EEG features or seizures and outcome (Miller, et al. 1994). One study of 36 children who underwent cEEG after congenital heart disease repair reported that over 48 hours there was a substantial increase in delta power in 24 children, including significantly more children without any neurologic deficits than with neurologic deficits at follow-up (86% versus 50%). Further, patients with more delta activity had shorter bypass durations and lower markers of oxidative stress and inflammation (Schmitt, Finckh, Christen, et al. 2005). Similarly, in a study of 39 infants undergoing Norwood-type operations and amplitude integrated EEG, delay in recovery of amplitude integrated background beyond 48 hours was associated with higher mortality and worse neurodevelopmental outcome among survivors (Gunn, Beca, Penny, et al. 2012). This suggests that increasing slowing in the post-operative period may actually be a marker of recovery. More data are needed regarding the prognostic implications of EEG findings in children with congenital heart disease.

Extracorporeal Membrane Oxygenation

Seizure Occurrence

Pediatric patients who undergo extracorporeal membrane oxygenation (ECMO) represent a unique population potentially exposed to both *diffuse* and *focal* neurological injury. In order to qualify for ECMO, critical inability to maintain adequate system perfusion and oxygenation must be demonstrated, indicating a risk for hypoxic-ischemic brain injury. Initiating ECMO typically involves cannulation of the right carotid artery and jugular vein which exposes the child to a superimposed focal brain injury. Thus, the ECMO population lies at the interface between the HIE and stroke populations.

A study of the United States Extracorporeal Life Support Organization (ELSO) Registry of 26,529 children that excluded children with cardiopulmonary arrest reported clinical seizures in 8.4% and electrographic seizures in 2.1% of patients. Seizures occurred in 9% of neonates with respiratory conditions, 8.1% of neonates with cardiac conditions, 6% of pediatric patients with respiratory conditions, 11% of pediatric patients aged one month to one year with cardiac conditions, and 7.4% of pediatric patients older than one year with cardiac conditions (Hervey-Jumper, et al. 2011). A registry study that included only cardiac cases reported acute clinical seizures in 8.1% of neonates, 10% of children aged 31 days to one year, and 5.5% aged 1-16 years (Haines, et al. 2009). A single center study of infants receiving ECMO reported an even higher occurrence of clinical seizures, occurring in 30% of 50 infants (Campbell, et al. 1991). Electrographic seizures may be even more common. A study of 36 neonates undergoing ECMO reported NCS in 17%, including 11% with NCSE (Hahn, et al. 1993). Similarly, a second study of 26 neonates undergoing ECMO reported NCS in 11% (Horan, Azzopardi, Edwards, et al. 2007). However, none of these studies performed cEEG in all consecutive patients, and thus they likely under-represent the incidence of seizures in this population.

Seizures may be a risk factor for neurodevelopmental disorders. A study of 145 neonates treated with ECMO reported that 11 had electrographic seizures which were associated with a significantly increased risk of short-term adverse outcome (Streletz, et al. 1992). A study

of 36 neonatal ECMO patients reported that the occurrence of electrographic seizures or status epilepticus was associated with a significantly increased risk of death or severe outcome (Hahn, Vaucher, Bejar, et al. 1993). A longitudinal prospective study of 64 ECMO survivors reported that children with seizures during or before ECMO had significantly lower intelligence quotient scores and higher rates of cerebral palsy and language disorders (Parish, et al. 2004). Another study reported that neonates with seizures requiring treatment had an increased relative risk (2.25) of disabilities at four years of age (Bennett, et al. 2002). A study of 50 ECMO survivors at two years of age, showed that seizures were associated with significantly lower developmental quotients than those without seizures (89.6 versus 105.5) (Campbell, Bunyapen, Gangarosa, et al. 1991). An example of NCS identified during ECMO is shown in Figure 2.

EEG Background and Prognosis after ECMO

The value of EEG background abnormalities in predicting outcome after ECMO has received some attention. A study of 36 neonatal ECMO patients reported that a burst suppression pattern was associated with a significantly increased risk of death or severe outcome (Hahn, Vaucher, Bejar, et al. 1993). A study of 199 neonates following ECMO at 12-45 months of age reported that if two EEG tracings during the acute course demonstrated either electrographic seizures or burst suppression, then there was an increased odds ratio for poor prognosis. These features on only one EEG tracing were not predictive of unfavorable outcome (Graziani, et al. 1994). However, a follow-up study by the same group initially described at younger than 45 months of age (Graziani, Streletz, Baumgart, et al. 1994) reported that in 66 school age survivors of neonatal ECMO without severe brain injury who could undergo neuropsychological testing, EEG severity during ECMO did not predict academic and achievement testing at school age (Goodman, et al. 2001).

Stroke

Children with various subtypes of stroke often present with clinical seizures (Del Balzo, et al. 2009, Nagaraja, et al. 1994, Al-Sulaiman, et al. 1999, Chung and Wong 2004, Bojinova, et al. 2000, Beslow-Kaye, et al. In press.). Clinical seizures are reported at presentation in 19-44% of children with arterial ischemic stroke (Abend, et al. 2011, Steinlin, et al. 2005, Delsing, et al. 2001, Mancini, et al. 1997, Lanska, et al. 1991), 36-41% of children with intraparenchymal hemorrhage (Beslow-Kaye, Abend, Gindville, et al. In press., Al-Jarallah, et al. 2000, Beslow, et al. 2010), and 40-58% with sinovenous thrombosis (deVeber, et al. 2001, Sebire, et al. 2005).

There have been no studies in which consecutive children with acute stroke of any type underwent cEEG. While detailed epidemiologic data are lacking, NCS occur in at least some children with acute stroke. Retrospective series of children with NCS or NCSE have also identified acute ischemic and hemorrhagic stroke as common etiologies (Jette, Claassen, Emerson, et al. 2006, Abend and Dlugos 2007, Saengpatrachai, Sharma, Hunjan, et al. 2006, Tay, Hirsch, Leary, et al. 2006). A prospective series of 100 children who underwent cEEG due to altered mental status reported that 5 of 7 children with acute stroke had NCS (Abend, Gutierrez-Colina, Topjian, et al. 2011). However, many more children with stroke were managed in the intensive care unit during the study period, suggesting that these seven children likely had clinical features suggesting a higher risk of NCS, and that this high NCS occurrence is not representative of the overall stroke population. In a study of 60 children with arterial ischemic stroke, 13 had clinical seizures on presentation. Although cEEG was not performed in a standardized manner, four underwent cEEG and NCS were identified in three (Abend, Beslow, Smith, et al. 2011). Similarly, in a study of 55 children with spontaneous intracerebral hemorrhage, 19 had clinical seizures on presentation. Although cEEG was not performed in a standardized manner, 19 children underwent cEEG and NCS

were identified in four. Three of the four had clinical seizures at presentation and had already received anticonvulsants when electrographic seizures were identified (Beslow-Kaye, Abend, Gindville, et al. In press.). Similar data have been reported in adults. In a study of 102 consecutive adults with intracerebral hemorrhage who underwent cEEG, electrographic seizures occurred in 18% and were associated with hemorrhage expansion (Claassen, et al. 2007).

The impact of seizures on outcome after stroke is unknown. Many stroke models regard the core of the infarction to be non-vital and impervious to potentially adverse effects of seizures. However, the surrounding stroke penumbra is a zone of graded injury, blending full scale infarction with lesser degrees of injury; seizures emanating from the surviving but unstable neurons could amplify the pace and extent of total injury. Theoretically, seizures could exacerbate brain injury directly by causing cerebral hypoxia, lactic acidosis, and higher metabolic demand and indirectly by inducing catecholamine release, with resulting cardiovascular, metabolic, and thermal instability. These changes may be responsible for the higher in hospital mortality seen in adults with early seizures compared to those without seizures (33% versus 14%) (Arboix, et al. 1996). Studies of neonatal arterial ischemic stroke (Sreenan, et al. 2000), pediatric arterial ischemic stroke (Delsing, Catsman-Berrevoets and Appel 2001), and pediatric stroke of multiple types (Chung and Wong 2004) have reported an association between seizures at presentation and worse outcome, including subsequent epilepsy with ischemic stroke in children (Lee, et al. 2009). In contrast studies of children with hemorrhagic stroke have not identified an association between seizures and overall outcome (Beslow, Licht, Smith, et al. 2010) or later risk for remote symptomatic seizures or epilepsy (Beslow-Kaye, Abend, Gindville, et al. In press.).

A recent pediatric stroke management scientific statement recommended that (1) stabilizing measures should include controlling seizures, (2) in the absence of clinical or electrographic seizures, prophylactic administration of antiepileptic medications in children with ischemic stroke is not necessary and (3) given the frequency of epileptic seizures in children with an acute cerebral sinus venous thrombosis, cEEG monitoring may be considered for individuals who are unconscious and/or mechanically ventilated (Roach, et al. 2008). Further study is needed regarding the epidemiology of NCS in various stroke subtypes and the impact of NCS identification and management on outcome.

Duration of EEG Monitoring

Studies of critically ill children undergoing clinically indicated cEEG suggest that about half of patients with seizures are identified in the first hour and about 90% are identified within the first 24 hours of the onset of cEEG (Abend, Gutierrez-Colina, Topjian, et al. 2011, Jette, Claassen, Emerson, et al. 2006, Abend and Dlugos 2007, Williams, Jarrar and Buchhalter 2011, Greiner, Holland, Leach, et al. 2012, Shahwan, Bailey, Shekerdemian, et al. 2010, Schreiber, et al. 2012), and this is consistent with large studies of critically ill adults (Claassen, et al. 2004) (Figure 3). However, these studies may be confounded by the fact that cEEG duration was not pre-determined and applied uniformly to all patients and if cEEG duration was longer, seizures may have been identified later in some patients. *Acute symptomatic seizures* are defined as those provoked seizures which occur as a reaction to an insult within one week of their triggering events such as hypoxic-ischemic brain injury, stroke, intracranial surgery, central nervous system infection, or surgery for congenital heart defects (Beghi, et al. 2010). To date, there have been no comprehensive studies in which cEEG monitoring persisted throughout the entire first week following an index event for all patients.

Seemingly small changes in intensive care unit cEEG monitoring pathways related to monitoring duration have a substantial impact on resource needs (Gutierrez-Colina, et al. 2012), necessitating investigations that will guide efficient cEEG utilization. Studies of children with specific types of acute brain injury and management may better focus the question of the optimal duration of cEEG monitoring. In a prospective study of 19 children undergoing therapeutic hypothermia after cardiac arrest, cEEG was initiated urgently (within five hours) of the arrest and continued throughout the entire clinical protocol, terminating after the patient had been normothermic for 24 hours. No children had electrographic seizures in the initial six hours of monitoring (early hypothermia), one had seizures in the next six hours (early hypothermia), four had seizures during the next 12 hours (late hypothermia), and four had seizures in the next 24 hours (re-warming) (Abend, Topjian, Ichord, et al. 2009). Similarly, in neonates and infants who underwent repair of CHD, electrographic seizure onset occurred at a mean of 21 hours (Gaynor, Nicolson, Jarvik, et al. 2005, Clancy, Sharif, Ichord, et al. 2005). These data suggest that with further study the timing of cEEG initiation and the duration of cEEG could be tailored to the individual profile of the patients' age, clinical status and the etiology of the acute encephalopathy.

Electrographic Seizures and Outcome

The neurodevelopmental impact of electrographic seizures remains unknown. Aside from studies in children with CHD (described above), the few studies addressing the impact of NCS and NCSE on outcome have involved cohorts with heterogeneous types of injury. A prospective study of 200 critically ill children with heterogeneous acute brain injury etiologies reported that electrographic status epilepticus but not electrographic seizures was associated with higher mortality and worse hospital discharge outcomes even after accounting for age, acute brain injury etiology, and EEG background score (Topjian, et al. In press.). Similarly, a study of 204 critically ill neonates and children described that among 111 survivors at one month electrographic seizures were associated with worse neurologic outcome, even after controlling for acute brain injury etiology and pediatric index of mortality scores (Kirkham, Wade, McElduff, et al. 2012). A study of 75 children (not all of whom were critically ill) reported that the presence of NCS was associated with higher mortality and neurologic morbidity (Greiner, Holland, Leach, et al. 2012). A study of 94 critically ill children reported that electrographic seizures were associated with "bad" outcome (Schreiber, Zelleke, Gaillard, et al. 2012). In adults with traumatic brain injury, electrographic seizures have been associated with elevations in intracranial pressure and lactate-pyruvate ratios (suggesting metabolic dysfunction) (Vespa, et al. 2007) and with later hippocampal atrophy ipsilateral to non-convulsive seizure occurrence (Vespa, et al. 2010). Even if electrographic seizures are associated with worse outcome, further study is needed to determine whether identification and management of electrographic seizures improves outcome.

Summary

Electrographic seizures are common in critically ill children with hypoxic ischemic encephalopathy, congenital heart disease, and stroke. Many are undetectable without EEG monitoring and even electrographic status epilepticus can be missed by unaided clinical observation. There is growing concern from animal and human data that electrographic seizures and particularly electrographic status epilepticus may contribute to the ultimate extent of brain injury. Additionally, EEG background features may be helpful in predicting outcome in some patients. Future prospective studies are needed to better determine the risk factors for electrographic seizures and establish whether seizure identification and management improves neurodevelopmental outcome.

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Seizures 47% (9 of 19)

Status Epilepticus 32% (6 of 19)

Figure 1.

Electrographic seizures during therapeutic hypothermia management in children resuscitated from cardiac arrest. Each child is shown as a bar. Gray bars represent time during which cEEG was performed. Thin black bars represent periods with electrographic seizures and thick black bars represent status epilepticus. Figure based on (Abend, Topjian, Ichord, et al. 2009).

Figure 2.

Frequent electrographic seizures in a 7 month old with congenital heart disease and multi-focal ischemic strokes undergoing ECMO. Top panel: Left parietal predominant seizure. Bottom Panels: Multiple electrographic seizures are visible on a 12 hour amplitude-integrated EEG tracing (arches) and density spectral array tracing (upward spikes in frequency and frequency).

Figure 3.
Duration between cEEG onset and first electrographic seizure identification.