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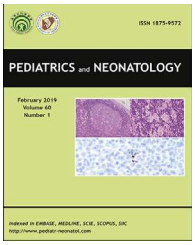

Original Article

Automated EEG background analysis to identify neonates with hypoxic-ischemic encephalopathy treated with hypothermia at risk for adverse outcome: A pilot study

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Keywords
hypoxic-ischemic encephalopathy;

Background: To improve the objective assessment of continuous video-EEG (cEEG) monitoring of neonatal brain function, the aim was to relate automated derived amplitude and duration parameters of the suppressed periods in the EEG background (*dynamic* Interburst

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automated EEG analysis;
dynamic Interburst Interval;
outcome prediction

Interval = *d*IBIs) after neonatal hypoxic-ischemic encephalopathy (HIE) to favourable or adverse neurodevelopmental outcome.
Methods: Nineteen neonates (gestational age 36—41 weeks) with HIE underwent therapeutic hypothermia and had cEEG-monitoring. EEGs were retrospectively analyzed with a previously developed algorithm to detect the *dynamic* Interburst Intervals. Median duration and amplitude of the *d*IBIs were calculated at 1 h-intervals. Sensitivity and specificity of automated EEG background grading for favorable and adverse outcomes were assessed at 6 h-intervals.
Results: Dynamic IBI values reached the best prognostic value between 18 and 24 h (AUC of 0.93). EEGs with *d*IBI amplitude $\geq$15 μV and duration $<$10 s had a specificity of 100% at 6—12 h for favorable outcome but decreased subsequently to 67% at 25—42 h. Suppressed EEGs with *d*IBI amplitude $<$15 μV and duration $>$10 s were specific for adverse outcome (89—100%) at 18—24 h (n = 10). Extremely low voltage and invariant EEG patterns were indicative of adverse outcome at all time points.
Conclusions: Automated analysis of the suppressed periods in EEG of neonates with HIE undergoing TH provides objective and early prognostic information. This objective tool can be used in a multimodal strategy for outcome assessment. Implementation of this method can facilitate clinical practice, improve risk stratification and aid therapeutic decision-making. A multicenter trial with a quantifiable outcome measure is warranted to confirm the predictive value of this method in a more heterogeneous dataset.

1. Introduction

Despite therapeutic hypothermia (TH) as standard treatment in neonates with hypoxic-ischemic encephalopathy (HIE),[1] up to 30—50% of neonates still have adverse neurodevelopmental outcome.[2—4] Early identification of those highest risk neonates remains a challenge to optimize therapeutic strategies, guide clinical care and counsel families. The predictive value of clinical and serum biomarkers have declined in the era of TH.[3] Moreover, several studies highlight the importance of evaluation over time of clinical and neurophysiological parameters since TH and sedative medication can alter the prognostic utility of these predictors.[3,5] Continuous assessment of brain function by EEG provides a sensitive and objective evaluation of neurophysiologic health. Previous studies have proven the prognostic value of functional neuromonitoring with amplitude EEG (aEEG) and multichannel cEEG,[6,7] but interpretation remains subjective.

The EEG in neonates with HIE reflects the severity of brain injury and evolves over time. Grading of HIE using EEG is done by assessment of discontinuity, amplitude, synchrony and presence of sleep—wake cycles (SWC).[8,9] In clinical practice, discontinuity is the most commonly used parameter to assess the severity of HIE and it is most useful in severe grades.[10—12] EEG features associated with poor outcome are persistent low background amplitude, persistent discontinuity or a burst-suppression (BS) pattern.[7,9,11—13] Recovery of EEG is characterized by progressive shortening of the suppressed periods, increase in amplitude of the suppressed periods, reactivity of the EEG, change in burst amplitudes and timing of reappearance of SWC. To monitor the evolution of brain injury more accurately and assist clinicians with an objective, reproducible measure, our group has developed an algorithm, which detects *dynamic* Interburst Intervals (*d*IBIs), derived from both amplitude and duration of the suppressed periods.[14,15] We have shown previously that this algorithm is able to assess the different grades of EEG discontinuity in high agreement with subjective pattern recognition and is better than traditional IBI measures based on only duration thresholds, since it deals more accurately with the dynamic changes that can be observed during the improvement or deterioration of the EEG in neonatal HIE.[10,16] Previous studies have also used automated analysis for grading the severity of the background abnormalities compared to subjective rating.[17—21] Others have evaluated quantitative features of the aEEG for prognostication in neonates with HIE during hypothermia to overcome interrater-variability.[11,22,23] However, no studies have used fully automated analysis of both amplitude and duration of cEEG discontinuity as an objective measure to predict outcome after HIE in the era of therapeutic hypothermia. Moreover, early identification of those at highest risk would also be useful to stratification into future trials designed to test adjuvant therapies. Therefore, we aimed to assess the early prognostic value of automated derived *d*IBI values after neonatal HIE during TH to predict adverse outcome in a small cohort of term neonates.

2. Methods

2.1. Patients

All term neonates admitted to the UZ Leuven NICU and treated with TH for HIE between January 2011 and May 2015 were retrospectively studied. Whole-body hypothermia was initiated according to the Dutch-Flemish cooling

protocol[24] within 6 h. Two infants with normal delivery, who experienced a life-threatening event within the 24 h after birth and who met the cooling criteria, were also treated with hypothermia, as reported by Pejovic et al.[25] Infants with congenital malformations or syndromes were excluded. Clinical data were retrospectively collected from medical records. This study (as part of Neoguard: the development of a neonatal EEG monitor with real-time, bedside data visualization and automated decision support) was conducted with approval from the hospital Ethical Review Board, for a retrospective, anonymous data analysis.

2.2. Multichannel cEEG monitoring

After admission, multichannel cEEG was measured during TH and rewarming. If seizures were suspected before start of the EEG, treatment was at the discretion of the attending clinician. Neonates received sedative drugs throughout TH (fentanyl, tramadol or midazolam). EEG recordings were done with 9—17 electrodes (Fp1-2, C3-4, T3-4, O1-O2, Fp3-4, Fp7-8, T5-6, P3-4, reference electrode Cz) at a sampling frequency of 250 Hz, according to the modified international 10—20 standard. Recordings were done using a BRAIN RT EEG system, OSG BVBA, Rumst, Belgium. All EEG signals were filtered using high and low-pass filters at 0.27 Hz and 70 Hz.

2.3. Brain imaging

Cranial ultrasound was performed at admission or at day 1 and repeated at day 3 or 4. MRI was performed between day 2 and 7. The severity of brain injury was assessed by using conventional T1 and T2 sequences with diffusion-weighted imaging and apparent diffusion coefficient maps. An independent neonatologist, experienced in neuroradiology (PG), and blinded to the clinical history, reviewed the MRIs. Injury patterns were separately scored for lesions in the basal ganglia and cortical white matter by a previously described method.[26] Normal to mild MRI injury was defined as watershed score <3 or basal ganglia/thalamus score <2, and moderate to severe injury was watershed injury score ≥ 3 or basal ganglia/thalamus score ≥ 2, combined in 6 different injury patterns.

2.4. Neurodevelopmental outcome

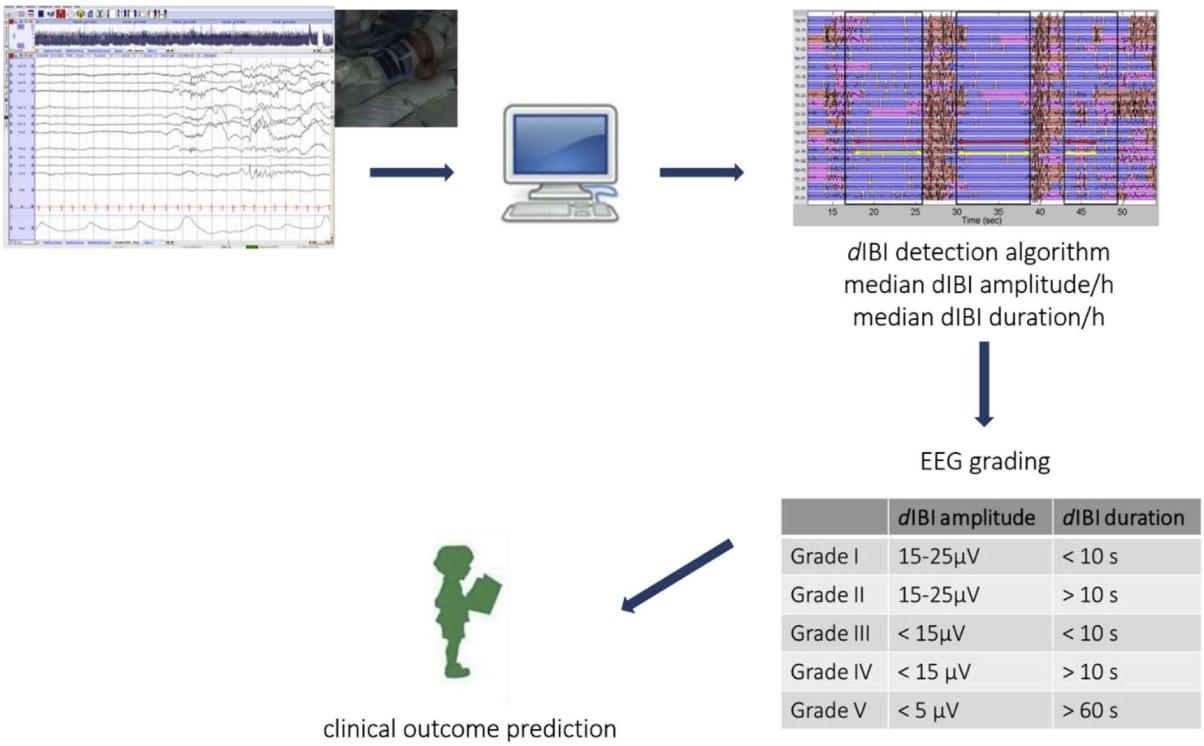
Neurodevelopmental follow-up was performed by a trained child neurologist at 12 and 24 months of age with the Bayley Scales of Infant Development, version 2 (BSID-II) cognitive and motor score. Adverse outcome was defined as death, cerebral palsy that impaired independent walking, refractory epilepsy, deafness, bilateral cortical impairment with no useful vision or a BSID-II cognitive and motor score less than 70 ($\geq$2SD below the mean). Infants with better outcome were placed in the favorable outcome group and scored as: normal BSID-II ≥ 85 for both motor and cognitive score or mild disabilities with 1 subscale of the BSID-II (cognitive/language or motor score) between 70 and 84 at 24 months.[3,27,28]

2.5. Automated analysis of continuous multichannel EEG

EEG analysis was performed using algorithms implemented in MATLAB (The MathWorks, Massachusetts, USA). A flowchart of the automated EEG assessment is given in Fig. 1. Whole EEG recordings were processed with the *dynamic* IBI detection algorithm, comprehensively described in Matic et al., which was developed on a different dataset and compared with visual assessment.[10] The first part of the algorithm detects *dynamic* IBIs, and for this single EEG channels are initially adaptively segmented. The detected segments are further classified based on their amplitude. Subsequently, only segments with low amplitudes (peak-to-peak amplitude below 25 μV) are further processed to define *d*IBI labels across all EEG channels. Finally, the median duration and median amplitude of the detected *d*IBIs are automatically calculated within each 1 h EEG. Based on these automated derived values, EEG background was classified in 5 grades for each hour: 1) *d*IBI amplitude from ≥ 15 μV to <25 μV and duration $<$10s. 2) *d*IBI amplitude from ≥ 15 μV to <25 μV and duration $>$10s. 3) *d*IBI amplitude <15 μV and duration $<$10s (Fig. 2), 4) *d*IBI amplitude $<$ 15 μV and duration $>$10s and (Fig. 3) 5) *d*IBI amplitude $\leq$ 5 μV and duration $>$60s. Compared with previously reported visual rating,[7,13,14,29] these grades relate to: 1) mildly abnormal pattern with transient discontinuous activity, 2) excessively discontinuous (*d*IBI duration $>$10s) and mildly suppressed amplitude ($\geq$15 μV but <25 μV), 3) depressed, and undifferentiated, with marked voltage attenuation and discontinuous EEG for $<$10s, 4) severe abnormal with depressed, and undifferentiated low voltage activity, and discontinuity for $>$10s or a burst suppression pattern and 5) extremely low voltage, unreactive and invariable pattern (iso-electric). In trace alternant, bursts and IBIs have nearly the same duration (6s, $<$10s) and IBIs amplitude is $>$ 25 μV,[14,29] so TA will not be detected by the algorithm.[15] For each 6 h-interval, the median EEG score was assessed based on 1 h measurements.

2.6. Statistical analysis

Patient characteristics were summarized as mean $\pm$ SD or as median and range where appropriate. Fisher's exact tests were used to compare dichotomous variables, independent sample t-test for continuous variables, and non-parametric data were analyzed with the Independent-Samples Kolmogorov—Smirnov Test. Sensitivity and specificity of 6 h-EEG background scores related to outcome prediction were calculated. Sensitivity and specificity were calculated as follows: True positive (TP): an abnormal EEG which predicts an adverse outcome. False positive (FP): an abnormal EEG despite actually having favorable outcome. True negative (TN): a normal EEG which predicts a favorable outcome. False negative (FN): a normal EEG, despite actually having adverse outcome.



	*d*IBI amplitude	*d*IBI duration
Grade I	15-25μV	< 10 s
Grade II	15-25μV	> 10 s
Grade III	< 15μV	< 10 s
Grade IV	< 15 μV	> 10 s
Grade V	< 5 μV	> 60 s

Figure 1 Flowchart of the automated EEG assessment for neonates with HIE undergoing therapeutic hypothermia.

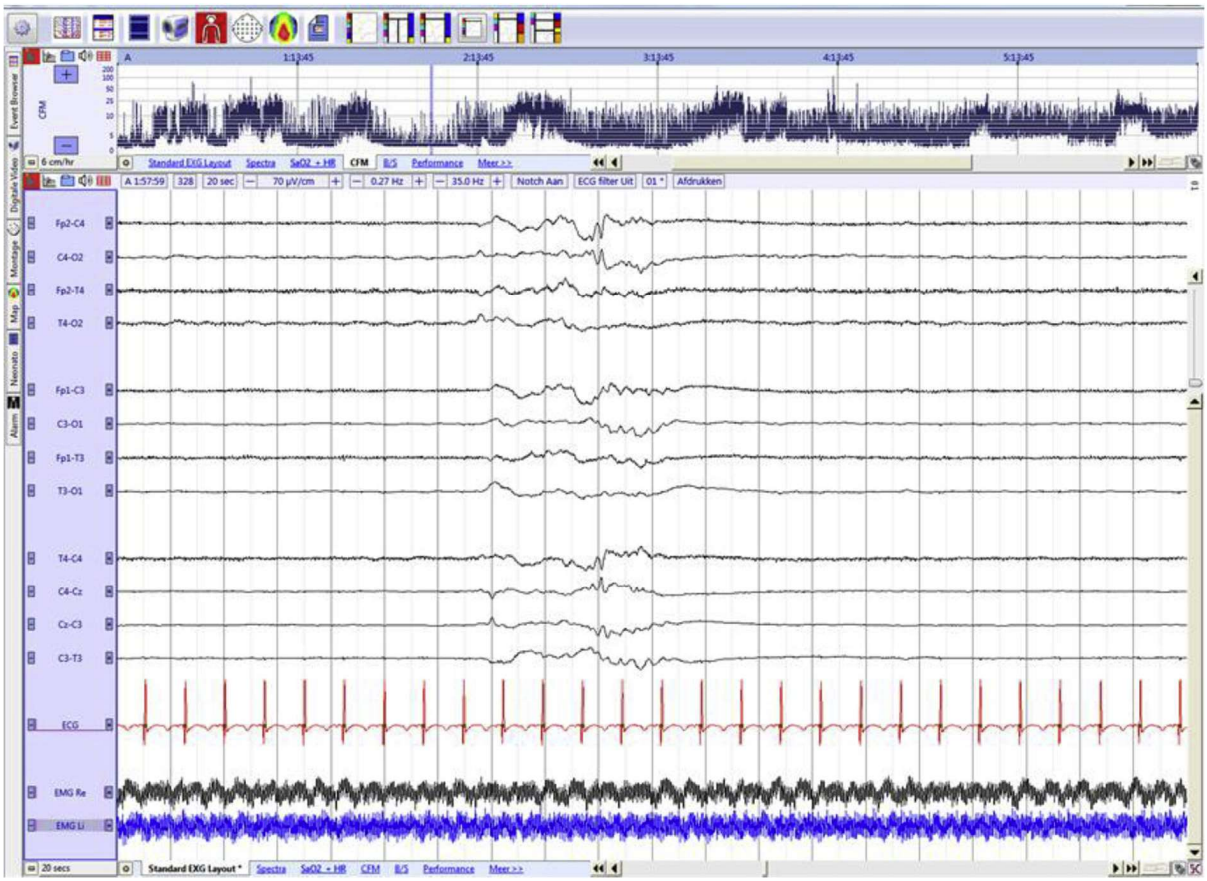


Figure 2 Male, 37 6/7 weeks GA, placental abruption. Thompson score 13. EEG at 8 h of age. Grade 4. background score based on *d*IBI amplitude <15 μV and duration >10s.

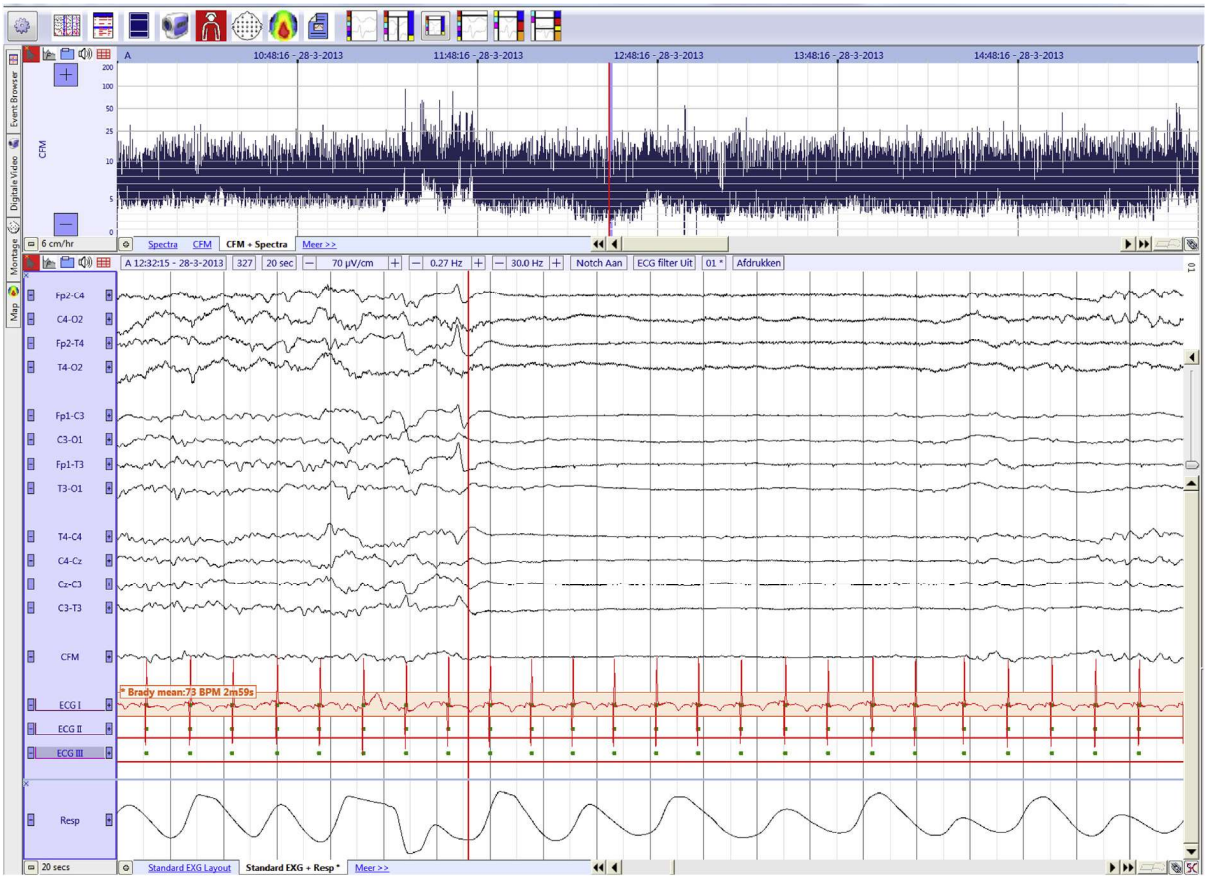


Figure 3 Male, 37 6/7 weeks GA, placental abruption. Thompson score 13. EEG at 18 h of age. Grade 3 background score based on *d*IBI amplitude <15 μV and duration <10s. Favorable outcome.

The area under the receiver operating characteristic (ROC) curve was calculated to assess the prognostic value of EEG background at these 6 h-intervals. For this pilot study, we did not adjust for multiple comparisons; a two-sided p value < 0.05 was considered significant. Statistical analyses were performed in SPSS version 24 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

During this period, 21 neonates were treated with TH and had cEEG monitoring. Of these, two neonates were excluded because of the lack of cEEG in the first 24 h. Clinical characteristics of the 19 included neonates are presented in Table 1. Ten of the 19 patients had adverse outcome, 9 of whom died following redirection of care. One infant had global developmental delay with BSID-II cognitive score of 55 and motor score of 67. Nine neonates had a favorable outcome at 24 months of age: seven infants had normal BSID-II cognitive and motor scores. One infant had normal BSID-II motor score and mild language delay due to hearing impairment with a family history of speech and hearing problems and one had a BSID-II mental score of 84 and motor score of 99.

3.2. Association between EEG background score and outcome

Video-EEG was started at a mean of 7.2 ± 4.9 h of life (time 0 h = time of birth/time of presentation after the acute life-threatening event for two cases). EEG data were incomplete, limiting an integral comparison within the first 12 h for all patients. Of those with cEEG at 6—12 h (n = 15), an EEG with median score 1 or 2 had a specificity of 100% and a sensitivity of 67% for normal outcome, which decreased to a specificity of 67% for EEG score 1, and to a specificity of 50% and a sensitivity of 89% for EEG score 2 at 42 h of life. Of the newborns who died following redirection of care, EEGs were discontinued prior to rewarming in 5 (<48 h). Therefore, we scrutinized the final results of the available data between 13 and 42 h: comparison of two different outcome groups showed significant differences in EEG background over this 13—42 h interval, with more severe EEG scores in the group with adverse outcome (Supplementary Materials Table 2).

The EEG improved in this time period in 9 (47%), remained the same in 7 (37%) and worsened in 3 (16%). The best prognostic value, with the greatest sensitivity and specificity of the automated *d*IBI values, was already achieved at 18—24 h, with an AUC of 0.93 (both $p < 0.01$) (Supplementary Materials Table 3). A severely attenuated background pattern (score 4, *d*IBI <15 μV and duration

Table 1 Demographic and clinical characteristics of the 19 neonates with HIE treated with therapeutic hypothermia.

	Favorable outcome: n = 9 Normal outcome n = 7 Mild disabilities n = 2	Adverse outcome: n = 10 Moderate to severe disabilities: n = 1 Neonatal death: n = 9	*P* value
Gestational age, weeks (SD)	39 ± 1.6	38.8 ± 1.8	ns
Birthweight, grams	3374 ± 718 g	3223 ± 474 g	ns
Gender			ns
Male, n (%)	6 (67%)	8 (80%)	
Female, n (%)	3 (33%)	2 (20%)	
Outborn, n (%)	3 (33%)	7 (70%)	ns
5 min Apgar, median (range)	4 (2–5)	1 (0–4) (n = 7)	ns
Initial pH (mean)	6.93 ± 0.16 (n = 7)	6.82 ± 0.19 (n = 10)	ns
Thompson score, median (range)	9 (7–13)	12 (12–14)	0.006
Ventilation support, n (%)	9 (100%)	10 (100%)	
Acute kidney injury	0	2	ns
Multi-organ failure	0	3	ns
Electrographic seizures			
(0–6 h)	2 (22%)	1	ns
(6–48 h)	0	5 (50%)	0.02
Sedatives/anti-epileptic drugs, median	2	2	ns
MRI score (n) [a]	9/9	5/10	
Basal ganglia/thalamus (median (range))	0 (0–3)	6 (3–6)	0.01
Cortical white matter (median (range))	0 (0–2)	1 (0–6)	ns
Bayley cognitive score, median (range)	96 (78–123)	55 (n = 1)	
Bayley motor score, median (range)	106 (92–119)	67 (n = 1)	

[a] Brain MRI was performed in all newborns with HIE and favorable outcome. Only 5 of the 10 newborns with adverse outcome were evaluated with MRI. Nine neonates died following redirection of care after considering the severity of a combination of clinical, electrophysiological and neuroimaging data and parents' opinion.

>10s), if not improved before 19–24 h, yielded a Positive Predictive Value (PPV) of 100%. None of the infants with an EEG background pattern with *d*IBI values ≤5 μV and duration >60 s (EEG background score 5) had a normal MRI (if performed) and long-term outcome; moreover, this pattern was indicative of abnormal outcome at early time points.

During 25–36 h, sensitivity and specificity values dropped slightly, with AUC from 0.82 to 0.86 (both $p < 0.05$). Two neonates, with normal MRI and favorable outcome and a background score of respectively 2 and 3 at 13–18 h interval, had a worsening of EEG background later on, due to additional doses of sedative drugs (midazolam). Three neonates with adverse outcome and *d*IBI values < 15 μV at 6–24 h had an increase of the *d*IBI values by mid-cooling (25–30 h). EEG scores during 37–42 h of TH did not add extra prognostic value. One neonate with a Thompson score of 13 and a severely suppressed EEG at beginning of TH had an improved EEG score of 1 by 18 h (Fig. 4). This newborn showed moderate MRI injury with MRI basal ganglia score of 3 but still had normal developmental outcome at 24 months. Two infants with mild disabilities had an EEG score of 1 at 13–24 h, and no signs of injury on MRI.

Three infants with an EEG score ≥3 throughout the duration of monitoring presented with multi-organ failure. One infant with uncontrollable, severe hypotension had electrographic seizure activity within 13–24 h after birth and a background score of 3 at that time point. Five infants with severe background attenuation (EEG score ≥4) persisting after 19–36 h had maximal MRI injury scores and goals of care were redirected to comfort measures. The surviving infant with abnormal developmental outcome and MRI basal ganglia score of 3, had a severely attenuated background (EEG score 4) in the first 18 h of monitoring and an EEG grade 2 during subsequent monitoring. Due to limited MRI data in the abnormal outcome group (5/10), the association between the evolution of the EEG score and MRI injury was not assessed; however, the correlation between MRI injury and outcome proved to be high: Pearson's $R = 0.85$ ($p < 0.001$).

4. Discussion

This pilot study evaluates the feasibility of automated *d*IBI analysis to assist clinicians in an interpretable and objective EEG assessment in neonates with HIE. The major benefit of this method for clinical practice is that EEG recordings were analyzed in an automated manner, without any visual pre-selection, which makes the results quantifiable and reproducible.

Our findings suggest that integrating the dynamic changes in both the amplitude and duration of *d*IBI's can help to differentiate between favorable and adverse outcomes (e.g., predicting mortality). A normal or mildly depressed EEG (respectively *d*IBI amplitude ≥15-<25 μV, *d*IBI duration <10 s), is associated with no or mild MRI brain injury and favorable outcome if already present at 12 h of cooling but the specificity decreases after 24 h. More interestingly, the best prognostic value, with the greatest sensitivity and specificity of the automated *d*IBI values, was already achieved between 18 and 24 h. A suppressed EEG (*d*IBI amplitude <15 μV, duration >10 s) at 18 h and no

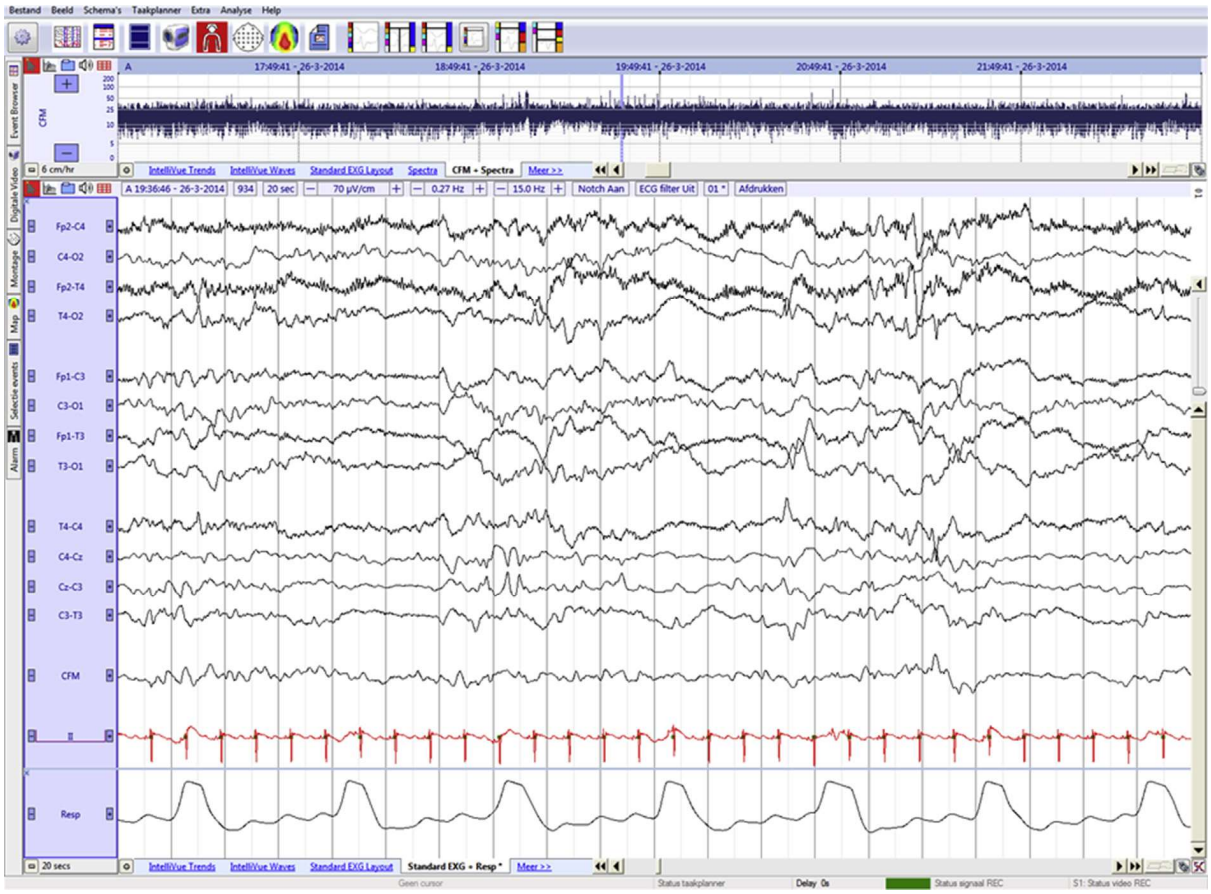


Figure 4 Male, 40 weeks GA, home birth with complicated labour. Thompson score 13. EEG at 18 h of age. Grade 1 background score based on *d*IBI amplitude >15 μV-25 μV and duration <10s. Favorable outcome.

further improvement in the next 6 h, was highly specific for predicting mortality.

Comparable results were achieved by Shellaas et al.[22] who used quantitative aEEG (mean EEG amplitude, aEEG lower margin). The lower aEEG margin was significantly higher as early as 12 h for those with good outcomes. Recently, Dunne et al. used a novel algorithm to detect discontinuity in aEEG.[11] A mean aEEG discontinuity of >30s/min-epochs and <10 μV threshold at 24 h had a specificity of 100% and sensitivity of 71% for adverse neurodevelopmental outcome; however; these results required visual preselection of 2 h epochs to identify seizure-free and artefact free data. Nash et al.[7] evaluated qualitative cEEG data in relationship to MRI injury and reported normalization of severely abnormal EEG (≥score 4) by 12—18 h of life in infants with normal MRI. This study achieved the best prognostic value for burst suppression patterns and moderate-severe injury on MRI only by mid-cooling, a slightly later time point compared to our results. Temko et al.[30] used a multimodal predictor, including 9 quantitative EEG features obtained from 1 h EEG recordings at 24 h after birth. This study reported an accuracy of 84% to predict neurodevelopmental outcome at 24 months. Our results are further substantiated by Iyer et al.,[23] who demonstrated the difference in cortical burst dynamics in infants with early signs of functional brain recovery after HIE during TH versus neonates with similar brain lesions and adverse outcome. This highlights the critical first 24 h during hypothermia, which may indicate that rapid improvement of severe background attenuation should be achieved before the second day of life to be spared of severe brain injury and adverse outcome. Moreover, evidence of severe irreversible HIE which led to basal ganglia or diffuse brain injury is identified with high specificity within 18 h after the insult, making additional therapeutic interventions in a selected group of patients possible.

This study has methodological and technical limitations. First, the time points used to determine the association between quantitative EEG features and outcome are influenced by clinical practice. Initiation of cEEG was delayed due to the referral pattern of our NICU. Redirection of care to comfort measures only limited also data collection. However, there is increasing evidence that (a)EEG data after the second day of cooling does not add extra prognostic value for neonates with a devastating prognosis.[7,11,22,31] Our retrospective study is biased due to the withdrawal of intensive care in neonates believed to have extremely poor prognosis, inducing the risk of a self-fulfilling prophecy.[2,4,22,32] However, the automated derived *d*IBI values and related background scores were not used to guide treatment. Based on our results of clinical, functional and imaging data, one can assume that this

group represents a fair sample of cases encountered in clinical practice,[33] despite the fact that the culture regarding withdrawal of intensive care may diverge in different countries.[2,11,34]

Second, we can only present results of two extreme outcome categories (favorable versus mortality) due to the small sample size. Within this cohort, we cannot comment on the predictive value of EEG features for neonates with moderate HIE, who might present with more persistent discontinuity after 24 h (grade 3), among whom EEG assessment is undoubtedly more challenging and important. This might require the integration of multiple quantitative EEG features (e.g., *d*IBI, symmetry, sleep—wake cycle) and other factors (e.g. medication, seizure burden and status epilepticus) that could affect brain function. Multichannel EEG has been proven to be more accurate to assess brain maturation, capture spatial information and seizure detection, compared to single channel EEG.[35—37] There are some technical limitations of automated EEG analyses, which should be considered. Repetitive patterns such as seizure activity can disturb the adaptive segmentation of the algorithm. Technical influences such as artefacts and variable EEG quality (scalp oedema), are possible limitations. However, to test the practical applicability of this method, no preselection of data was performed, which makes it straightforward to implement in a larger number of neonates and of benefit in clinical practice.

Concern may arise due the influence of medication, which can suppress EEG activity which we did not adjust for. Wood and Thoresen described longer half-lives for most sedatives during hypothermia,[38] which can lead to higher drug levels, resulting in a significant delay in improvement of EEG background. However, the use of AED and sedative medication might be even more accurately targeted with video-cEEG monitoring.[39] Therefore, automated EEG analysis needs to be considered as a tool for accelerating visual assessment and supporting clinical decision-making in a busy NICU. Interpretation in the context of co-influencing factors and the clinical management decisions are best left to the treating team.

In conclusion, despite TH, a significant number of neonates remain at elevated risk for adverse outcome after HIE. Early identification of persistent severe encephalopathy is a priority in clinical care.[11] Automated EEG background analysis based on *d*IBI values can provide a reliable and objective biomarker during the first 13—24 h for non-EEG skilled neonatologists. Integration of this method can improve optimal risk stratification to identify neonates who can potentially benefit from adjunctive neuroprotective interventions and for whom TH might not be sufficient. It can support therapeutic decision-making in the ones with devastating prognosis in early postnatal life. Larger multicenter trials with a quantifiable outcome measure are warranted to validate these results in a more heterogeneous dataset.

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Conflict of interest statement

None of the authors has any conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.03.010.