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EEG MONITORING DURING THERAPEUTIC HYPOTHERMIA AND ITS CORRELATION WITH NEURONAL BRAIN INJURY ON MRI IN NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY

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ABSTRACT

Background: Therapeutic hypothermia (TH) is becoming a neuroprotective strategy for neonatal hypoxic-ischemic encephalopathy (HIE).The prognostic value of the EEG for neuronal outcome during TH is still uncertain. **Aim:** To determine EEG background, incidence of seizures during Therapeutic hypothermia, and to identify different patterns of EEG predictive for MRI brain injury. **Patients and Methods**: This study was conducted on 70 newborns with HIE who underwent TH. Continuous video-EEG monitoring was performed during hypothermia and rewarming. EEG background and seizure patterns were reported in a standardized fashion. Newborns had undergone MRI brain after rewarming. Sensitivity and specificity of EEG background for moderate to severe MRI brain injury was assessed at 6-hour intervals during TH and rewarming Findings: At all-time points, a normal EEG was associated with no or mild MRI brain injury and predictive of a favorable MRI outcome (100% specific) than at later time points (90% specific). Burst suppression and low voltage patterns held the greatest prognostic value only after 24-48 hours of monitoring, with a specificity of 85%. Electrographic seizures occurred in 50% (35/70), and 10% (7/70) developed status epileptics. **Conclusions:** Continuous video-EEG monitoring in newborns with HIE undergoing TH has a prognostic value about early MRI brain-findings.

KEYWORDS: Therapeutic hypothermia, EEG, MRI.

INTRODUCTION

Hypoxia-ischemia is a significant cause of brain damage in the human newborn and can result in long-term neurodevelopmental disability.[1] Neonatal seizures are an important risk factor for impaired neurodevelopment in the setting of hypoxic-ischemic encephalopathy.[2] Although the adverse outcome is thought to be primarily related to brain injury caused by hypoxia-ischemia, there is also increasing evidence from animal models and human studies that seizures themselves may be harmful to the developing brain, especially in the setting of underlying injury.[3]

Most studies of neonatal seizures have relied on clinical observation. However, increased use of video-electroencephalogram (EEG) monitoring has highlighted the fact that seizures in newborns are often subclinical, and that clinicians are poor at clinically distinguishing seizures from non-seizure spells.[4] There has been debate as to the importance of seizures that are electrographic only as compared with those that manifest obvious clinical signs .Early and accurate prediction of outcome in infants with encephalopathy is important for early clinical management decisions and counseling parents regarding long-term outcome.[5]

Previous studies have demonstrated a clear relationship between seizure burden, and injury on MRI. However, little is known regarding seizure frequency, localization, timing of onset and clinical expression of seizures and their relationship to MRI injury, especially in the setting of therapeutic hypothermia.[6]

Aims and objectives

The aim of this study was to evaluate the value of video EEG monitoring in newborns with hypoxic ischemic encephalopathy treated by hypothermia through determination of EEG background and incidence of seizures during hypothermia, and to identify different patterns of EEG predictive for MRI brain injury.

MATERIAL AND METHODS

This work was conducted on 70 newborns with hypoxic ischemic encephalopathy admitted to NICU at our hospital between 2011 to2014. All newborns included in the study gave consent from participant parents. All cases were subjected to therapeutic hypothermia(TH) with whole body cooling according to standard protocols.

Inclusion criteria for TH included:

1) Gestational age at birth ≥36 weeks.
2) Any of the following:
3) PH <7.0 of cord or first blood gas.
4) Base deficit >16 of cord blood.
5) 10-minute Apgar score <5,
6) Moderate to severe encephalopathy within 6 hours of birth.

Exclusion criteria: included known or suspected cases of congenital malformation and inborn errors of metabolism, gestation less than 36 weeks, birth weight less than 2 kg.[3]

TH was initiated as soon as possible after birth or at the time of referral from the outside hospital and consisted of whole-body hypothermia (target temperature 33C) for 72 hours followed by rewarming gradually over approximately 6-12 hours. Clinical and electrographic seizures were treated with antiepileptic drugs (AEDs) according to institutional guidelines.[1] Clinical data were reported from medical records. All patients were under sedation throughout TH to prevent discomfort.

Video-EEG monitoring

A trained technician applied surface electrodes EEG according to the international 10–20 system of electrode placement, as modified for neonates. A Nicolet One EEG monitor was used to record continuous video-EEG recordings for approximately 72 h. Recordings commenced as soon as possible after birth. Physiologic measurements of heart rate, respiration, oxygen saturation, and, where available, direct arterial blood pressure were recorded from the infants' intensive care monitor and were recorded simultaneously with the EEG.[7] An electrographic seizure was defined as repetitive rhythmic activity of >10 s duration, with a distinct beginning, middle, and end . Status epilepticus was defined as continuous electrographic seizure activity for at least 20 minutes, or recurrent electrographic seizures for at least 60% of 1-3 hours of recording time.[8] EEG background at the onset of recording was classified into one of 5 patterns: 1) Normal for gestational age, including recordings with transient discontinuity for less than 50% of the recording, with presence of distinct state changes; 2) Excessively discontinuous, with persistence of discontinuous activity occupying more than 50% of the recording, and consisting of bursts of normal activity separated by abnormally long, interburst intervals of more than 6 seconds duration, and amplitude >5**μ**V and<25**μ**V, with poor state changes 3) Depressed and undifferentiated,

with persistently low-voltage background activity with amplitude between 5**μ**V and 15**μ**V and without normal features 4) Burst suppression, invariant and unreactive pattern of bursts of paroxysmal activity with mixed features but no age-appropriate activity, lasting less than 10 seconds, and alternating with periods of marked voltage attenuation with amplitude ≤5**μ**V 5) Extremely low voltage, invariant and unreactive pattern, with amplitude <5**μ**V or with no discernible cerebral activity.[9]

Brain Magnetic Resonance Imaging

Neonates were imaged with conventional T1-weighted, T2-weighted and diffusion-weighted imaging sequences. Infants were imaged shortly after rewarming with median of 6 days of life.[10] We defined normal to mild MRI injury as basal ganglia/thalamus score <2 and watershed score <3 and moderate to severe MRI injury as basal ganglia/thalamus score ≥2 (involving both the thalamus and the lentiform nucleus) or watershed pattern ≥3 (involving both watershed cortex and white matter). A similar classification was highly predictive for neurologic disability at 18 months of age in newborns with HIE treated with hypothermia.[11]

Statistical analysis

All analyses were performed with computerised software programs. t test was used for continuous variables. $\chi 2$ and Fisher exact tests were used to compare dichotomous variables. Sensitivity and specificity were used to assess the prognostic value of EEG background patterns at each time interval. a p value < 0.05 was considered significant.

Findings

During the study period, 70 newborns were treated with hypothermia and all had continuous video-EEG available for review. All were evaluated with MRI. The results of our study are shown in the tables.

Beginning of cooling

None of the newborns with a normal background at the beginning of cooling had moderate to severe injury. Of the 19 newborns with an excessively discontinuous pattern, 6 had moderate to severe injury, 4 had mild injury, and 5 were normal. In contrast, of the newborns with BS or extremely low voltage patterns, 62.5% had moderate to severe injury Of these, 4 had maximal MRI injury scores. Interestingly, 4 newborns with BS or extremely low voltage patterns at the beginning of cooling had a normal MRI or only mild injury. In all 6 cases, however, the EEG improved by 12–18 hours of recording, and background normalized by

middle of cooling. None of newborns with a normal EEG during middle of cooling had moderate to severe injury. Of the infants with a discontinuous EEG, again 19% had moderate to severe injury. By this time period, all newborns (100%) with BS or extremely low voltage patterns had moderate to severe injury, with 2 having maximal MRI injury scores.

End of cooling

Moderate to severe MRI injury was present in 19% whose background was normal and infants 16% whose background was excessively discontinuous, compared with all 100% whose background showed BS or extremely low voltage.

After cooling

During this interval, the same newborns with a normal background 19% had moderate to severe injury.

Electrographic seizures and status epilepticus (SE).

Electrographic seizures were identified in 50%, 7(10%) of whom had SE. Among the newborns with seizures, 85% had seizure onset within the first 15 hours of recording, 13 in the first 6 hours. One infant had seizure onset during rewarming. Recurrent seizures were recorded during middle of cooling in 2 patients and during rewarming in another 2. 43% never showed a clinical correlate during seizures, including those with subclinical SE. All infants with SE had BS or extremely low voltage patterns at the beginning of cooling and never recovered better than depressed and undifferentiated at last time point. Isolated or recurrent seizures were more frequent in patients with moderate to severe MRI injury compared with those with no or mild injury (48% vs 22%, $p = 0.05$), and SE was only seen in newborns with moderate to severe injury ($p = 0.01$).

Table(1): Clinical characteristics of newborns in relation to brain injury.

Character	No or mild MRI injury	Moderate to severe MRI injury	P value
Gestational age,mean ±SD	36±14	39±18	0.6
Sex ratio,M:F	1.2:1	1:1.3	0.4
Birth weight, mean ±SD	2.6±0.4	3.3±0.4	0.6
Cord or blood gas pH , mean±SD	6.58±0.16	6.52±0.33	0.05
10- minutes apgar score median(range)	41-8)	4(0-8)	0.06

This table shows that none of clinical characteristics was significantly associated with brain injury in MRI**.**

Table(2):Evolution of EEG background with hypothermia by severity of MRI injury

EEG background	Start		Middle		End		After	
	None|Mild injury	Moderate |severe injury	None|Mild injury	Moderate |severe injury	None|Mil d injury	Moderate |severe injury	None|Mild injury	Moderate |severe injury
Normal	18	0	14	5	11	3	16	3
Excessively discontinuous	19	6	11	4	14	4	10	5
Depressed And undifferentiated	6	3	4	5	4	8	4	5
Burst suppression	9	7	0	4	0	5	0	4
Extremely low voltage	8	5	0	6	0	4	0	4

Table (3): Evolution of EEG background, seizures and status epilepticusand MRIoutcome

EEG background pattern,median(range)	No|mild MRI injury	Moderate|severe MRI injury	P-value
Start of cooling	4(1-8)	3 (0-5)	0.009
Middle of cooling	3.5 (1-6)	3 (1-5)	0.001
End of cooling	3 (1-5)	3 (1-7)	0.006
After cooling	3(1-5)	3(1-5)	0.005
Seizures no.(%)	5(28)	5(49)	0.04
Status epilepticus no.(%)	0	5(24)	0.01

Table(4): Sensitivity and specificity of EEG background during and after hypothermia for moderate to severe MRI injury

EEGbackgroundcutpoint	Phase of hypothermia							
	Start		Middle		End		After	
	Sensitivity %b	Specifcity %c	Sensitivity %b	Specifcity %c	Sensitivity %b	Specifcity %c	Sensitivity %b	Specifcity %c
1va2,3,4,5	100	39	82	64	88	39.5	88	58
1,2va3,4,5	85	72.5	77	95	78	93	78	96
1,2,3va4,5	77	85	57	100	39	100	48	100
1,2,3,4va5	35	85.5	20	100	15	100	15	100

a 1= normal ,2= excessively discontinuous ,3= depressed and undifferentiated ,4= burst suppression suppression ,5=extremely low voltage.

[b]Sensitivity: Given moderate to severe injury, % identified as positive by EEG.

[c]Specificity: Given no moderate to severe injury, % identified as negative by EEG

DISCUSSION

After perinatal asphyxia, the occurrence of seizures remains a significant neurologic event. The outlook for neurologic development is changed dramatically by the occurrence of clinical seizures, which place the infant in the category of moderate-to-severe encephalopathy.[2] All of the previous studies examining the prediction of seizures were based on clinically diagnosed seizures, confirmed by intermittent electroencephalographic (EEG) recordings. However, it is now known that ~60% of neonatal seizures are subclinical and will not be recognized without continuous EEG monitoring. Continuous EEG monitoring is the gold standard for accurate neonatal seizure detection.[12] Thepotential of neuroprotective therapies, such as hypothermia, has raised the importance of accurate prediction of outcome in the first hours of life.[13] This study showed that none of clinical characteristics was associated with brain injury in MRI. These data were concordant with murray et al.,2006 who reported that neither the condition at birth nor the degree of metabolic acidosis reliably predicts the occurrence of seizures.[2] In our study, EEG background was associated with early MRI findings throughout the treatment periods. At all-time points, a normal EEG was associated with no or mild MRI brain injury although a normal background at the beginning of cooling was even more predictive of a favorable MRI outcome (100% specific) than at later time points (80% specific), as the EEG background of one newborn with moderate to severe MRI injury improved from excessively discontinuous to normal over the first 24 hours of monitoring .Our data are in agreement of nash et al.,2011 who reported that, normal background at the beginning of cooling was more predictive of a favorable MRI outcome (100% specific) versus 93% at later time points.[14] In contrast, the prognostic value of a BS pattern or extremely low voltage background for moderate to severe injury increased from the beginning of cooling (75% specific) to middle of cooling and thereafter (100% specific), reflecting 6 newborns with these patterns at the onset of monitoring who rapidly improved by middle of cooling and were protected from moderate to severe MRI injury. The greatest prognostic value of EEG background in this population for predicting moderate to severe MRI brain injury was not achieved until middle of cooling, highlighting the importance of continuous monitoring or sequential EEGs in this population . simillar results were reported by Nash et al.(2011)[14]. In this cohort, a BS or extremely low voltage EEG was not highly predictive for moderate to severe MRI injury until the second day of life, around the time of middle of cooling. Similarly, a recent study evaluating the prognostic value of amplitude-integrated EEG in newborns with HIE exposed to normothermia compared to those treated with TH showed that a severely abnormal background pattern in the hypothermia-treated

group was not specific for abnormal developmental outcome until 48 hours of life.[15]

The few studies that reported EEG background in this population within the first 24 hours of life showed a relatively poor specificity for adverse developmental outcome following a severely abnormal background during the first 12 hours of life because of EEG normalization by 12 to 24 hours of life in some infants with normal outcome.[2] These findings are substantiated by prior studies in non- cooled infants with HIE, which revealed that a normal EEG within the first 2–7 days of life is associated with favorable developmental outcome and a severely abnormal EEG (BS or extremely low voltage) on the second day of life or thereafter is associated with poor outcome.[16] This finding is supported by a prior study evaluating EEG during hypothermia in neonatal HIE by a single sample recorded sometimes in the first 48 hours of life, which found that a background of <5 μV was associated with death or major neurologic disability.[17] Most of newborns in this cohort (75%) with an excessively discontinuous pattern after rewarming had no or only mild MRI injury. These findings differ from prior studies of non-cooled newborns with HIE as they found that a discontinuous EEG the first several days of life is often associated with poor outcome.[18] This difference can be attributed to differences in methodology and the wide range of definitions of discontinuous background in the literature, the outcome of newborns with an excessively discontinuous background appears to be different in newborns treated with hypothermia .Given emerging data suggesting that seizures may be associated with increased brain injury following neonatal HIE, accurate seizure detection is becoming an important issue in the context of neuroprotection. Future studies that evaluate whether rapid and effective treatment of seizures will improve neurologic outcome will rely on continuous EEG monitoring.[3,19]

In this study, electrographic seizures were found in 31% of newborns during TH. This was in agreement of Wusthoffet al.2011 who found 65% of subjects had electrographic seizures during or immediately after treatment with hypothermia. These findings are consistent with the "pre-hypothermia" literature, which describes seizures in 22%-64%, suggesting that hypothermia as employed for hypoxic-ischemic encephalopathy does not substantially affect the incidence of seizures.[20] In this study, continuous video-EEG revealed 43% never showed a clinical correlate during seizures, including 3 with subclinical SE. Bjorkman et al .,2010 reported that almost 50% of newborns with seizures, including 3 with SE, had seizures without clinical correlate.[1,4] Although experimental studies showed a potent effect of hypothermia in controlling seizures, a high incidence of seizures has been reported in

children during TH.[21] Also, Srinivasakumar et al.,2013 stated that, therapeutic hypothermia was associated with a reduced seizure burden in infants with mild and moderate injury, but not in those with severe injury.[6] This discrepancy may be attributed to the earlier and deeper cooling used in animal models.[20] Most studies rely on clinical evaluation for seizure diagnosis and classification of seizure severity in newborns. However, it is known that the majority of seizures, especially in critically ill infants, do not have a clinical correlate and will not be recognized without continuous EEG.[2] Moreover, it is often impossible to accurately differentiate between seizure-related and non-seizure movements in infants using clinical evaluation alone.[22] While isolated or recurrent seizures were recorded in more than 50% of infants with moderate to severe brain injury, not all were associated with moderate to severe brain injury. In contrast, all newborns with SE had severely abnormal MRI. These results are in keeping with a recent work suggesting that a significantly worse outcome occurs in newborns with SE compared to newborns with recurrent seizures.[23]

CONCLUSIONS

We can conclude the importance of continuous EEG monitoring in newborns with HIE to assist with seizure management and discussions regarding prognosis and goals of care. Even in the setting of hypothermia, EEG remains a strong predictive tool, and its routine use alongside clinical evaluation and MRI is warranted.

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REFERENCES

1. Björkman ST, Miller SM, Rose SE, et al. Seizures are associated with brain injury severity in a neonatal model of HIE. Neuroscience, 2010; 66(1): 157-67.
2. Murray DM, Boylan GB, Ryan CA,et al. Early EEG findings in HIE predict outcomes at 2 years. Pediatrics., 2009; 124(3): e459–67.
3. Hannah CG, Kendall BH, Sonia LF, et al. Seizures and MRI brain injury in newborns cooled for hypoxic ischemic encephalopathy. JPediatr., 2011; November 159(5): 731–735.
4. Rutherford M, Ramenghi LA, Edwards AD. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested sub study of a randomised controlled trial. Lancet Neurol., 2010; 9: 39–45.

5. Sudhin T, Manigandan C, Andrew T,et al. Cerebral Magnetic Resonance Biomarkers in Neonatal Encephalopathy. Pediatrics., 2010; 125(21): 382-395.
6. Srinivasakumar P, Zempel J, Wallendorf M, et al. TH in neonatal HIE, electrographicseizures and magnetic resonance imaging evidence of injury .J Pediatr., 2013; 163(2): 465-70.
7. De Weerd AW, Despland PA, Plouin P. Neonatal EEG. The international federation of clinical neurophysiology.ElectroencephalogrClinNeurophysiol Suppl., 1999; 52: 149–57
8. Tekgul H, Bourgeois BF, Gauvreau K, et al. Electroencephalography in neonatal seizures: Comparison of a reduced and a full 10/20 montage. Pediatr Neurol., 2005; 32: 155–61.
9. Hannah CG, Kendall BN,SoniaLB,et al. Seizures and MRI brain injury in newborns cooled for hypoxic ischemic encephalopathy. J Pediatr., 2011; 159(5): 731–735.
10. Barkovich AJ, HajnalBL, Vigneron D. Prediction of neuromotor outcome in perinatal asphyxia. Am J Neuroradiol., 1998; 19: 143–149.
11. Rutherford M, Ramenghi LA, Edwards AD.Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy. Lancet Neurol., 2010; 9: 39–45.
12. Shellhaas RA, Saoita AI, Clancy RR. The Sensitivity of amplitude-integrated EEG for neonatal seizure detection.Pediatrics., 2007; 120(4): 770-7.
13. Glass HC, Glidden D, Jeremy RJ,etal.Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. J Pediatr 2009; 155: 318–323.
14. Monod N, Pajot N, Guidasci S. The neonatal EEG: statistical studies and prognostic value in full-term and pre-term babies. ElectroencephalogrClinNeurophysiol., 1972; 32: 529–544.
15. Thoresen M, Hellström- Westas L, Liu X, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics., 2010; 126: 131–139.
16. Jose A, Matthai J, Paul S: Correlation of EEG, CT, and MRI Brain with Neurological Outcome at 12 Months in Term Newborns with Hypoxic Ischemic Encephalopathy. J ClinNeonatol., 2013; 2(3): 125-30.
17. Mariani E, Scelsa B, Pogliani L, et al. Prognostic value of electroencephalograms in asphyxiated newborns treated with hypothermia. Pediatr Neurol., 2008; 39: 317–324.
18. Menache CC, Bourgeois BF, Volpe JJ. Prognostic value of neonatal discontinuous EEG. Pediatr Neurol., 2002; 27: 93–101.

19. PabonMM ,Borlongan CV. Advances in the cell- based treatment of neonatal hypoxic brain injury. Future Neurol., 2013; 8(2): 193-203.
20. Wusthoff CJ, Dlugos DJ, Colina AG, et al. Electrographic Seizures during Therapeutic Hypothermia for Neonatal Hypoxic-ischemic Encephalopathy. J Child Neurol., 2011; 26(6): 724-8.
21. Abend NS, Topjian A, Ichord R. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest.
22. Malone A, Ryan CA, Fitzgerald A, et al. Interobserver agreement in neonatal seizure identification.Epilepsia., 2009; 50: 2097 –2101.
23. Pisani F, Cerminara C, Fusco C, etal.Neonatal status epilepticusvs recurrent neonatal seizures: clinical findings and outcome. Neurology., 2007; 69: 2177.