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Original Article

Prognostic Value of Electroencephalography in Hypothermia-Treated Neonates With Hypoxic-Ischemic Encephalopathy: A Meta-Analysis

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ABSTRACT

Background: Electroencephalography (EEG) background activity is associated with neurological outcome in neonates with hypoxic-ischemic encephalopathy. There is uncertainty about the prognostic value of EEG background activity after hypothermia was introduced.

Methods: Searches were made on Pubmed, Embase, and the Cochrane Library, from inception to March 1, 2018. Pooled sensitivities and specificities were calculated to assess the diagnostic power of burst suppression, low voltage, and flat trace background activities in the prediction of an adverse neurological outcome in the follow-up period in hypothermia-treated neonates with hypoxic-ischemic encephalopathy. I^2 was used to assess heterogeneity, and meta-regression was done to explore the source of heterogeneity.

Results: Eighteen studies with 940 neonates were included. Pooled sensitivities and specificities in predicting the combination of death and neurodevelopmental impairment were burst suppression (sensitivity 0.87 [95% confidence interval (CI) 0.79 to 0.93], specificity 0.60 [95% CI 0.44 to 0.74]), low voltage (sensitivity 0.84 [0.75 to 0.90], specificity 0.80 [0.58 to 0.92]), and flat trace (sensitivity 0.85 [0.75 to 0.92], specificity 0.94 [0.77 to 0.99]). Subgroup analysis revealed the sensitivities of background patterns obtained after 24 hours of life were higher than those within age 24 hours, whereas the specificities were just the reverse. Flat trace performed best on sensitivity 0.93 (0.60 to 0.99) and specificity 0.90 (0.64 to 0.98) in predicting death. Burst suppression demonstrated the highest sensitivity 0.87 (0.58 to 0.97) and flat trace performed best on specificity 0.85 (0.60 to 0.96) in predicting neurodevelopmental impairment.

Conclusions: EEG background activity is predictive of long-term neurological outcome in hypothermia-treated neonates with hypoxic-ischemic encephalopathy. Burst suppression, low voltage, and flat trace are potential predictors of death or neurodevelopmental impairment.

Introduction

Hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia is an important cause of death or neurodevelopmental impairment (NDI) in term neonates. An estimate of the incidence of HIE is between 1.3 and 1.7 per 1000 live births.[1] Reliable early predictive indicators for neurological outcome in this population are essential for counseling parents and making rational clinical decisions. The prognostic value of conventional and amplitude-integrated electroencephalography (aEEG) in neonates with HIE has been well validated under normothermia. Persistently abnormal electroencephalography (EEG) background patterns involving burst suppression, low voltage, and flat trace in the first few hours are associated with neurological dysfunction or death in noncooled neonates.[2,3]

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Therapeutic hypothermia is a neuroprotective intervention that significantly improves survival and neurological outcome in term neonates with moderate to severe HIE.[4,5] However, the prognostic utility of EEG was altered when hypothermia was introduced. Recent studies have reported a modest decline in the positive predictive value of EEG for adverse outcome in cooled neonates compared with noncooled neonates.[6,7] Existing relevant studies have been based on small cohorts, most of which have not further classified burst suppression, low voltage, and flat trace background patterns, and thus have not yielded an accurate estimate of prognostic value of EEG background activities. We undertook a meta-analysis to calculate pooled sensitivities and specificities of burst suppression, low voltage, and flat trace to assess the diagnostic power of each background activity in the prediction of an adverse neurological outcome in hypothermia-treated neonates with HIE.

Methods

Search strategy and selection criteria

We followed the guidance specified in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[8] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[9] A comprehensive search for relevant full-text articles was done on Pubmed, Embase, and Cochrane Library from inception to March 1, 2018.

The search was performed based on Medical Subject Headings with various combinations of free terms "hypoxia-ischemia," "hypoxic ischemic encephalopathy," "asphyxia," "hypox*," AND "infant, newborn," "neonat*," "newborn," "term," "infant," AND "hypothermia, induced," "hypothermia," AND "electroencephalography," "electroencephalogram," "EEG." The references of primary studies and previous meta-analyses were also checked for potentially relevant studies.

Studies were identified if they assessed the prognostic value of EEG background activities for neurological outcome in neonates who were diagnosed with HIE and had undergone hypothermia therapy. To reduce heterogeneity, the gestational age of newborns had to be 36 weeks or more. The neurodevelopmental assessment was available at a minimum follow-up at postnatal age 12 months and the outcome was well defined as good or adverse (death or NDI). Studies that clearly classified the EEG background patterns as normal, burst suppression, low voltage, or flat trace were included. Only studies concerning humans and published in English were eligible. Reviews, expert opinions, editorials, conference proceedings, and case reports were excluded.

Data extraction and quality assessment

Two reviewers extracted data independently from the selected studies. Discrepancies were resolved by a consensus meeting until agreement was reached. The extracted data included severity of HIE (Sarnat staging system),[10] type of EEG (aEEG or EEG), time window of EEG, EEG background pattern, duration of follow-up, details of neurodevelopmental assessment, and definition of adverse outcome. Information to construct the 2×2 diagnostic table—false and true positives and negatives— was recorded. Methodologic quality of the studies was assessed by the revised quality assessment of diagnostic accuracy studies two checklist, which consists of four key domains containing patient selection, index test, reference standard, and flow and timing.[11] Each domain consists of a set of signaling questions to help reach a judgment on the risk of bias. These questions are scored as "yes," "no," or "unclear," where yes indicates low risk of bias.

Statistical analysis

Pooled sensitivity and specificity of each background pattern to predict the combination of death and NDI were calculated using bivariate mixed effects model.[12] Similarly, the analysis was repeated in the prediction of death and NDI separately. Forest plot was constructed to visualize the sensitivity and specificity of each included study. I^2 was used to assess heterogeneity between studies. If significant heterogeneity existed ($I^2 > 50\%$ or $P < 0.005$), sources of heterogeneity were investigated by meta-regression with a P value < 0.05 considered statistically significant. Publication bias was assessed by Deeks' funnel plot asymmetry test. All statistical analyses were done using the MIDAS module for STATA/MP 14.0 (StataCorp, College Station, TX, USA).

Results

Our literature search generated 620 studies, of which 422 remained after removing duplications. After reviewing the titles and abstracts, 53 were selected for review of full-text articles. One additional study was identified by checking reference lists of the 53 studies. After excluding 36 studies that did not report classification of abnormal EEG background patterns and that did not provide sufficient data to estimate pooled sensitivity and specificity because of loss to follow-up, 18 studies were included in the final meta-analysis. Figure 1 shows the flowchart of selection and exclusion process.

The main study characteristics are summarized in Table 1. A total of 940 term neonates with HIE after perinatal asphyxia were investigated. The Sarnat stage of HIE was available in 388 (41%) neonates, of whom 23 (6%) had mild HIE (stage 1), 239 (62%) had moderate HIE (stage 2), and 126 (32%) had severe HIE (stage 3). The remaining 552 neonates did not report the classification of severity of HIE.

The 18 included studies described seven different neurodevelopmental assessments, including neurological examination and mental and motor developmental scales. The age at neurodevelopmental assessments ranged from 12 to 36 months.

In 18 included studies, 12 (67%) studies used aEEG or one or two channel EEG, and the remaining six (33%) studies used multichannel EEG according to the International 10-20 System. Twelve (67%) studies reported a time window of EEG within 24 hours after the perinatal asphyxia event, whereas six (33%) studies reported a time window after 24 hours.

The methodologic quality assessment of included studies according to the quality assessment of diagnostic accuracy studies two checklist is shown in supplementary Fig S1. Thirteen studies met all the items.[6,15,17-22,24-28] All studies met at least 12 of the 14 items. The risks of bias in the patient selection were low. In index text, two studies did not provide specific details on the definition of low-voltage background activity.[16,23] In reference standard, three studies did not offer more specifics on how the neurological examination was performed.[13,16,29] In flow and timing, two studies did not include all the patients in the analyses.[14,29] Overall, most of the included studies did not have high risk of bias.

In the prediction of the combination of death and NDI, the burst suppression demonstrated a pooled sensitivity of 0.87 (95% CI 0.79 to 0.93, based on data from 10 studies involving 465 neonates) and pooled specificity of 0.60 (95% CI 0.44 to 0.74), with significant heterogeneity between the studies ($I^2 = 87\%$, $P < 0.001$). The low voltage demonstrated a sensitivity of 0.84 (95% CI 0.75 to 0.90, 14 studies involving 366 studies) and specificity of 0.80 (95% CI 0.58 to 0.92), $I^2 = 93\%$, $P < 0.001$. The flat trace demonstrated a sensitivity of 0.85 (95% CI 0.75 to 0.92, 11 studies involving 266 studies) and performed best on specificity 0.94 (95% CI 0.77 to 0.99), $I^2 = 88\%$,

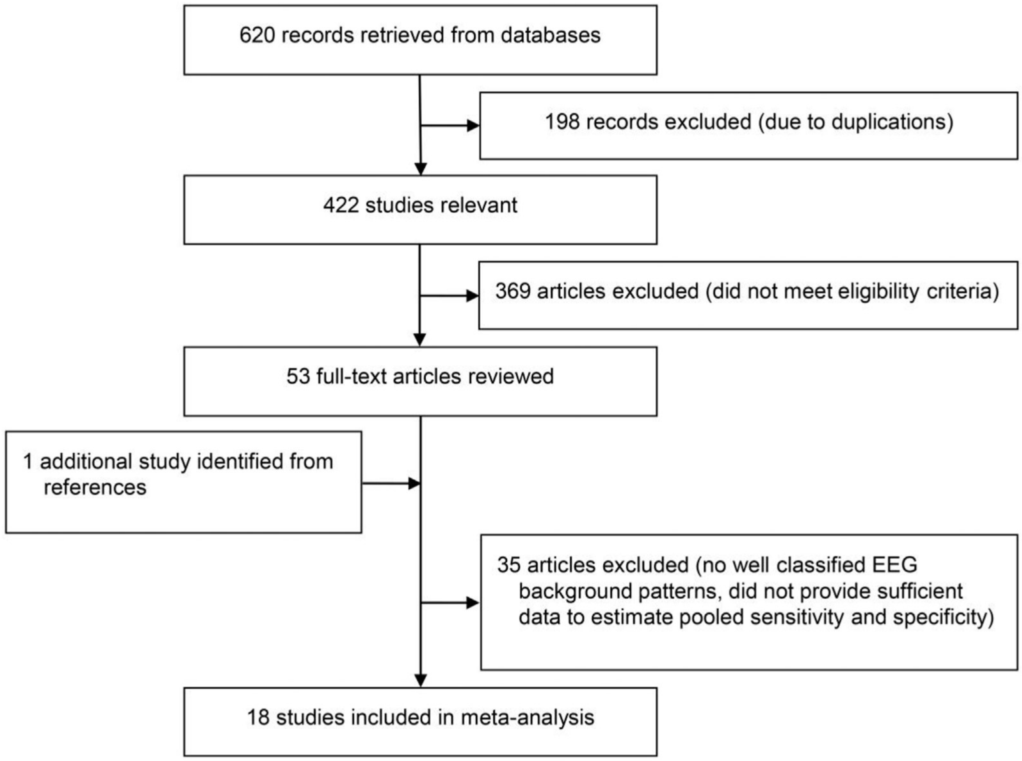

FIGURE 1. Flowchart of literature search and extraction.

$P < 0.001$. Forest plots of sensitivity and specificity for different EEG background patterns are shown in Fig 2.

To identify the source of heterogeneity, a meta-regression examining the effect of time window of EEG on study outcomes was performed. The sensitivities of burst suppression, low voltage, and flat trace patterns obtained after 24 hours of life were all numerically greater than those within age 24 hours, although with burst suppression not tested for significance ($P = 0.48$, supplementary Table S1). However, the specificities of the three background patterns were just the reverse, i.e., numerically greater within 24 hours after the hypoxia-ischemia event, with low voltage not tested for significance ($P = 0.64$, Table S1). The meta-regression stratified by type of EEG was also performed. No significant difference was found between aEEG and EEG with statistically similar sensitivity and specificity (Table S2). No publication bias was detected for burst suppression ($t = 0.13$, $P = 0.90$), low voltage ($t = -0.36$, $P = 0.73$), or flat trace ($t = 0.16$, $P = 0.88$).

We repeated the analysis in the prediction of death and NDI separately. The pooled data are presented in Table 2. Flat trace performed best on sensitivity 0.93 (0.60 to 0.99) and specificity 0.90 (0.64 to 0.98) in predicting death. Burst suppression demonstrated the highest sensitivity 0.87 (0.58 to 0.97) and flat trace performed best on specificity 0.85 (0.60 to 0.96) in predicting NDI. Considerable heterogeneity existed between studies reporting the relationship between death and low voltage ($I^2 = 81\%$, $P = 0.003$, Table 2). Mete-regression was not done because of the limited number of studies (seven studies).

Discussion

EEG background activity can be useful for predicting neurological outcome and severity of neurological complications in neonates after perinatal asphyxia under normothermia.[30,31] Nevertheless, there has been uncertainty about the predictive value since the introduction of hypothermia. Previously, only one meta-analysis[32] has investigated the predictive utility of EEG background features, including 31 studies published between September 1980 and July 2013. Awal et al.[32] provided favorable evidence for the EEG background activities that best predict adverse outcome at age more than 12 months in asphyxiated neonates. Their findings concluded that the most promising background patterns were burst suppression, low voltage, and flat trace. However, the researchers did not distinguish between normothermia and hypothermia groups; therefore no accurate conclusion can be drawn for neonates exposed to hypothermia treatment.

Accordingly, 24 studies included in the previous meta-analysis[32] were excluded from our systematic review because 19 studies were performed in the era before the therapeutic hypothermia existed,[3,30,31,33-48] four studies did not distinguish cooled neonates from noncooled neonates and thus were not in conformity to our selection criteria.[2,49-51] In addition, one study did not supply sufficient information to construct the 2 × 2 diagnostic table.[52] In contrast, 11 additional studies were included in our systematic review.[6,13,18,22-29]

Furthermore, the previous meta-analysis[32] did not estimate the heterogeneity between studies. Thus potential sources of heterogeneity are neglected. Given the substantial heterogeneity in our systematic review, we performed a meta-regression and analyses stratified by the time window of EEG and type of EEG. The predictive value of EEG in the first few hours after birth asphyxia has been confirmed. Under normothermia, early detection of a severely abnormal background activity at six hours after birth was associated with a poor outcome,[53] whereas recovery of the background activity within the first 24 hours was associated with a good outcome.[54] However, this prediction changed after the hypothermia was introduced. A normal EEG at six hours in cooled patients had the best negative predictive value, with 7% of patients having a poor neurological outcome despite a normal EEG background.[55] In

TABLE 1.
Characteristics of Included Studies

Author, Year	HIE Stage 1/2/3 (n)*	Type of EEG	EEG Time Window	Follow-Up	Outcome Studied; Definition of Adverse Outcome	EEG and Outcome†
Mariani et al., 2008[13]	NA	EEG	Within 48 h	12 mo	Neurological examination, ophthalmologic, and auditory evaluations; adverse outcome = death or major disability (mental retardation, CP, deafness, or blindness)	5 normal EEG—3 normal outcome and 2 major disability 7 LV—3 normal outcome and 4 minor disability 4 FT—1 major disability and 3 death
Hallberg et al., 2010[14]	3/16/4	aEEG	6-24 h	2, 4, 6, and 12 mo	AIMS and neurological examinations; adverse outcome = death, CP, delay, or AIMS score less than the fifth percentile	6 normal aEEG—6 normal outcome 15 BS—10 normal outcome, 3 CP, and 2 death
Thoresen et al., 2010[15]	NA	aEEG	3-6 h	18 mo	Bayley II and GMFCS; adverse outcome = death or disability (MDI <70, GMFCS level 3-5, or no useful vision)	8 normal aEEG—8 normal outcome 18 BS—9 normal outcome, 5 disability, and 4 death 1 LV—1 death 8 FT—1 normal outcome, 2 disability, and 5 death
Hamelin et al., 2011[16]	NA	EEG	Within 6 h	≥12 mo	Neurological examination; death or neurological sequels	1 normal EEG—1 normal 4 FT—4 death
Shankaran et al., 2011[17]	0/71/37	aEEG	Within 9 h	18 mo	MDI score and GMFCS; death or severe disability (MDI <70, GMFCS level 3-5, hearing impairment, or blindness)	12 normal aEEG—9 normal, 2 severe disability, and 1 death 22 BS—11 normal, 4 severe disability, and 7 death 26 LV—13 normal, 5 severe disability, and 8 death 35 FT—13 normal, 8 severe disability, and 14 death
Takenouchi et al., 2011[18]	0/15/14	aEEG	Within 72 h	3, 6, 9, 12, and 18 mo	Bayley III; death or severe disability (MDI <70 or severe motor deficit restricting movement)	8 normal aEEG—5 normal and 3 abnormal 13 LV—5 normal and 8 abnormal
Gucuyener et al., 2012[19]	0/6/4	aEEG	Within 72 h	3, 6, 9, and 12 mo	Bayley Scales of infant development and neurological examination; death or severe disability (CP, MDI, or PDI <70).	8 normal aEEG—all normal 2 FT—2 death
Ancora et al., 2013[20]	0/8/4	aEEG	Within 24 h	≥12 mo	Griffiths' Mental Development Scales; death, CP, or global delay (GQ <88.7)	1 normal aEEG—1 normal 8 LV—4 normal, 2 CP, and 2 death
Csekő et al., 2013[21]	NA	aEEG	36-48 h	18-24 mo	Bayley II; death or MDI/PDI <70	41 normal aEEG—38 normal and 3 abnormal 10 BS—3 normal and 7 abnormal 6 LV—6 abnormal 1 FT—1 abnormal
Azzopardi, 2014[6]	NA	aEEG	Within 6 h	18 mo	Bayley Infant Developmental Scales and GMFCS; death or severe disability (MDI <70, GMFCS level 3-5, or bilateral cortical visual impairment)	28 normal aEEG—26 normal and 2 death or severe disability 60 BS—34 normal and 26 death or severe disability 59 LV—24 normal and 35 death or severe disability
Del Balzo et al., 2014[22]	NA	EEG	Within 72 h	12 and 18 mo	Bayley III; death or severe disability (cognitive development index 3 S.D.s below mean or severe sensorimotor disability)	10 normal EEG—all normal 7 BS—6 disability and 1 death 3 LV—1 normal, 1 disability, and 1 death
Kato et al., 2014[23]	0/11/9	aEEG	Within 12 h	18 mo	GMFCS and neurological examination; death or disability (motor disability of GMFCS level 3-5 or speech delay with no vocabulary)	4 normal EEG—3 normal and 1 disability 3 BS—2 normal and 1 disability 9 LV—3 death and 6 disability
Nanavati et al., 2015[24]	0/10/7	EEG	Within 24 h	6, 12, 24, 36 mo	DDST, Bayley Scales of Infant Development and neurological examination; adverse outcome = death, moderate, or severe delay	2 normal EEG—2 normal 3 LV—2 normal and 1 moderate delay 4 FT—2 severe delay and 2 death
Weeke et al., 2016[25]	NA	EEG	Within 24 h	24 mo	Bayley III, GMFCS, and neurologic examination; Bayley score <85 in all subscales or <70 in any subscale, CP, moderate to severe impairment in motor, hearing, vision or communication function, or death	4 normal EEG—4 normal 2 LV—2 moderate or severe impairment 3 FT—1 severe impairment and 2 death
Liu et al., 2017[26]	NA	aEEG	Within 6 h	6,12, and 24 mo	Bayley III and GMFCS; Bayley score <85, GMFCS 3-5, severe visual deficits, or severe bilateral hearing loss	32 normal aEEG—31 normal and 1 abnormal 73 BS—49 normal and 24 abnormal

TABLE 1. (*continued*)

Author, Year	HIE Stage 1/2/3 (n)*	Type of EEG	EEG Time Window	Follow-Up	Outcome Studied; Definition of Adverse Outcome	EEG and Outcome†
						7 LV—3 normal and 4 abnormal 15 FT—2 normal and 13 abnormal
Skranes et al., 2017[27]	4/32/11	EEG	Within 12 h	24 mo	Bayley III and GMFCS; death, Bayley score <85, GMFCS of 3-5, or severe vision or hearing impairment	15 normal EEG—12 normal and 3 moderate delay 14 BS—6 normal, 5 moderate delay, and 3 death
Weeke et al., 2017[28]	16/70/36	aEEG	Within 6 h	≥24 mo	Bayley III and Griffiths developmental quotient; death, CP, severe hearing, or visual impairments, or an adverse neurodevelopment (Bayley score <85, Griffiths developmental quotient <88)	39 normal aEEG—36 normal and 3 death 48 BS—31 normal, 6 CP or delayed development, and 11 death 9 LV—2 normal and 7 death 26 FT—5 normal, 1 CP or delayed development, and 11 death
Goenka et al., 2018[29]	NA	EEG	Days 4-5	24 mo	Assessments were based on the Center for Disease Control milestone guidelines; death and neurological deficit	5 normal EEG—4 normal and 1 neurological deficit 7 FT—1 normal, 4 neurological deficit, and 2 death 14 LV—5 normal, 8 neurological deficit, and 1 death

Abbreviations:
aEEG = amplitude-integrated electroencephalography
AIMS = Alberta Infant Motor Scale
BS = burst suppression
CP = cerebral palsy
DDST = Denver Developmental Scale
EEG = electroencephalography
FT = flat trace
GMFCS = Gross Motor Function Classification Scale
GQ = global quotient
HIE = hypoxic-ischemic encephalopathy
LV = low voltage
MDI = mental developmental index
NA = not available
PDI = psychomotor developmental index
* HIE stage was defined according to the criteria of Sarnat: stage 0, 1, 2 corresponding to mild, moderate, severe HIE, respectively.
† According to previous studies, normal or mild disability was defined as a normal outcome and death or moderate or severe disability was defined as an abnormal outcome.

contrast, Nash et al.[56] reported that a burst suppression or inactive pattern in the first 24 hours was not always predictive of disability or death, whereas after 36 hours these background patterns were considered as prognostic indicators for adverse outcome. Our meta-analysis found that the sensitivities of burst suppression, low voltage, and flat trace background patterns obtained after 24 hours of life were greater than those within age 24 hours, whereas the specificities were greater within age 24 hours, which arrived at a similar result to the previous studies.[56]

Chandrasekaran et al.[55] and several other studies[5,31] reported an analogous predictive utility between conventional and aEEG in asphyxiated neonates over the past two decades by performing meta-analysis. Both EEG and aEEG performed well in predicting the neurodevelopmental outcome. We did not find statistically difference between EEG and aEEG by doing the meta-regression, which was in line with the previous findings.

Definitions separating abnormal EEG background activities from those that were normal varied greatly between studies. The difficulty is that the variation in threshold may lead to the change in sensitivity at the expense of specificity and vice versa, thus a rational definition of the threshold for abnormal background features is required. The American Clinical Neurophysiology Society's guideline[57] and several studies with preferable predictive value[32,58] have defined burst suppression as a pattern with one to 10 second high amplitude delta, theta, and admixed sharp waves interrupted by interburst interval (IBI) activity less than 5 μV. A rigorous definition is possibly important because 14 of 15[59,60] neonates who had IBIs persistently less than 5 μV developed neurological sequelae or death, the ratio is, nevertheless, greater than three of eight neonates who had any IBI greater than 5 μV.[61] The definitions of low voltage as continuous background and maximum voltage around or less than 5 μV and flat trace as isoelectric background activity less than 5 μV were recommended in aEEG classifications described by Hellström-Westas et al.[62] and in the previous meta-analysis by Awal et al.[32] To reduce the threshold effect, definitions of abnormal background activities in most of the studies we include were similar to the definitions we discussed previously.

Our meta-analysis has several limitations. The research procedure of the included studies appears applicable to the treatment and care principles for neonates suffering from HIE. A reverse effect of the rigorous inclusion criteria is that only 940 neonates studied for more than 10 years were eligible for our systematic review. The primary reason for the relatively small sample size of patients is our inclusion criterion of a hypothermia therapy after perinatal asphyxia event. Therapeutic hypothermia has been proved significantly effective to improve the neurological prognosis and survival

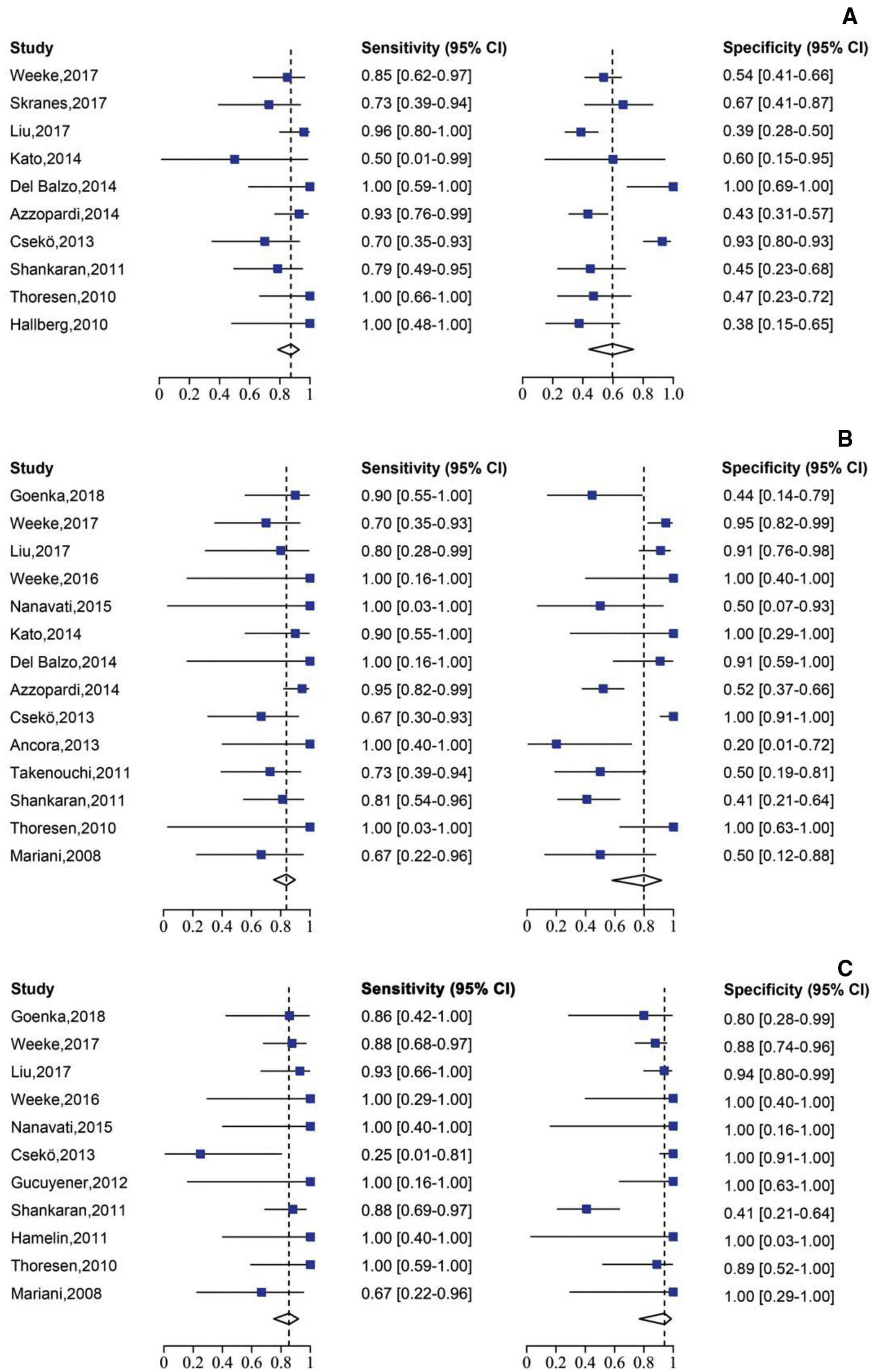

FIGURE 2. Sensitivity and specificity forest plots of (A) burst suppression, (B) low voltage, and (C) flat trace in the prediction of the combination of death and neurodevelopmental impairment. CI, confidence interval. The color version of this figure is available in the online edition.

TABLE 2.
Pooled Sensitivity and Specificity in the Prediction of Death and Neurodevelopmental Impairment Separately

Adverse Outcome	Burst Suppression	Low Voltage	Flat Trace
Death			
Number of studies	6	7	9
Number of patients	178	123	144
Pooled sensitivity (95% CI)	0.88 (0.67-0.97)	0.87 (0.64-0.96)	0.93 (0.60-0.99)
Pooled specificity (95% CI)	0.57 (0.44-0.70)	0.79 (0.44-0.94)	0.90 (0.64-0.98)
P value	0.494	0.003	0.079
I^2	0%	81%	46%
Neurodevelopmental impairment			
Number of studies	7	8	7
Number of patients	187	99	110
Pooled sensitivity (95% CI)	0.87 (0.58-0.97)	0.84 (0.66-0.93)	0.78 (0.54-0.92)
Pooled specificity (95% CI)	0.56 (0.37-0.74)	0.62 (0.38-0.82)	0.85 (0.60-0.96)
P value	0.385	0.338	0.138
I^2	0%	0%	22%

Abbreviation:
CI = confidence interval

rate in newborns with HIE.[63] To identify the predictive utility of EEG in cooled neonates, we restricted the selection criteria.

The existence of bias is inevitable in different degrees in meta-analysis. Publication bias, the preferential publication of studies with desirable results, may result in an overestimation of the prognostic value. We assessed publication bias of the included studies; fortunately, no publication bias was tested. Language bias caused by the restriction to certain language articles may lead to an overestimation or underestimation of diagnostic reliability. We only included studies that were published in English, and this might have affected the final results.

Finally, the number of patients in each study included in our meta-analysis was small; the 95% CI of sensitivity and specificity was therefore wide, thus precluding robust estimation of the prognostic value. As more prospective studies in large cohorts become available, this confidence level will increase, yielding more accurate estimate of the prognostic value.

Despite these limitations, this is the first meta-analysis to suggest that burst suppression, low voltage, and flat trace background activities might represent potential predictors of death or NDI in asphyxiated neonates when hypothermia is used. EEG cannot be advised as the single predictive indicator; it should be interpreted in context with medical history, neurological examination, and neuroimaging changes.

Conclusions

EEG background activity is predictive of a long-term neurological outcome in hypothermia-treated neonates with HIE. Burst suppression, low voltage, and flat trace may be promising predictors of death or NDI. However, substantial heterogeneity between studies and wide 95% CI for sensitivity and specificity suggest that there is a need for well-designed large sample size studies to perform more accurate prediction.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2018.12.013.

References

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:329–338.
2. Polat M, Simşek A, Tansuğ N, et al. Prediction of neurodevelopmental outcome in term neonates with hypoxic-ischemic encephalopathy. Eur J Paediatr Neurol. 2013;17:288–293.
3. Shany E, Goldstein E, Khvatskin S, et al. Predictive value of amplitude-integrated electroencephalography pattern and voltage in asphyxiated term infants. Pediatr Neurol. 2006;35:335–342.
4. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2012;166:558–566.
5. Davidson JO, Wassink G, van den Heuij LG, Bennet L, Gunn AJ. Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy—where to from here? Front Neurol. 2015;6:198.
6. Azzopardi D, on behalf of the TOBY study group. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. Arch Dis Child Fetal Neonatal Ed. 2014;99:F80–F82.
7. Padden B, Scheer I, Brotschi B, Wohlrab G, Latal B, Bernet V. Does amplitude-integrated electroencephalogram background pattern correlate with cerebral injury in neonates with hypoxic-ischaemic encephalopathy? J Paediatr Child Health. 2015;51:180–185.
8. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. In: Analysing and presenting results. Chapter 10. New York: John Wiley & Sons; 2010:1–61.
9. Mcinnes M, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA. 2018;319:388–396.
10. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33:696–705.
11. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529–536.
12. Vogelgesang F, Schlattmann P, Dewey M. The evaluation of bivariate mixed models in meta-analyses of diagnostic accuracy studies with SAS, Stata and R. Methods Inf Med. 2018;57:111–119.
13. Mariani E, Scelsa B, Pogliani L, Introvini P, Lista G. Prognostic value of electroencephalograms in asphyxiated newborns treated with hypothermia. Pediatr Neurol. 2008;39:317–324.
14. Hallberg B, Grossmann K, Bartocci M, Blennow M. The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment. Acta Paediatr. 2010;99:531–536.
15. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010;126:e131–e139.
16. Hamelin S, Delnard N, Cneude F, Debillon T, Vercueil L. Influence of hypothermia on the prognostic value of early EEG in full-term neonates with hypoxic ischemic encephalopathy. Neurophysiol Clin. 2011;41:19–27.

17. Shankaran S, Pappas A, Mcdonald SA, et al. Predictive value of an early amplitude integrated electroencephalogram and neurologic examination. Pediatrics. 2011;128:e112–e120.
18. Takenouchi T, Rubens EO, Yap VL, Ross G, Engel M, Perlman JM. Delayed onset of sleep-wake cycling with favorable outcome in hypothermic-treated neonates with encephalopathy. J Pediatr. 2011;159:232–237.
19. Gucuyener K, Beken S, Ergenekon E, et al. Use of amplitude-integrated electroencephalography (aEEG) and near infrared spectroscopy findings in neonates with asphyxia during selective head cooling. Brain Dev. 2012;34:280–286.
20. Ancora G, Maranella E, Grandi S, et al. Early predictors of short term neurodevelopmental outcome in asphyxiated cooled infants. A combined brain amplitude integrated electroencephalography and near infrared spectroscopy study. Brain Dev. 2013;35:26–31.
21. Csekő A, Bangó M, Lakatos P, et al. Accuracy of amplitude-integrated electroencephalography in the prediction of neurodevelopmental outcome in asphyxiated infants receiving hypothermia treatment. Acta Pediatr. 2013;102:707–711.
22. Del Belzo F, Maiolo S, Papoff P, et al. Electroencephalogram and magnetic resonance imaging comparison as a predicting factor for neurodevelopmental outcome in hypoxic ischemic encephalopathy infant treated with hypothermia. Pediatr Rep. 2014;6:5532.
23. Kato T, Tsuji T, Hayakawa F, et al. A new electroencephalogram classification with reduced recording time in asphyxiated term infants. Brain Dev. 2014;36:372–379.
24. Nanavati T, Seemaladinne N, Regier M, Yossuck P, Pergami P. Can we predict functional outcome in neonates with hypoxic ischemic encephalopathy by the combination of neuroimaging and electroencephalography? Pediatr Neonatal. 2015;56:307–316.
25. Weeke LC, Boylan GB, Pressler RM, et al. Role of EEG background activity, seizure burden and MRI in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischaemic encephalopathy in the era of therapeutic hypothermia. Eur J Paediatr Neurol. 2016;20:855–864.
26. Liu X, Jary S, Cowan F, Thoresen M. Reduced infancy and childhood epilepsy following hypothermia-treated neonatal encephalopathy. Epilepsia. 2017;58:1902–1911.
27. Skranes JH, Løhaugen G, Schumacher EM, et al. Amplitude-integrated electroencephalography improves the identification of infants with encephalopathy for therapeutic hypothermia and predicts neurodevelopmental outcomes at 2 years of age. J Pediatr. 2017;187:34–42.
28. Weeke LC, Vilan A, Toet MC, van Haastert IC, de Vries LS, Groenendaal F. A comparison of the Thompson Encephalopathy Score and amplitude-integrated electroencephalography in infants with perinatal asphyxia and therapeutic hypothermia. Neonatology. 2017;112:24–29.
29. Goenka A, Yozawitz E, Goenka A, Yozawitz E. Prognostic markers in term infants with hypoxic–ischemic encephalopathy: comparative analysis of MRI, EEG, and Apgar scores. J Pediatr Neurol. 2018;16:008–014.
30. Naqeeb NA, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103:1263–1271.
31. Toet MC, Hellströmwestas L, Groenendaal F, Eken P, de Vries LS. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 1999;81:19–23.
32. Awal MA, Lai MM, Azemi G, Boashash B, Colditz PB. EEG background features that predict outcome in term neonates with hypoxic ischaemic encephalopathy: a structured review. Clin Neurophysiol. 2016;127:285–296.
33. Azzopardi D, Guarino I, Brayshaw C, et al. Prediction of neurological outcome after birth asphyxia from early continuous two-channel electroencephalography. Early Hum Dev. 1999;55:113–123.
34. Biagioni E, Mercuri E, Rutherford M, et al. Combined use of electroencephalogram and magnetic resonance imaging in full-term neonates with acute encephalopathy. Pediatrics. 2001;107:461–468.
35. Eken P, Toet MC, Groenendaal F, Vries LSD. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 1995;73:F75–F80.
36. Finer NN, Robertson CM, Peters KL, Coward JH. Factors affecting outcome in hypoxic-ischemic encephalopathy in term infants. Am J Dis Child. 1983;137:21–25.
37. Holmes G, Rowe J, Hafford J, Schmidt R, Testa M, Zimmerman A. Prognostic value of the electroencephalogram in neonatal asphyxia. Electroencephalogr Clin Neurophysiol. 1982;53:60–72.
38. Lieshout HBM, Jacobs JWFM, Rotteveel JJ, Geven W, Hof MVT. The prognostic value of the EEG in asphyxiated newborns. Acta Neurol Scand. 2010;91:203–207.
39. Rooij LGMV, Toet MC, Osredkar D, Huffelen ACV, Groenendaal F, Vries LSD. Recovery of amplitude integrated electroencephalographic background patterns within 24 hours of perinatal asphyxia. Arch Dis Child Fetal Neonatal Ed. 2005;90:F245–F251.
40. Selton D, André M. Prognosis of hypoxic-ischaemic encephalopathy in full-term newborns—value of neonatal electroencephalography. Neuropediatrics. 1997;28:276–280.
41. Takeuchi T, Watanabe K. The EEG evolution and neurological prognosis of neonates with perinatal hypoxia [corrected]. Brain Dev. 1989;11:115–120.
42. ter Horst HJ, Sommer C, Bergman KA, Fock JM, van Weerden TW, Bos AF. Prognostic significance of amplitude-integrated EEG during the first 72 hours after birth in severely asphyxiated neonates. Pediatr Res. 2004;55:1026.
43. Thornberg E, Ekström-Jodal B. Cerebral function monitoring: a method of predicting outcome in term neonates after severe perinatal asphyxia. Acta Paediatr. 2010;83:596–601.
44. Toet MC, Meij WVD, Vries LSD, Uiterwaal CSPM, Huffelen KCV. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. Pediatrics. 2002;109:772–779.
45. Watanabe K, Miyazaki S, Hara K, Hakamada S. Behavioral state cycles, background EEGs and prognosis of newborns with perinatal hypoxia. Electroencephalogr Clin Neurophysiol. 1980;49:618–625.
46. Wertheim D, Mercuri E, Faundez J, Rutherford M, Acolet D, Dubowitz L. Prognostic value of continuous electroencephalographic recording in full term infants with hypoxic ischaemic encephalopathy. Arch Dis Child. 1994;71:F97–F102.
47. Hellstrm-Westas L, Rosn I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. Arch Dis Child Fetal Neonatal Ed. 1995;72:F34.
48. Zeinstra E, Fock JM, Begeer JH, Weerden TWV, Maurits NM, Zweens MJ. The prognostic value of serial EEG recordings following acute neonatal asphyxia in full-term infants. Eur J Paediatric Neurol. 2001;5:155–160.
49. Bourez-Swart MD, Rooij LV, Rizzo C, et al. Detection of subclinical electroencephalographic seizure patterns with multichannel amplitude-integrated EEG in full-term neonates. Clin Neurophysiol. 2009;120:1916–1922.
50. Elayouty M, Abdelhady H, Elmogy S, Zaghlol H, Elbeltagy M, Aly H. Relationship between electroencephalography and magnetic resonance imaging findings after hypoxic-ischemic encephalopathy at term. Am J Perinatol. 2007;24:467–473.
51. 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 Clin Neonatal. 2013;2:125–130.
52. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics. 2000;106:684–694.
53. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. Pediatrics. 2009;124:e459.
54. Pressler RM, Boylan GB, Morton M, Binnie CD, Rennie JM. Early serial EEG in hypoxic ischaemic encephalopathy. Clin Neurophysiol. 2001;112:31–37.
55. Chandrasekaran M, Chaban B, Montaldo P, Thayyil S. Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuroprotection for hypoxic ischemic encephalopathy: a meta-analysis. J Perinatol. 2017;37:684–689.
56. Nash KB, Bonifacio SL, Glass HC, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. Neurology. 2011;76:556–562.
57. Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. J Clin Neurophysiol. 2013;30:161–173.
58. Tsuchida TN. EEG background patterns and prognostication of neonatal encephalopathy in the era of hypothermia. J Clin Neurophysiol. 2013;30:122–125.
59. Holmes GL, Rowe J, Hafford J. Significance of reactive burst suppression following asphyxia in full term infants. Clin Electroencephalogr. 1983;14:138–141.
60. Pezzani C, Radvanyibouvet MF, Relier JP, Monod N. Neonatal electroencephalography during the first twenty-four hours of life in full-term newborn infants. Neuropediatrics. 1986;17:11–18.
61. Sinclair DB, Campbell M, Byrne P, Prasertsom W, Robertson CM. EEG and long-term outcome of term infants with neonatal hypoxic-ischemic encephalopathy. Clin Neurophysiol. 1999;110:655–659.
62. Hellström-Westas L, Rosén I, Vries LSD, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. Neoreviews. 2006;7:1199–1205.
63. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365:663–670.