Poor aEEG background recovery after perinatal hypoxic ischemic encephalopathy predicts postneonatal epilepsy by age 4 years

Jenna Nyman, Kirsi Mikkonen, Marjo Metsäranta, Sanna Toiviainen-Salo, Sampsa Vanhatalo, Leena Lauronen, Päivi Nevalainen

Aims: Measures to predict later epilepsy after perinatal hypoxia-ischemia are lacking. We show that poor aEEG background recovery predicts epilepsy at individual level.

Methods: This study evaluated the accuracy of neonatal amplitude-integrated electroencephalography (aEEG) brain monitoring for predicting development of postneonatal epilepsy after perinatal hypoxic ischemic encephalopathy (HIE).

Results: At group level, total seizure burden (p = 0.003), maximum hourly seizure burden (p = 0.007), and aEEG background recovery (p < 0.001) were all significantly associated with outcome. At individual level, six children developed epilepsy, and the most accurate predictors for later epilepsy were inactive aEEG at 24 hours (accuracy 97%, positive predictive value 100%, two false negatives) and inactive aEEG at the onset of seizures (accuracy 97%, sensitivity of 100%, one false positive).

Conclusions: At individual level, aEEG background recovery was a better predictor for later epilepsy than neonatal seizures, although both were associated with epilepsy at group level.

Significance: Poor aEEG background recovery predicts development of epilepsy after perinatal HIE at individual level.
Additionally, previous studies show an association of development of epilepsy or other poor neurologic outcome with occurrence of seizures in the neonatal period (Glass et al., 2020; Inoue et al., 2014), high neonatal seizure burden (thresholds vary between studies; Clancy and Legido, 1991; Glass et al., 2016; Kharoshankaya et al., 2016), and occurrence of seizures during three or more days after initial injury in the neonatal period (Glass et al., 2020; Shellhaas et al., 2021). High seizure burden is, however, associated with the severity of brain injury (Basti et al., 2020), thus making it unclear whether seizure burden has additional predictive value for development of epilepsy. Although several risk factors for epilepsy are known, most earlier studies fail to determine which individual patients will later develop epilepsy. Early diagnosis and treatment may be of great importance for favorable neurodevelopment and for preventing or reducing the burden on the patients and families (Glass et al., 2020; Merchant and Azzopardi, 2015; O’Callaghan et al., 2011). We previously showed that EEG background, somatosensory evoked potentials and type and severity of brain injury in MRI provided tools for early identification of neonates with HIE, who during their first year developed infantile spasms syndrome or other postneonatal epilepsy (Nevalainen et al., 2020). However, in that study, seizures or evolution of EEG background were not evaluated as the included registration were of short duration.

Here, we set out to study how aEEG background recovery and neonatal seizures in patients with perinatal HIE link to later childhood development of infantile spasms syndrome or other type of epilepsy. We hypothesized that aEEG background per se would be better than perinatal seizure occurrence in predicting future development of epilepsy. In addition, we examined if the epilepsy risk persists after the first year by following the children until age 4.

2. Patients and methods

2.1. Patients (Fig. 1)

We used a previously characterized and published population-based cohort of 92 neonates (Nevalainen et al., 2020), born at near full-term age (mean gestational age 39.6 weeks, range 36.1–42.3 weeks). They were admitted to the Helsinki University Hospital in 2011–2016 for treatment of moderate or severe HIE and monitored with aEEG during their first days of life as a part of the routine clinical protocol.

Seven neonates were excluded due to missing aEEG trace (N = 1), aEEG onset later than 12 hours (N = 3) from birth or missing some perinatal details due to being born outside of our hospital district (N = 3). Hence, 85 neonates with aEEG data were included. Of them, 73 were treated with therapeutic hypothermia. The neonates received antiseizure medication according to hospital protocols for seizures detected in aEEG. Phenobarbital was administered as the first-line drug, and levetiracetam or phenytoine as the second-line drug. Finally, midazolam was given as the third-line drug. The antiseizure medication were discontinued after seizure control in the neonatal period or at discharge in all but one newborn. Institutional Research Review Board at HUS diagnostic center approved the study, including waiver of consent due to the retrospective and observational nature of the study.

2.2. Decisions on withdrawal of treatment

Any decisions to withdraw intensive care were based on a combination of poor overall clinical condition including severe HIE, severe MRI findings, and poor EEG. Decisions were made after discussions with parents.

2.3. aEEG recording and analysis

The aEEG recordings were started by the NICU staff as soon after birth as possible (median 3.4 hours, interquartile range, IQR 1.5 hours, min 0.7 hours, max 11.3 hours). aEEG recordings continued until a median postnatal age of 90 hours (IQR 34 hours, min 27 hours, max 237 hours). There were some breaks during the aEEG recordings due to medical procedures with a median total duration of 2.75 hours per neonate (IQR 6.7 hours, min 0 hours, max 19.9 hours). We used four needle electrodes at F3, F4, P3 and P4 locations and a NicoletOne system (Cardinal Healthcare/Natus, USA) to collect the aEEG at 250 or 256 Hz.

Two neonatal EEG experts (PN and LL or SV) scored the aEEG according to a previously published scheme (Nevalainen et al., 2020); modified from (Murray et al., 2009): 1 = continuous activity with sleep-wake cycling (SWC, discontinuity allowed during quiet sleep), 2 = continuous activity without clear SWC, 3 = burst suppression (interburst interval (IBI) 10–60 s, amplitude during suppression < 10 µV, no SWC), 4 = inactive (activity < 10 µV or IBI > 60 s i.e. severe discontinuity). This scoring system is slightly modified from the most frequently used aEEG scoring system (e.g. Thoresen et al., 2010), because the present score is based on raw data as well as the aEEG trace. Artefacts (e.g. ECG, breathing, muscle, movement, and electrode artefacts) were detected visually based on their characteristic form in the raw EEG data.

The first expert scored the aEEG by assigning each hour the score that was most representative of the epoch, in practice present > 50% of the time. SWC was considered to start at the beginning of at least two sequential sleep cycles. When artefacts or
seizures occupied over 50% of a given hour, no background grade was assigned (approximately 1.6% or all epochs). All subsequent analysis was primarily based on these scores. The second expert (SV or LL) marked the timing of the aEEG background class improvement: from inactive to burst-suppression, to continuous EEG, and to continuous EEG with alternating sleep states. These second reviewer scores are presented in the Supplementary Table 1 and Supplementary Fig. 2, and they were used to verify the main findings regarding aEEG background evolution. Consensus scoring was not used because it does not reflect clinical reality where the aEEG is typically reviewed by one expert at a time.

The first neonatal EEG expert (PN) further marked the aEEGs for seizures, defined as rhythmic, evolving EEG patterns lasting longer than 30 s and not explained by artefacts. Both the raw 4-channel EEG and the aEEG traces were used to mark seizures. We chose the 30-second limit as supported by prior literature on interrater agreement and seizure burden measures (Stevenson et al., 2015), and we only considered electrographic seizures irrespective of their possible clinical correlates. For each neonate, we calculated the following predefined parameters: the total seizure burden, maximal hourly seizure burden, maximal length of a single seizure, average seizure length, and age at onset and end of seizures. Occurrence of status epilepticus was also noted, defined as seizures covering >50% of the given 1-hour epoch.

2.4. Neuroimaging

All 85 neonates underwent brain MRI with a 1.5Tesla scanner (82 neonates; Philips Intera Achieva, Philips Medical Systems, Best, the Netherlands) or a 3Tesla scanner (three neonates; Siemens Magnetom Skyra, Siemens Healthcare GmbH, Erlangen, Germany) between 1 and 16 days age (median 5 days). The imaging protocol included T1-weighted axial, T2-weighted axial and coronal, and diffusion weighted images. We used the MRI classification (Shankaran et al., 2012) performed for our previous study (Nevalainen et al., 2020). Score 0 = normal, score 1A = minimal cerebral lesions, score 1B = more extensive cerebral lesions alone (no involvement of basal ganglia, thalamus or anterior or posterior limb of the internal capsule, and no area of watershed infarction), score 2A = any involvement of the basal ganglia, thalamus, anterior or posterior limb of the internal capsule or watershed infarction (no other cerebral lesions), score 2B = 2A + addition cerebral lesions, and score 3 = cerebral hemispheric devastation.

2.5. Outcome

We reviewed the children’s medical records retrospectively to determine whether the child had died (eleven children), developed epilepsy (six children, all six also developed CP), or developed CP (seven children in addition to the six with concurrent epilepsy). An experienced pediatric neurologist made the CP diagnosis based on repeated neurological assessments and repeated assessments by an occupational therapist, and a physiotherapist. Observations made by the guardians/parents were also considered.

At the time of the review, the children were aged 4–10 years. To determine outcome at age 4, we searched the pediatric neurologist or pediatric appointment closest to age 4. If the follow-ups were discontinued before age 4 but the child still lived in the Helsinki and Uusimaa Hospital (HUS) district, we assumed that he/she did not have epilepsy or CP diagnosis since, due to the Finnish region-based health care system, all children with these diagnoses would be patients of our hospital. We considered the children to be lost to follow-up if the most recent outcome information was before age 2, and they no longer lived in the HUS district. Consequently, we included two children with the latest follow-up between 2 and 4 years, that no longer lived in the HUS district. Additionally, we reviewed the most recent pediatric neurologist or pediatrician appointment to see if the risk for pediatric neurologist or pediatrician appointment to see if the risk for epilepsy persisted beyond age 4.

2.6. Statistics

We analyzed the data using IBM SPSS Statistics 25. In the group level analysis, we used Chi-Square test or Fisher’s exact test for comparisons of categorial data. For continuous data we used Kruskal-Wallis test and Mann-Whitney U test or Student’s t-test depending on the normality of the data, which we assessed with Shapiro-Wilk’s test. We compared the aEEG background evolution between different outcome groups using the Kaplan-Meier method with Bonferroni correction to correct for multiple comparisons: i.e. we analyzed the cumulative probability of an individual remaining free of an endpoint (i.e. reaching an improvement in the aEEG background grade: from inactive to burst-suppression, to continuous background, and to continuous background with SWC) at any time after baseline. In this analysis, we only included the time-points when each background score improvement occurred for the first time (i.e. possible later worsening of the score was not considered). We considered p ≤ 0.05 to be statistically significant.

To determine the accuracy of the aEEG background in predicting the development of epilepsy amongst the surviving neonates at a single patient level, we used as predictors the aEEG background grades at predefined time points: 12, 24, 36 and 48 hours as well as at the time point when seizures begun. We chose these time-points as they have been previously used in the literature (e.g. Hallberg et al., 2010, Cseko et al., 2013) and because they are practical enough for clinical work. We calculated the accuracy, sensitivity, specificity, and positive (PPV) and negative predictive values (NPV). To investigate whether total neonatal seizure burden above a certain threshold predicted development of postneonatal epilepsy, we used receiver operating characteristic (ROC) curves, because predefining a threshold was not possible due to lack of prior studies of this issue.

3. Results

Five children were lost to follow-up, which resulted in inclusion of 80 children in the final analysis (69 of whom were cooled, Fig. 1). Based on the outcome at the age 4 years, we categorized the children into four groups: deceased (n = 11), epilepsy (n = 6, all also developed CP), CP without epilepsy (n = 7) and favorable outcome meaning no CP or epilepsy diagnosis (n = 56). Most of the deceased neonates died during the neonatal period, except for one that died in early infancy (before 3 months of age). Of those who developed epilepsy, five were diagnosed with infantile spasms syndrome and one with focal onset epilepsy. All children with a diagnosis of epilepsy at age 4, had been diagnosed before age 1, and all but one of those with a CP diagnosis at age 4 had been diagnosed before age 1.

3.1. Group level correlation of aEEG parameters with outcome at age 4 years

Of the 80 newborns, 41 had seizures during the aEEG (Table 1), and there was no difference in the overall seizure occurrence between the outcome groups (p = 0.056). However, the occurrence of SE was significantly associated (p = 0.008) with outcome: Those neonates who died or developed epilepsy were more likely to have SE than the favorable outcome group (deceased 45.5% vs favorable 14.3%, p = 0.031; epilepsy 66.7% vs favorable 14.3%, p = 0.011). No significant difference existed between the other outcome groups.

The total seizure burden (p = 0.003) and maximum hourly seizure burden (p = 0.007) were both significantly associated with
outcome. Compared to those with a favorable outcome, those who died or developed epilepsy had a higher total seizure burden [deceased median 3.7 h (range 0–12.0 h) vs favorable 0 (0–10.4) h, \( p = 0.03 \); epilepsy 3.9 (1.5–9.7) h vs favorable 0 (0–10.4) h, \( p < 0.001 \)] and higher maximum hourly seizure burden [deceased median 0.5 (range 0–0.9) h vs favorable 0 (0–1 h), \( p = 0.03 \); epilepsy 0.7 (0.2–1) h vs favorable 0 (0–1) h, \( p < 0.001 \)]. These results remained essentially the same, if only cooled neonates were included in the comparisons. Within the group of neonates with seizures, only the total seizure burden was significantly associated with outcome (\( p = 0.01 \)).

The maximum or average seizure durations, or the postnatal age at the onset or end of seizures were not significantly associated with outcome (Table 1); however, the total length of seizure occurrence was associated with outcome (\( p = 0.045 \)), with longer duration linked to later development of epilepsy (\( p = 0.041 \)).

The outcome was significantly associated with the age at which the neonate’s cortical activity had recovered to at least burst-suppression, continuous activity, as well as to exhibiting SWC (\( p < 0.001 \) for all steps of improvement in aEEG background, Kaplan-Meier Log Rank test). Children who died or developed epilepsy were slower in reaching each improvement in the neonatal aEEG background grade when compared to children with a favorable outcome or CP without epilepsy. No difference was found between the children who died and those who developed epilepsy (see Fig. 2 for statistics). The same group level differences remained, when only cooled neonates were included in the analysis (Supplementary Fig. 1) or when the analysis was repeated based on the second expert’s scoring (Supplementary Fig. 2).

### 3.2. Individual level prediction of outcome

Furthermore, we investigated the possibility for predicting epilepsy at individual level based on 1) the aEEG background patterns at 12, 24, 36 and 48 hours after birth and at the beginning of seizures, and 2) the total seizure burden, which was the seizure parameter most closely linked to outcome. The most accurate predictors for later epilepsy amongst the survivors were inactive aEEG at the onset of seizures (accuracy of 97%, sensitivity of 100%, PPV of 86% i.e. one false positive and no false negatives, Table 2), and inactive aEEG at 24 hours (accuracy 97%, sensitivity 67%, PPV 100% i.e. two false negatives and no false positives). At the other timepoints, the best predictions were as follows: at 12 hours inactive EEG had an accuracy of 96%, sensitivity 83%, PPV 71% (two false positives and one false negative), whereas at 36 or 48 hours of age an inactive or burst-suppression aEEG had an accuracy of 96%, sensitivity 100%, and PPV 67% (no false negatives and three false positives at both ages).

In three neonates, the aEEG background improved during the brief breaks in the aEEG monitoring (due to e.g. medical procedures); however, this timing uncertainty did not affect individual level predictions. Therapeutic hypothermia also did not confound the results: All the six neonates that developed epilepsy and all the neonates that were falsely predicted to develop epilepsy based on their aEEG background activity at seizure start, 36 or 48 h were cooled. Hence, including only cooled neonates in the individual level analysis did not affect the number of true positive predictions or false prediction. Finally, when calculated based on the second expert’s scoring the predictive values of the aEEG background at 24- and 48-hours age were exactly the same, however there was one additional false prediction at 12- and 36-hours age and at seizure start (Supplementary Table 1).

The aEEG background grade at all the predefined timepoints was also strongly associated with the severity of brain injury in MRI (Table 2, \( p < 0.01 \) for all timepoints). For a discussion of the MRI findings and their association with outcome see Nevalainen et al., 2020.

Of the seizure parameters, we used total seizure burden to test how well seizures predicted epilepsy at individual level, because at group level it was most closely related to development of epilepsy in the survivors (Total seizure burden \( p = 0.001 \), eta-squared (\( \eta^2 \)): 0.17, max hourly seizure burden \( p = 0.002 \), \( \eta^2 \):0.14). Total seizure burden did not provide useful predictions over the predictive information from the aEEG background measures. Our data-driven ROC analysis indicated 6 false predictions at the optimal accuracy which was lower than the prediction accuracy achieved with the aEEG background. Including only cooled neonates in the analysis, resulted in five false predictions (all false negatives) at the optimal accuracy. Fig. 3 shows the total seizure burdens individually for the 41 neonates with seizures.

### 3.3. Outcomes at the latest follow-up

In addition to following the children until the pediatric neurologist’s appointment closest to age 4, we also examined whether they developed epilepsy later. Of the 63 children that were alive

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**Table 1**

Comparison of aEEG seizure parameters with outcome at age 4 years.

| Parameter                                      | All N = 80 | Deceased N = 11 | Epilepsy N = 6 | CP w/o epilepsy N = 7 | Favorable outcome N = 56 | \( p \)-value |
|------------------------------------------------|------------|-----------------|----------------|----------------------|--------------------------|-------------|
| aEEG onset-age (h)                             | 3.4 [0.7–11.3] | 3.6 [1.6–6.2] | 3.3 [2.8–8.2] | 2.8 [2.4–3.5] | 3.5 [0.7–11.3] | 0.244       |
| Seizures (n)                                   | 41 (51.3%) | 7 (63.6%) | 6 (100%) | 3 (42.9%) | 25 (44.6%) | 0.056       |
| Status epilepticus (n)                         | 19 (23.8%) | 5 (45.5%) | 4 (66.7%) | 2 (28.6%) | 8 (14.3%) | 0.008       |
| Total seizure burden (h)                       | 0.05 [0–12.0] | 0.37 [0–12.0] | 0.39 [1.5–9.7] | 0 [0–9.5] | 0 [0–10.4] | 0.003       |
| Maximum hourly seizure burden (h)              | 0.04 [0–1.0] | 0.5 [0–0.9] | 0.7 [0.2–1.0] | 0 [0–1.0] | 0 [0–1.0] | 0.007       |
| Maximum seizure duration (h)                   | 0.02 [0–5.3] | 0.07 [0–0.8] | 0.1 [0.04–1.9] | 0 [0–5.3] | 0 [0–1.5] | 0.099       |
| Average seizure duration (h)                   | 0.01 [0–0.3] | 0.02 [0–0.2] | 0.04 [0.02–0.2] | 0 [0–0.2] | 0 [0–0.3] | 0.127       |
| Time between the start and the end of seizures (h) | 13.5 [3.4–115.0] | 16.3 [6.3–17.8] | 10.1 [4.5–14.4] | 36.0 [13.9–122.3] | 115.0 | 0.244       |
| Time between birth and the end of seizures (h) * | 43.3 [4.4–135.6] | 47.2 [20.5–135.6] | 49.1 [26.2–75.7] | 82.9 [62.7–134.7] | 35.1 [4.4–121.1] | 0.108       |
| Time between the start and the end of seizures (h) * | 21.9 [0–124.8] | 31.0 [14.3–124.8] | 36.6 [21.7–67.5] | 46.9 [19.6–48.9] | 12.4 [0–105.3] | 0.045       |

Data is shown as N (%) or median [range]. *Comparisons include only neonates with seizures. CP = cerebral palsy.
and free of epilepsy at age 4, three developed epilepsy later. One of them, with severe HIE and MRI score 2A developed unspecified epilepsy. As a neonate, this child (patient 29 in Fig. 3) had slow aEEG recovery (burst-suppression at onset, continuous at age 59.9 hours, and continuous with SWC at age 68.9 hours), and high seizure burden (total seizure burden 7 hours, and maximum hourly seizure burden 3.14 minutes i.e. SE). Another child with severe HIE had no seizures during the neonatal period but the aEEG background recovery was slow (burst-suppression at age 12.4 hours, and continuous at age 23.4 hours continuing until the end of the recording). The ticks over the lines show time points of aEEG termination in cases where the given grade was present until the end of the recording i.e. the end point was not reached during monitoring. Altogether five neonates did not reach burst-suppression background, 14 neonates did not reach continuous background, and 17 neonates did not reach continuous background with SWC during the aEEG monitoring. Black arrows and p-values show significant results of the pairwise comparison of the groups using Kaplan-Meier Log Rank Mantel-Cox test. P-values in gray show those comparisons that were not significant after the Bonferroni correction.

4. Discussion

Our findings show that recovery of cortical activity (aEEG background patterns) and seizure burden are strongly linked to the development of postneonatal epilepsy after moderate or severe perinatal HIE. Although perinatal seizure burden was identified as a risk factor, the recovery of aEEG background patterns provided more accurate, individual-level prediction. These findings are compatible with the generally accepted notion that aEEG background is highly predictive of neurodevelopmental outcomes (Liu et al., 2020). Here, we extend the prior literature by showing that the prediction is true also for the development of postneonatal epilepsy. Our findings also show that neonatal seizures during the perinatal period per se are not an independent factor of later development of epilepsy; this observation supports the view that neonatal seizures represent a reactive condition to the perinatal brain injury (Kwon et al., 2011; Peeples et al., 2021; for a thorough discussion see also Zhou et al., 2021), the outcome of which is better reflected in the recovery of cortical activity.

In accordance with previous literature (Glass et al., 2020; Kharoshankaya et al., 2016; Pisani et al., 2007), in our study, children who developed epilepsy had higher seizure burden during the neonatal period than children who survived without epilepsy. Glass et al. (2020) reported in neonates with seizures due to various etiologies that those with a high seizure burden had a greater risk for developing epilepsy. Furthermore, in a cohort of neonates with HIE, Kharoshankaya et al. (2016) showed an association between a high seizure burden and abnormal outcome, which included epilepsy. Although they did not report the predictive values specifically for epilepsy, similar to the present study, all children that developed epilepsy had had seizures as a neonate (Kharoshankaya et al., 2016).

Fig. 2. Kaplan-Meier curves displaying the group level differences of aEEG background class improvement over time. The x-axis shows the postnatal age. The y-axis shows the proportion of neonates that remain with the following aEEG grades: A) inactive, B) burst-suppression (BS) or worse and C) continuous aEEG without sleep wake cycling (SWC) or worse. In other words, the proportion on the y-axis represents the neonates that have not yet reached a better background score (i.e. have not yet reached the end point) at the postnatal age defined by the x-axis. The colors of the lines indicate the outcome groups (blue = deceased, red = epilepsy, green = cerebral palsy, CP, without epilepsy, yellow = favorable). The colors and shape of the figures show the MRI score: ■ = 3, † = 2B, ◊ = 2A, ○ = 1B, □ = 1A, △ = 0. BS = burst-suppression, SWC = Sleep-wave cycling, CP = cerebral palsy. The neonates that were not cooled are underlined.

Table 2

Association of the aEEG background with MRI findings and outcome. A) aEEG background grade at 24 h postnatally (n = 80), and B) at seizure onset (n = 41). Each figure in the table represents one neonate. The color and shape of the figures show the MRI score: ■ = 3, † = 2B, ◊ = 2A, ○ = 1B, □ = 1A, △ = 0. BS = burst-suppression, SWC = Sleep-wave cycling, CP = cerebral palsy. The neonates that were not cooled are underlined.

| A | Inactive | BS | Continuous w/o SWC | Continuous with SWC |
|---|---|---|---|---|
| Deceased (n=1) | ■■■■■■■ | ■ | | |
| Epilepsy (n=6) | ■■■ | | | |
| CP w/o epilepsy (n=7) | | | | |
| Favorable (n=56) | | | | |
| B | Inactive | BS | Continuous w/o SWC | Continuous with SWC |
| Deceased (n=7) | ■■■■■ | | | |
| Epilepsy (n=6) | ■■■■■ | | | |
| CP w/o epilepsy (n=3) | | | | |
| Favorable (n=25) | | | | |

Table 2
In our study, neonatal aEEG background patterns were distinctly worse, and the recovery was slower in children developing epilepsy than in those with a favorable outcome or even those who developed CP without epilepsy. This finding complements our previous study from the same cohort, which showed an association between the EEG background pattern and later epilepsy (Nevalainen et al., 2020), but could not evaluate background evolution as it only included a short EEG recording. Similarly, Glass et al. (2020), who used a combined variable consisting of seizures and EEG background, showed this variable to be useful in predicting development of infantile spasms in a cohort of neonates with seizures of varying etiologies.

Our most important findings concern the individual-level prediction of later epilepsy. Whereas seizure burden was not an accurate individual-level predictor for epilepsy, the aEEG background grade at specific time points predicted development of epilepsy with high accuracy, even already at the time of the first seizure. The high predictive value of the poor aEEG background probably reflects the fact that all six children diagnosed with epilepsy by age 4 had severe brain injury and developed severe epilepsy including five with infantile spasms syndrome. In line with this assumption, those who developed epilepsy did not differ from those who died in any aEEG parameter, but on the other hand differed quite much from those with a favorable outcome and even from those who developed CP without epilepsy. The difference between the epilepsy and CP without epilepsy groups was particularly distinct when comparing the age when these groups reached burst-suppression and continuous aEEG background, as well as when comparing the aEEG background at the onset of seizures.

Some false predictions expectedly occurred as we used discrete aEEG background classes to predict outcome of HIE - a condition, that truly is a spectrum. In our work, the strictest predictor (inactive aEEG at 24 h) failed to detect two target neonates (epilepsy) which possibly had a less severe brain injury than the other four (the two false negatives had MRI score 2B, whereas three of the four true positives had MRI score 3, and one had score 2B). On the contrary, the less strict predictors (inactive or burst suppression aEEG at 36 h/48 h) picked up 3–4 (depending on the expert) neonates that did not develop the target condition. All of them still had significant brain injury that was also reflected in the slow aEEG.

![Fig. 3. Individual aEEG background grades and seizure metrics for the first 72 h in the 41 newborns with seizures. Left side of the figure displays aEEG background grades: red = inactive, orange = burst-suppression, yellow = continuous without sleep wake cycling, green = continuous with sleep wake cycling, turquoise = status epilepticus (seizures > 50% of time), grey = artefact, and blank = aEEG recording paused or stopped. CP = cerebral palsy."](image-url)
recovery. In addition, there is also a notable phenomenological ambiguity in the aEEG background classes per se, as they attempt to categorize a continuous spectrum of cerebral states into discrete categories. Future work should strive to develop quantitative measures capturing the whole spectrum of EEG background activity.

No new epilepsy cases were diagnosed between 1- and 4-years age, which supports earlier studies reporting the incidence of epilepsy to be highest during the first year of life (Bergamasco et al., 1984; Gailly et al., 2016; Wirrell et al., 2011). However, three children developed epilepsy after age 4. In concordance with earlier studies (Liu et al., 2017) the risk for developing epilepsy, thus, persisted in later childhood. Except for the self-limited epilepsy with centrotemporal spikes, the two children who developed epilepsy after age 4 had slow aEEG recovery and significant brain injury in MRI. In fact, one of them had burst-suppression aEEG at 36 months of life. The other child with slow aEEG recovery and significant brain injury in MRI after age 4 had self-limited epilepsy with centrotemporal spikes and slow aEEG recovery and significant brain injury in MRI. In fact, one of them had burst-suppression aEEG at 36 months of age. In concordance with earlier studies (Bergamasco et al., 1984; Gailly et al., 2016; Wirrell et al., 2011), slow aEEG recovery and significant brain injury in MRI has been reported in children with epilepsy development after age 4. However, for seizure detection in the neonatal intensive care unit, the 4-electrode montages used in routine aEEG monitoring, and in the present study, are comparable to the 8-electrode neonatal montage used in many previous studies (Stevenson et al., 2018). Seizures were also only evaluated by one expert, which might affect the exact numerical estimates for each patient. However, the previously reported very high intra-rater consistency in seizure detections and a high inter-rater agreement with longer seizures (duration > 30 s; Stevenson et al., 2015) such as used in our work, suggest that additional experts would not have affected the relative seizure burden estimates across the infant cohort. Finally, there were some brief breaks in the aEEG monitoring due to medical procedures, and they pose some uncertainty to the exact timing of background recovery or seizure burden estimates; our post hoc evaluation suggests, however, that these breaks cannot introduce any meaningful qualitative changes to our core results.

A strength of this study is that the aEEG recordings were started very shortly after birth and, hence, it was possible to obtain reliable estimates of the total seizure burden and aEEG background recovery. Other strengths are that the study is exposure-based (HIE) and has a long-term follow-up of a population-based cohort. Finally, we were able to validate our main findings using an independent second expert, which indicated robustness of the reported neurological measures.

5. Limitations and strengths of the study

A limitation of our study is the low number of children who developed epilepsy, although the cohort consisted of patients with neonatal HIE from a relatively large tertiary hospital over a period of six years. Secondly, due to the study design we could not assess questions related to e.g. association of treatment of neonatal seizures and postneonatal epilepsy. Also, the limited number of electrodes could be seen as a limitation. However, for seizure detection in the neonatal intensive care unit, the 4-electrode montages used in routine aEEG monitoring, and in the present study, are comparable to the 8-electrode neonatal montage used in many previous studies (Stevenson et al., 2018). Seizures were also only evaluated by one expert, which might affect the exact numerical estimates for each patient. However, the previously reported very high intra-rater consistency in seizure detections and a high inter-rater agreement with longer seizures (duration > 30 s; Stevenson et al., 2015) such as used in our work, suggest that additional experts would not have affected the relative seizure burden estimates across the infant cohort. Finally, there were some brief breaks in the aEEG monitoring due to medical procedures, and they pose some uncertainty to the exact timing of background recovery or seizure burden estimates; our post hoc evaluation suggests, however, that these breaks cannot introduce any meaningful qualitative changes to our core results.

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6. Conclusions

Slow recovery of the aEEG background, reflecting the severity of brain injury, predicts development of severe, early postneonatal epilepsy at individual level. Although neonatal seizure burden was associated with postneonatal epilepsy at group level, at individual level it was not as accurate for prediction of epilepsy as the aEEG background.
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