EEG background activity, seizure burden and early childhood outcomes in neonatal encephalopathy in Uganda: a prospective feasibility cohort study

Sean R. Mathieson,[a,g] Carol Nanyunja,[b,c,g] Samantha Sadoo,[c,d] Sherinah Nakalembe,[b] Eleanor Duckworth,[d] Stella Muryasingura,[b] Natalia Niombi,[b] Jacopo Proietti,[a] Mariam Busingye,[b] Annettee Nakimuli,[e,f] Vicki Livingstone,[a] Emily L. Webb,[c] Ivan Mambule,[b] Geraldine B. Boylan,[a,h] and Cally J. Tann[b,c,d,h,*]

[a]INFANT Research Centre and Department of Paediatrics & Child Health, University College Cork, Ireland
[b]MRC/UVRI & LSHTM Uganda Research Unit, Entebbe
[c]London School of Hygiene & Tropical Medicine, Keppel Street, London
[d]University College London Hospitals NHS Trust, Euston Road, London
[e]Kawempe National Referral Hospital, Kampala, Uganda
[f]Makerere University, Kampala, Uganda

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Summary

Background Intrapartum-related neonatal encephalopathy (NE) is a leading cause of childhood mortality and morbidity. Continuous electroencephalography (EEG) is gold standard for neonatal brain monitoring; however, low-income country data is lacking. We examined EEG in a Ugandan cohort with NE to describe feasibility, background activity, seizure prevalence and burden, and associations with clinical presentation and outcome.

Methods Neonates with NE were recruited from a single hospital referral centre in Kampala, Uganda (Oct 2019–Oct 2020) and underwent EEG monitoring. Feasibility was assessed as to whether EEG monitoring of diagnostic quality could be achieved from days 1–5. Evolution of clinical presentation was assessed by Sarnat classification and daily Thompson score was performed. EEG background severity was graded at 12, 24, 48 and 72 h after birth, and at time of Thompson score. Seizures were annotated remotely by experts and assessed for frequency, duration, burden, and status epilepticus. Early childhood outcome was assessed at follow up, and adverse outcome defined as death or neurodevelopmental impairment (NDI) at 18–24 months of age.

Findings In this prospective feasibility cohort study, diagnostic quality EEGs were recorded for 50 of 51 recruited neonates (median duration 71.4 h, IQR 52.4–72.2), indicating feasibility. Of 39 participants followed to 18–24 months, 13 died and 7 had NDI. Daily Thompson score and EEG background grade were strongly correlated across all timepoints (days 1–5). Thompson score of ≥7 was most predictive of moderate-severe EEG background abnormality (AUC 0.83). Prognostic accuracy of moderate-severe EEG background grade to predict NDI was high (AUC 0.74). Electrographic seizures were seen in 52% (26); median seizure burden was high at 264 min (IQR 27.8–523.7, range 1.3–1374.1); half (13) had status epilepticus.

Interpretation EEG monitoring was feasible as a research tool in this sub-Saharan Africa setting. EEG background activity correlated strongly with scored neurological assessment and predicted adverse early childhood outcome. Seizure prevalence and burden, including status epilepticus, were high in this uncooled cohort with important potential longer-term implications for survivors.

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*Corresponding author. Department of Infectious Disease Epidemiology and International Health, London School of Hygiene & Tropical Medicine, Keppel Street, UK.
E-mail address: Cally.tann@lshtm.ac.uk (C.J. Tann).
[g]Joint first author.
[h]Joint last author.

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Research in context

Evidence before this study

Neonatal encephalopathy related to complications around the time of birth, is one of the leading causes of death among children globally, affecting more than one million newborns each year. It has one of the highest age-standardised rates of disability-adjusted life years amongst all neurological disorders, second only to stroke. We searched Medline, and subsequent reference lists, without date or language restrictions, using combinations of terms related to 'neonatal encephalopathy' ('asphyxia neonatorum', 'birth asphyxia', 'perinatal asphyxia', 'hypoxic-ischaemic encephalopathy'), 'EEG' ('electroencephalography', 'encephalogram', 'cerebral function monitor'), seizure ('fit', 'convulsion'), and 'outcome' ('death', 'neurodevelopment', 'disability', and 'impairment'), last updated on 01 May 2024. Electroencephalography (EEG) is the gold standard investigative modality to describe electrographic background EEG activity and detect seizures. Effective targeting of anti-seizure medications using clinical manifestations alone is challenging. However, there is a lack of newborn EEG data from sub-Saharan Africa where the burden of neonatal encephalopathy is highest. The Thompson score is a neurological assessment developed in South Africa to assess for the presence and severity of neonatal encephalopathy, however, few studies have examined associations with brain function. EEG background activity, and the prevalence and burden of seizures, have been linked to adverse childhood outcomes, however, data from low-income country settings are sparse.

Added value of this study

This study is the first to our knowledge, to describe findings from continuous video-EEG monitoring amongst a sub-Saharan African cohort with neonatal encephalopathy, without access to neonatal intensive care. EEG provided unique insights into background brain activity, seizure prevalence and burden, and associations with clinical presentation including early childhood outcomes in our Ugandan population. EEG background abnormalities strongly correlated with clinical presentation with a Thompson score of ≥7 day most predictive of moderate-severe brain dysfunction at any timepoint (day 1–5). In this cohort without access to therapeutic hypothermia, half experienced electrographic seizures, and seizure burden was high, particularly amongst those with a moderately and severely abnormal background EEG. Half of those experiencing seizures had at least one episode of status epilepticus. EEG background score was predictive of early childhood outcomes, with prognostic accuracy decreasing over time and increasing with severity of brain dysfunction. Importantly, resolution of background EEG within 72 h was associated with favourable early childhood outcome.

Implications of all the available evidence

EEG monitoring was a feasible research tool in this sub-Saharan African setting and provided unique insights into background brain activity, seizure prevalence and burden. Clinical assessment of newborns using an established scored neurological assessment (Thompson score) can identify those with moderate to severe brain dysfunction for targeted intervention. Seizure prevalence and burden, including status epilepticus, were high in this uncooled cohort with important potential implications for longer term outcomes among surviving children. Novel innovations to monitor brain dysfunction in diverse settings could substantially improve our understanding of neonatal encephalopathy and support clinical management of seizures. More data is needed from low- and middle-income country settings to better understand the role of brain dysfunction and seizures, including the longer-term impacts for affected children and families, and to identify potential neuroprotective strategies.

Introduction

Globally, intrapartum-related neonatal encephalopathy (NE) is a leading cause of under-five child mortality and neurodevelopmental impairment amongst survivors including cerebral palsy, global developmental delay, epilepsy, and hearing and visual impairments.[1] The vast majority of affected children are born in low- and middle-income countries (LMICs), where incidence of NE is estimated to be ten-fold higher than in high-income countries (HICs).[2] NE is estimated to affect more than one million children globally each year, with 42% born in sub-Saharan Africa.[2] Whilst therapeutic hypothermia is strongly evidenced to improve disability-free survival in HICs, it is not currently recommended in low-income country (LIC) settings due to lack of evidence on effectiveness, meaning NE care is largely supportive.[3]

Continuous electroencephalography (EEG) is the gold standard investigation modality to assess background brain wave activity and detect seizures in neonates with NE. EEG abnormalities associated with hypoxia-ischaemia include disrupted sleep wake cycling (SWC), low amplitude, discontinuous recording with interburst intervals >30 s, asymmetry/asynchrony, and electrographic seizures.[4] These features evolve over the first hours and days of life following a hypoxic ischaemic insult; both the severity of background activity and evolution on sequential recordings are strong

prognostic indicators for later outcome.[4,5] Increased seizure burden, particularly a total seizure burden of over 40 min, have also been shown to be associated with adverse neurodevelopmental outcome in a HIC setting, independent of other factors.[6] However, to date, EEG data from NE cohorts in LMICs are lacking. EEG is rarely available in LMICs due to cost and technical expertise required for implementation and interpretation. Seizures are often diagnosed based on clinical manifestation alone, however this is unreliable given over 70% of suspected clinical seizures are not associated with epileptiform discharges on EEG, and conversely, 50–80% of seizures are subclinical.[7] The International League Against Epilepsy (ILAE) classification of neonatal seizures now requires EEG changes to be present for a diagnosis of seizures.[8]

The objectives of this study were to i) examine the feasibility of EEG in neonates with NE in a Ugandan setting; ii) describe the findings of EEG monitoring including background electrographic activity, seizure prevalence and burden; iii) examine associations between EEG abnormalities, clinical presentation, and early childhood outcome at 18–24 months of age. This work was part of the Baby BRAiN study, which aimed to establish the feasibility of a cohort with NE utilising gold standard investigative modalities in a Ugandan setting, to investigate the clinical course of newborn brain injury, and examine associations with early childhood outcomes.[9]

Methods

Setting

Kawempe National Referral Hospital (KNRH) is a national referral centre in Kampala, Uganda's capital city. The estimated incidence of NE in this facility is 15–20 per 1000 live births, with 300–350 neonates with moderate-severe encephalopathy admitted each year [unpublished data]. During the study period, intrapartum continuous fetal monitoring and assisted vaginal delivery with ventouse or forceps were not routinely offered. After birth, midwife-led neonatal resuscitation included oxygen and bag-mask ventilation, simple continuous positive airway pressure ventilation, intravenous fluids, antibiotics, and first line anti-seizure medication. Therapeutic hypothermia was not available, and care largely supportive. Cord/neonatal blood gas measurement were not available.

Ethics

The study protocol was approved by the ethics committees of the London School of Hygiene and Tropical Medicine (LSHTM), Uganda Virus Research Institute (UVRI), Ugandan National Committee of Science and Technology (UNCST), and Ugandan President's Office. Written informed consent was obtained from the parents of all participating infants.

Study design and participants

This was a facility-based prospective feasibility cohort study amongst near-term and term born neonates with NE.[9] Participants were recruited by the Medical Research Council/UVRI (MRC/UVRI) and LSHTM Uganda Research Unit clinical research team between October 2019 and October 2020. Inclusion criteria included: term or near-term neonates (≥36 weeks' gestation on Ballard examination), Thompson score ≥5,[10] recruited within 48 h of birth, birth weight ≥1.8 kg, need for continued resuscitation after birth/5-min Apgar score ≤5, and informed written parental consent. Exclusion criteria included: absent heart rate at 10 min/imminent death, major congenital malformations, and mother living permanently >20 km from KNRH. A continuous approach to consent was utilised. Full study procedures have been published previously.[9]

Screening and recruitment

Inborn and outborn neonates were screened for eligibility and written informed parental consent was sought. All study staff were trained on the consenting process and were Good Clinical Practice (GCP)-certified prior to the start of recruitment. Consenting was performed in the preferred language of the caregiver, and appropriate time was given for caregivers to decide on participation in the study. Recruitment numbers were limited due to Covid-19 related research suspensions and lockdowns, and occasionally by availability of EEG equipment. Baseline demographic and clinical information was collected according to study standard operating procedures.

Clinical procedures

All participants were managed clinically according to standard practice at KNRH. To define the evolution and severity of NE as mild, moderate or severe, a daily neurological examination was performed (days 1–5). Sarnat classification, inclusive of EEG criteria, was assigned daily to define NE severity (highest grade on days 1–5). Thompson score, developed in South Africa where cerebral function monitoring including EEG is frequently unavailable, was also assigned daily to examine its diagnostic accuracy in predicting moderate-severe EEG background activity.[10] Relevant clinical data including anti-seizure medications administered, were also collected. National and local guidance on Covid-19 screening and management were followed including provision of Personal Protective Equipment to staff and participants.

EEG recording and seizure analysis

EEG was applied and maintained by clinical research staff supervised by the research coordinator (CN). EEG training was provided by ED and CT supported by neurophysiology experts from the INFANT research centre, University College Cork, Ireland. The staff

received hands-on EEG training for 2 weeks and mentorship on leads placement throughout the data collection period, to facilitate high quality EEG acquisition. Multichannel video-EEG was commenced as soon as possible after birth and continuously recorded on days one to five (Lifelines iEEG, UK). Electrodes were positioned at F3, F4, C3, C4, Cz, T3, T4, O1 and O2 according to the 10–20 EEG electrode placement system adapted for neonates. Recording and review settings included a bipolar montage (F4–C4, C4–O2, F3–C3, C3–O1, T4-C4, C4-CZ, CZ-C3, C3-T3), high pass filter 0.5 Hz, low pass filter 70 Hz, notch filter, sensitivity 7–10 μV/mm, timebase 15–20 mm/s and single channel electrocardiography and respiration monitoring synchronised with EEG trace. The video-EEG was uploaded subject to network availability to a cloud-based server (Kvikna Medical, Iceland). INFANT centre personnel provided signal quality assessment and technical feedback to the local team where possible. When 4G signal quality was insufficient for live upload, the recording was stored on the device and uploaded and reviewed post-acquisition. Due to challenges with timely uploading of raw EEG data, it was not possible to provide continuous 24-h feedback to the clinical team, however, when available, any concerns were communicated to the principal investigator and cascaded. Clinically recognised seizures were otherwise treated based on clinical diagnosis, according to local protocols. EEG monitoring is not routinely available in any government facility in Uganda, and as EEG interpretation is recognised to be a highly specialised skill with risk of harm if interpreted incorrectly, the video-EEG screen was covered. Post-acquisition analysis was performed by neurophysiology experts at INFANT (SM, JP, GB), blind to clinical information except gestational age at birth. EEG background activity was classified for 1-h epochs (12, 24, 48, 72 h of age) and at the time of daily Thompson score. The EEG grades were assigned according to criteria described by Murray et al. (Table 1).[4] EEG seizures were annotated with duration and total seizure burden, calculated as the accumulated duration of seizure in the entire record. We also calculated the seizure burden as a percentage of the total recording time, the maximal hourly seizure burden as the seizure burden in the hour in which the highest seizure burden was recorded, the hour after birth that the maximal seizure burden occurred, and the seizure period as the duration between the start of the first and the end of the last seizure recorded. Seizures were defined as 'a sudden repetitive, stereotyped discharge of minimum 10 s duration on one or more EEG channels with evolving frequency, amplitude and morphology', and status epilepticus was defined as 'seizures occupying greater than 50% of the record in any given hour'.[11] Examples of the background grades and seizure annotation are shown in Fig. 1.

Grade	Findings	Description
0	Normal EEG findings	Continuous background pattern with normal physiologic features such as anterior slow waves
1	Normal/mild abnormalities	Continuous background pattern with slightly abnormal activity (e.g., mild asymmetry, mild voltage depression, or poorly defined sleep wake cycle)
2	Moderate abnormalities	Discontinuous activity with interburst interval of <10 s, no clear sleep wake cycle, or clear asymmetry or asynchrony
3	Major abnormalities (severe)	Discontinuous activity with interburst interval of 10–60 s, severe attenuation of background patterns, or no sleep wake cycle
4	Inactive EEG findings (severe)	Background activity of <10 μV or severe discontinuity with interburst interval of >60 s

Table 1: **EEG background activity classification (adapted from Murray et al[4]).**

Neurodevelopmental outcome

Participants surviving to discharge were followed at 28 days, 12 months and 18–24 months of age.[9] Bayley Scales of Infant Development-III (BSID-III) assessed neurodevelopment across five domains: cognition, receptive language, expressive language, fine motor and gross motor; a cut-off score <70 for cognitive/motor domains to define disability were used, in accordance with a recent South African study.[12] The Hammersmith Infant Neurological Examination (HINE) assessed child neurology, and cerebral palsy was classified using the Gross Motor Function Classification System for Cerebral Palsy (GMFCS). Adverse outcome was defined as combined death or moderate-severe neurodevelopmental impairment (NDI). NDI was defined as BSID-III cognitive/motor score <70, and/or HINE ≤67, and/or GMFCS level 3–5, at 18–24 months of age, or at 12 months where 18–24 month data was not available.[9]

Statistics

A purposive sample size of 70 neonates was planned for this feasibility study but ultimately reduced due to accommodating Covid-19 restrictions. Feasibility of EEG was assessed by the number consenting for EEG recording at the start of the study, number undergoing EEG between days 1–5, and number of quality recordings that could be included in the analysis. EEG resolution was defined as a change from an EEG background score of 2–4 (moderate to severe) to 0–1 (normal to mild) over days 1–5.

Categorical variables were summarised using counts and percentages. Continuous variables were assessed for normality by visually inspecting histograms, and summarised using the mean and standard deviation (SD) when normally distributed, and the median and interquartile ranges (IQR) when not normally distributed. Fisher's exact test was used to evaluate associations between categorical variables. To compare continuous variables that were not normally distributed

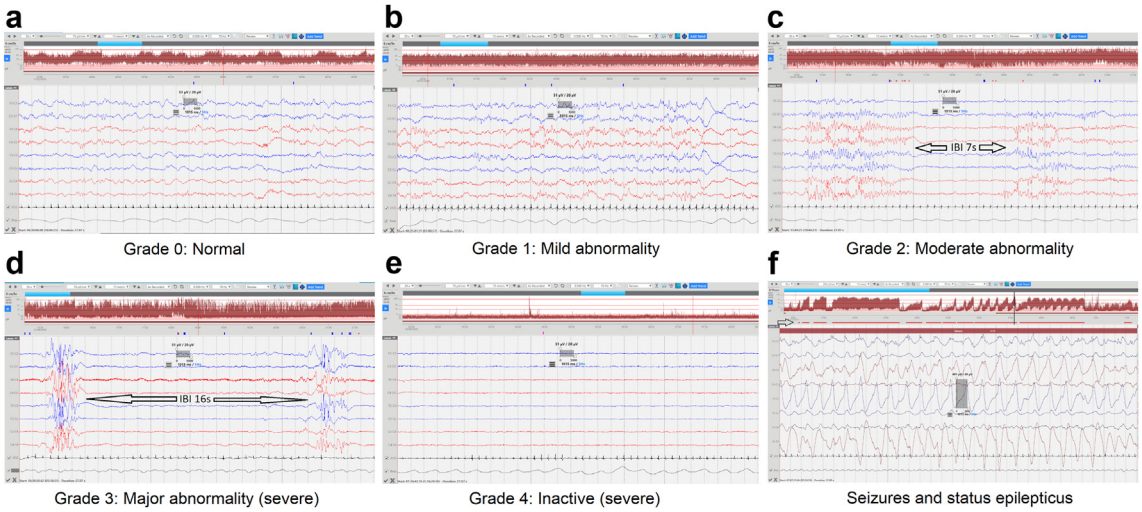

Fig. 1: Examples of EEG findings in intrapartum-related neonatal encephalopathy. a) Grade 0 - normal, EEG shows continuous mixed frequency activities in active sleep, note the fluctuating amplitude integrated EEG (aEEG) trace indicating sleep cycling. b) Grade 1 – mild abnormality, Continuous EEG but no clear sleep cycling. c) Grade 2 – moderate abnormality, discontinuous with interburst interval (IBI) of 7 s. d) Grade 3 – severe abnormality, discontinuous with IBI 16 s. e) Grade 4 – flat trace, highly suppressed background with no EEG activity over 10 μV. f) Seizures and status epilepticus: EEG shows an ongoing widespread, high amplitude discharge. The black vertical line indicates the position on the aEEG of the EEG page displayed. The aEEG shows a 12-h period of recording. Multiple prolonged seizures occupy the majority of the record and are indicated by multiple aEEG deflections and seizure duration annotations (red bars) at the level of the black arrow.

between groups, the Mann–Whitney U test was used when there were two groups and the Kruskal–Wallis test was used otherwise. Relationships between Thompson score, EEG background and outcome, as well as between EEG background severity/resolution and outcome, were assessed. The diagnostic accuracy of the Thompson score to predict EEG background and the prognostic accuracy of Thompson score and EEG background to predict early childhood outcome were examined using Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves and their associated measures - sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and area-under-the-curve (AUC), with 95% confidence intervals (CIs) were used to assess diagnostic accuracy. Youden's index (index = sensitivity + specificity-1) was used to find the optimal sensitivity-specificity cut-off point on the ROC curve. We did not statistically compare AUCs due to the variation in numbers of participants assessed by EEG and Thompson score across the different time points. These sample sizes are shown in Supplementary Tables S2, S3 and S4. Associations between seizures and outcome were not examined due to the small size of this sub-group and because full seizure burden could not be established for many as EEG was not commenced at the time of birth. A p-value < 0.05 was considered statistically significant. Stata (version 17, StataCorp LLC, College Station, TX, USA) was used for all analyses. Adjustments for multiple comparisons and multivariable analysis were not performed, as this was a pilot study with a limited sample size.

Role of the funding source

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Results

Of 51 recruited neonates, 50 had diagnostic quality EEG data. EEG monitoring was commenced at a median (IQR) [range] of 21.1 (14.2–29.8) [5.4–48.8] hours after birth. One neonate was very unwell and died shortly after recruitment (at 12 h of age); no EEG procedures were commenced prior to their death due to clinical instability. Of the 50 who underwent EEG, 13 died, 26 attended neurodevelopmental follow-up, 8 withdrew and 3 were lost to follow-up (Fig. 2). Early childhood outcome data were available for 39 participants; the majority at 18–24 months (35), with an additional four followed to 12 months. Of the 39 with outcome data, 20 (51%) had adverse outcomes; 13 died (12 neonatal deaths, one at three months of age), and seven had NDI;

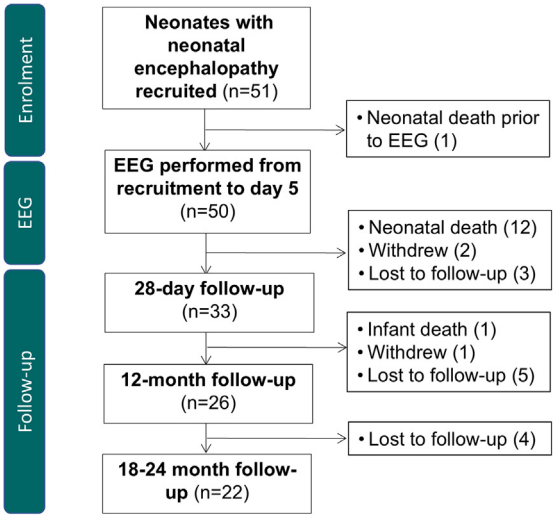

Fig. 2: Flow of participants. Footnote: Abbreviations: EEG = encephalogram.

five cerebral palsy and two severe global developmental delay (Supplementary Table S1). Of those with a favourable outcome (19); 14 (35%) had mild NDI, and 5 (12.5%) had normal development.

Baseline characteristics are described in Table 2.

EEG background grade and evolution

In total, 122 EEG epochs were available for analysis of background severity across the four time points after birth (n=13 at 12 h; n=30 at 24 h; n=42 at 48 h; n=37 at 72 h). Nearly half of neonates (24/50, 48%) had a severely abnormal EEG background (grade 3, 4) as the highest grade across all timepoints; eight (16%) had a moderately abnormal background; 16 (32%) were mildly abnormal; only 2 neonates had a normal background throughout.

Overall, the proportion of epochs classified as severe decreased at later time points, while the prevalence of milder grades increased (Fig. 3). Of 42 infants who had more than one EEG recording; 14 improved, 28 showed no change, and none worsened. Of these, 24 had moderate-severe abnormality on EEG, and of these, four normalised to grade 0–1; one by 24 h, two by 48 h, one by 72 h.

EEG background and thompson score

Daily Thompson score and EEG background grade were strongly correlated across all timepoints (Supplementary

	All participants (n = 50)[a]	Participants with early child outcome data (n = 39)[a]
Maternal baseline characteristics[b,c]		
Maternal age, years (yrs), median (IQR) [range]	23yrs (20–28) [16–38]	23yrs (20–29) [18–38]
HIV status - positive, % (n)	5% (2)	0% (0)
Primiparity, % (n)	50% (21)	39% (12)
Non-cephalic presentation, % (n)	10% (4)	13% (4)
Emergency caesarean section, % (n)	29% (12)	29% (9)
Neonatal clinical characteristics		
Sex - male, % (n)	66% (33)	64% (25)
Gestational age, weeks (wks), median (IQR) [range]	38wks (38–40) [36–42 g]	38wks (38–40) [36–42]
Birthweight, grams (g)[a], mean (SD) [range]	3117 g (451) [2300–4150 g]	3133 g (454) [2300–4150]
Outborn, % (n)	22% (11)	21% (8)
5-min Apgar score[b,c], median (IQR) [range]	6 (4.5–7) [0–10]	6 (5–7) [0–10]
Age at recruitment, hours (h), median (IQR) [range]	19 h (11–24.3) [3.1–46.1]	19.3 h (11–24.3) [3.9–42]
Age at start of EEG monitoring, hours (h), median (IQR) [range]	21.1 h (14.2–29.8) [5.4–48.8]	21.1 h (12.6–27.7) [6.5–48.8]
EEG started within 12 h of birth, % (n)	20% (10)	21% (8)
Duration of EEG, hours (h), median (IQR) [range]	71.4 h (52.4–72.2) [10.3–75.3]	71.8 h (47.0–72.2) [10.3–75.3]
NE Severity (Modified Sarnat grade): % (n)		
Normal	4% (2)	3% (1)
Mild	24% (12)	23% (9)
Moderate	30% (15)	26% (10)
Severe	42% (21)	49% (19)
Early childhood outcomes		
Neonatal death, % (n)	26.7% (12/45)	30.8% (12/39)
Post-neonatal death, % (n)		2.6% (1/39)
Moderate-severe NDI, % (n)		17.9% (7/39)
Disability-free survival, % (n)		48.7% (19/39)

HIV = human immunodeficiency virus; EEG = encephalogram; NDI = neurodevelopmental impairment. [a]Unless otherwise stated. [b]n = 42 and n = 31. [c]n = 48 and n = 38.

Table 2: **Baseline maternal and neonatal characteristics of participants undergoing EEG monitoring.**

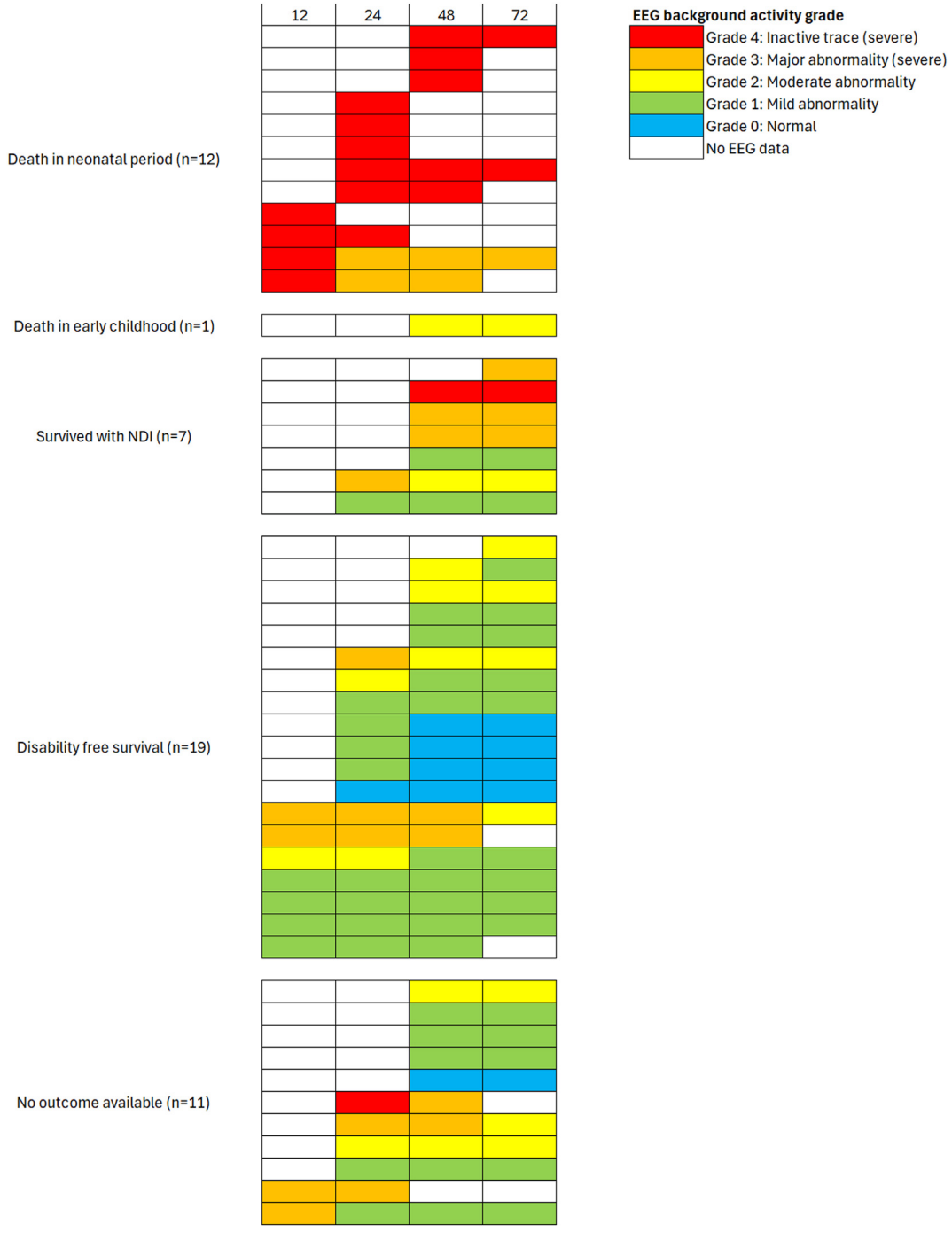

Fig. 3: EEG background activity grading over time and by outcome (n = 50). Each row represents the severity of EEG background activity over time for an individual neonate.

Fig. S1). For days two to five, EEG and Thompson scores were performed at the same time; on day one, as EEG was applied after the first Thompson assessment, EEG epochs were scored from the first available hour of EEG recording at a median (IQR) of 3.7 (2.4–5.1) hours after Thompson assessment. Correlation coefficients ranged from 0.62 to 0.76 and was highest on day four (0.76, $p < 0.001$).

To support clinical decision making where EEG is not routinely available, diagnostic accuracy of Thompson score to predict moderate-severe and severe EEG background activity was examined on days 1–5

(Supplementary Table S2). On day 1, a Thompson score of ≥7 was most predictive of moderate-severe EEG background (Youden's index = 0.67, n = 15) with sensitivity 67% (95% CI 35–90%), specificity 100% (29–100%), PPV 100%, (63–100%), NPV 43% (10–82%), and AUC 0.83 (0.69–0.97). Diagnostic accuracy of day 1 Thompson score ≥7 (Youden's index = 0.73) for severe EEG background at a similar time was also high; sensitivity 88% (95% CI 47–100%), specificity 86% (42–100%), PPV 88% (47–100%), NPV 86% (42–100%) and AUC 0.87 (0.68–1.00).

Highest Thompson score across days 1–5 was predictive of a moderate-severe EEG background and severe EEG background (highest EEG background across days 1–5). A Thompson score cutoff of ≥7 (Youden's index = 0.72) was found to be the most predictive of moderate-severe EEG background abnormality (n = 45, AUC 0.87; CI 0.75–0.97), correctly classifying 87% (39 of 45 neonates), with good sensitivity (89%; 95% CI 72–98%), specificity (82%; CI 57–96%), PPV (89%; CI 72–98%), NPV (82%; CI 57–96%). Diagnostic accuracy of highest Thompson score ≥7 (Youden's index = 0.59) for severe EEG background was lower (n = 45, AUC 0.80; CI 0.69–0.90) (Supplementary Fig. S2 and Table S2).

Seizure prevalence and burden

Overall, neonatal seizures occurred in 52% (n = 26). Amongst those with seizures, frequency and burden was high; median number of seizures was 65 (interquartile range (IQR) 20–147, range 1–442), and median total seizure burden 264.0 min (IQR 27.8–523.7, range 1.3–1374.1). Of these, half (n = 13) had at least one period of status epilepticus. Median seizure burden as a percentage of total recording time was 6.1% (IQR 0.6–16.6, range 0.03–55.14). The median maximal hourly seizure burden was 25.4 (IQR 11.6–50.2, range 1.1–60) minutes per hour and the median hour after birth that the maximal seizure burden occurred was 36 (IQR 24–49, range 9–112) hours. Median seizure period was 29.3 (IQR 20.9–46.7, range 0.02–65.4) hours. Regarding timing, the median age of initiation of seizures was 23.7 (IQR 18.4–37.6, range 7–56.6) hours. However in 42% (11/26), seizures were already ongoing at the start of the EEG recording (defined as having seizures in the first hour of recording). For those neonates, the median age of seizure onset was 21.7 (IQR 19–27.7, range 7–37.6) hours. Of those who had seizures not already initiated at the start of the EEG recording (no seizures in the first hour, n = 15), the median age of seizure onset was 36.1 (IQR 13.1–48.3, range 9.4–56.6) hours.

Associations between seizure prevalence/burden and EEG background

Associations between seizure prevalence, seizure burden and grade of background EEG abnormality (highest grade at any timepoint) were examined. A statistically significant association was observed between seizure prevalence and the highest-grade severity of background abnormality from 12 to 72 h (p = 0.001 (Fig. 4a). Infants with a moderately abnormal background EEG (grade 2) had the highest seizure prevalence (88%; 7/8), followed by those with grade 3 (80%; 8/10), then grade 4 (57%; 8/14). Three infants (19%; 3/16) with mild background abnormality (grade 1) had seizures, all of short duration (all <15 min). No infants with a normal background EEG (grade 0) had seizures.

Fig. 4b describes the total seizure burden for each infant with seizures (n = 26), categorised by their highest background EEG grade from 12 to 72 h. Among infants with seizures, total seizure burden did not differ significantly between the highest EEG background grade groups (p = 0.167). The highest median seizure burden was seen amongst those with moderately

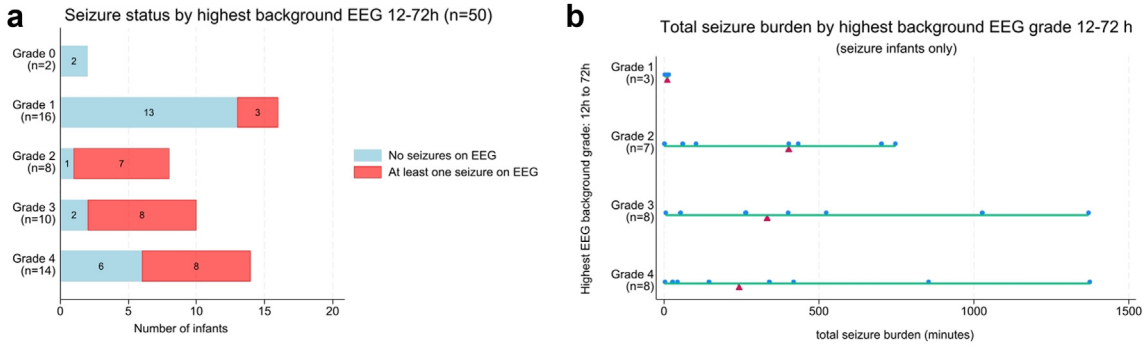

Fig. 4: Associations between seizure prevalence, burden and highest-grade EEG background activity 12–72 h. a) Seizure status by highest background EEG and b) total seizure burden by highest background EEG grade. Footnote: Abbreviations: EEG = encephalogram. A blue dot represents the total seizure burden (in minutes) for each infant with seizures, while a red triangle indicates the median total seizure burden for infants within each highest EEG grade.

abnormal EEG (grade 2) with a median of 402.8 min (IQR 60.1–701.7, n = 7).

Amongst neonates with moderate or severe background abnormalities, 41% (13/32) had at least one episode of status epilepticus. Episodes of status epilepticus were not seen amongst neonates with low background grades (0 and 1).

EEG findings and early childhood outcome

EEG background scores were significantly associated with early childhood outcome ($p < 0.001$) (Table 3). Prognostic accuracy of EEG for early childhood outcomes was higher at earlier timepoints and decreased over time (Supplementary Table S3). Amongst those with severe EEG background, 15% (3/20) had a favourable outcome; however, of those with moderate background, disability-free survival was high (83%, 5/6), though the total number of neonates in this group was small. Of the three infants with a mild background EEG (grade 1), two had a favourable outcome and one was lost to follow-up.

Assessing the association between EEG resolution and outcome; of the four infants who had a moderate-severe EEG (grades 2–4) that subsequently normalised within 72 h (grades 0–1), three had a favourable outcome and one was lost to follow-up.

The prognostic accuracy of moderate-severe EEG background and severe EEG background (at 12 h, 24 h, 48 h, 72 h and highest grade from 12 h to 72 h) for adverse outcome are presented in Supplementary Table S3. Severe EEG background (grade 3–4 at any timepoint from 12 h to 72 h) was strongly predictive of adverse outcome, with sensitivity 85% (95% CI: 62–97%), specificity 84% (60–97%), PPV 85% (62–97%), NPV 84% (60–97%), and AUC 0.85 (0.73–0.96). Moderate-severe EEG background (grade 2–4 at any timepoint from 12 h to 72 h) was also predictive of adverse outcome, but with reduced specificity; sensitivity 90% (95% CI: 68–99%), specificity 58% (34–80%), PPV 69% (48–86%), NPV 85% (55–98%), AUC 0.74 (0.61–0.87). The PPV of a severe EEG background showed a slight increase over time (67% at 12 h, 75% at 24 h, 83% at 48 h and 100% at 72 h). Based on Youden's index, the optimal cut-off was EEG grade 3–4 at 24 h (Youden's index = 0.69), 48 h (Youden's index = 0.60), 72 h (Youden's index = 0.64) and highest EEG grade 12–72 h (Youden's index = 0.69). At 12 h, the optimal cut-off was EEG grade 4 (Youden's index = 1.0) but the number included in this analysis was small (n = 11).

Of the 50 participants, 22 had EEG recordings commenced after 24 h of age and 11 of the 26 experiencing electrographic seizures (42%) had evidence of seizures within 1 h of EEG recording commencing. As we were unable to quantify the additional seizure burden prior to commencement of the EEG for many infants, associations between seizure burden and early childhood outcomes were not examined.

Background EEG score	n	Death in neonatal period % (n)	Death in early childhood % (n)	Survived with NDI % (n)	Adverse outcome (Death or NDI) % (n)	Favourable outcome (Disability free survival) % (n)
0 (normal)	1	0% (0)	0% (0)	0% (0)	0% (0)	100% (1)
1 (mild)	12	0% (0)	0% (0)	17% (2)	17% (2)	83% (10)
2 (moderate)	6	0% (0)	17% (1)	0% (0)	17% (1)	83% (5)
3 (severe – major abnormality)	7	0% (0)	0% (0)	57% (4)	57% (4)	43% (3)
4 (severe – inactive trace)	13	92% (12)	0% (0)	8% (1)	100% (13)	0% (0)

EEG = encephalogram; NDI = neurodevelopmental impairment.

Table 3: **Associations between highest background EEG score (12 h–72 h) and early childhood outcome, n = 39.**

Thompson score and early childhood outcome

As EEG is not available in the majority of LMIC settings in routine clinical practice, we also assessed the prognostic accuracy of the Thompson score for adverse outcome in this setting (Supplementary Fig. S2 and Table S4). We found similar strong predictive validity of the Thompson score compared with EEG background.

Discussion

This study is the first, to our knowledge, to describe findings from continuous video-EEG monitoring amongst neonates with NE from a low-income country, sub-Saharan Africa setting, without access to neonatal intensive care or therapeutic hypothermia. EEG was found to be feasible in this Ugandan research setting and provided unique insights into background brain activity, seizure prevalence and burden in this population. EEG background score strongly correlated with clinical presentation as assessed by Thompson score, with a score of ≥7 most predictive of moderate-severe background abnormalities. In this cohort with NE, without access to therapeutic hypothermia, half experienced electrographic seizures. Seizure burden was high and status epilepticus common, with potentially important implications for longer term outcomes. EEG background score was predictive of adverse early childhood outcomes, with validity increasing with higher background severity. Importantly, resolution of background EEG within 72 h was associated with favourable outcome.

It was feasible to record continuous EEG in this Ugandan research setting with multiple electrodes and video recording. All EEGs recorded were of diagnostic quality, indicating that the technical difficulty inherent in recording EEG is not preclusive to research centres naïve to this technology, given sufficient training and support. Whilst we found EEG monitoring to be feasible in this low-income country research setting, the research infrastructure included round-the-clock,

trained clinical research nurses and the introduction and maintenance of EEG equipment, prohibiting its use in routine clinical practice due to cost, staffing and technical expertise required. Telemedicine offers a potential solution for improving feasibility of EEG in LMICs, by offering expert interpretation and technical support remotely from specialised centres. In Brazil, Protecting Brains and Saving Futures (PBSF) have implemented a system in over 30 hospitals, transmitting encrypted data from EEG to a secure cloud-based server for remote monitoring; data on cost-effectiveness, legal and regulatory issues have not been reported.[13]

The prevalence of moderate-severe EEG background abnormalities in our study (64%) was similar to other published uncooled cohorts, despite the low Thompson score cut off used (≥5) in our inclusion criteria, with prevalence of 64–68% consistently reported from both HIC,[4,14] and LMIC settings.[15] Regarding the evolution of EEG background over time, we found just over a quarter showed an improvement on sequential recordings. Similarly, Murray et al. showed improvement with time in their uncooled hypoxic-ischaemic encephalopathy (HIE) cohort in Ireland, with the highest EEG grade seen on the earliest recording in all cases, and 20% improving by 48 h.[4]

We report significant correlation between grade of EEG background abnormality and Thompson score, suggesting that the severity of the clinical presentation is reflected by the corresponding brain activity on EEG. A Thompson score of ≥7 was the most predictive of moderate-severe background abnormalities. To date, relatively few studies have compared EEG and Thompson score. In South Africa, Horn et al. (n = 60) found that a Thompson score ≥7 predicted an abnormal aEEG at 6 h of age with 100% sensitivity and 67% specificity in a cooled cohort,[16] and Stofberg et al. (n = 29) reported Thompson scores >12 were associated with neonatal death (p = 0.007), amongst neonates with HIE.[17] In a HIC cohort, Weeke et al. (Netherlands, n = 122) found that early amplitude-integrated EEG abnormalities at <6 h were significantly associated with Thompson scores in a cooled NE cohort.[18] We were not able to examine correlation between Thompson score at ≤6 h of age, reflecting the time window within which current neuroprotection strategies are targeted, due to logistical delays in commencing the EEG for a high proportion of participants in our study; however a Thompson score of ≥7 was predictive of moderate-severe EEG background on day 1 of life with positive predictive value of 100% (AUC 0.83, n = 15) at a median age of 8.3 h.

We report a high prevalence of electrographic seizures (52%, n = 26), of which half had status epilepticus, similar to an uncooled NE cohort from India where seizure prevalence was 57%.[19] Seizure prevalence in cooled cohorts has been shown to be lower; in Brazil (n = 872) seizure prevalence was 34%, with status epilepticus affecting only 9% amongst cooled infants,[13] and a multi-centre US trial (n = 150) reported 31% with seizures, with 22% experiencing status.[20] As therapeutic hypothermia is well established to reduce the frequency and burden of seizures,[20] the seizure burden seen in our uncooled cohort is substantially higher than in many HIC cohorts; three HIC trials reported a median seizure burden of 55–63 min in their cooled groups, compared to a median seizure burden of 183–206 min in the uncooled groups.[5,6,21] As seizures in NE are typically seen early, often coinciding with the onset of secondary energy failure,[6] we may have missed early seizures.[22] Despite the very substantial seizure burden seen in our cohort, this likely represents a conservative estimate as EEG recording commenced at >24 h of age for 44% of neonates, and nearly half of neonates with seizures had seizures detected within an hour of commencing monitoring. In our population, the median seizure burden as a percentage of total recording time was high (6.1%) when compared to Glass et al. who reported percentage of time with seizures to be lower in both the erythropoietin (1.2%) and placebo groups (0.6%) amongst the US EPO trial.[20] Similarly, the median maximal hourly seizure burden (MSB) was higher in our cohort at 25.4 min per hour than that reported by Glass in their cooled cohort (Epo: 11.4, IQR 5.6–18.1 min/h; placebo: 9.7, IQR 4.9–21.0 min/h) and by Lynch et al. in their uncooled cohort (median MSB 8.9, IQR 4.1–14.6 min/h).[20] Lynch et al. also found the hour that MSB was reached at 22.7 h (IQR 19.0–29.9).[5] While the time of MSB in our group was considerably later at 36 h, this metric will be affected by the late start of the EEG, as indeed, will all our seizure metrics. Our high seizure burden is also likely affected by challenges in accurate targeting of anti-seizure medications by clinical staff.[23]

The highest proportion of neonates with seizures was seen in those with a grade 2 background (88%), followed by 80% in grade 3 and 57% in grade 4. This reduction in seizure burden in the most severely affected neonates is likely due to the increased suppression of all cortical activity, including seizures. A similar finding was reported by Weeke et al., who found a quadratic relationship between seizure burden and severity of MRI abnormality, with some neonates with more severe MRI abnormality having a lower seizure burden than those with less severe MRI changes.[24] Therapeutic hypothermia has been shown to reduce seizure burden most in those with moderate rather than severe NE, and this highlights the important role of therapeutic hypothermia in reducing seizure burden in this subgroup.[21]

Seizure semiology using video and EEG data in this cohort is discussed elsewhere[23] and provides data on the prevalence of clinical accompaniment, and when present, classification of seizure semiology according to the International League Against Epilepsy guidelines. This provides a valuable resource, particularly for clinicians

in this setting, regarding the expected seizure semiology for this NE group. In the live setting, where upload of video EEG was available, the video was of great utility particularly with regards to differentiating true seizures from seizure-like artefacts on the EEG and the causes. While video recording is of clear benefit, there are additional 'costs'. Video has a much greater data storage requirement than EEG, which has a financial cost if cloud storage is used. This can be mitigated somewhat with post-acquisition clipping and retention of only clinically useful portions of the video, although this in itself requires an investment in time. On occasion, the camera was accidentally moved and, if noted by the remote experts in the live setting, could be communicated to the local team for adjustment. We found the video to be acceptable to the families of infants participating in the study.

In our study, prognostic accuracy of EEG background grade for early childhood outcome was good. EEG background severity was strongly associated with adverse outcomes of death or NDI in early childhood. Severe EEG background (at any time 12–72 h) was strongly predictive of adverse outcome, with sensitivity, specificity, PPV and NPV all ≥84% (AUC 0.85). Evidence from HIC studies support this association, with a meta-analysis of five studies showing that EEG demonstrated a sensitivity of 63%, and specificity of 82% for adverse outcome (AUC 0.88).[25] Studies from LMICs are lacking, and frequently limited in size or duration of follow-up. In India, a moderate-severe background abnormality predicted outcome at 12-month with good predictive values (PPV and NPV both 100%), but lower sensitivity and specificity (40% and 59%, respectively) amongst 30 infants with NE,[15] and in Turkey, EEG was strongly associated with longer term childhood outcomes ($p < 0.001$).[26] In Malaysia, Ong et al. found that the PPV for adverse 18-month outcomes was the same (100%) for both the Thompson score (≥15) and EEG background (severe) performed at <8 h of age amongst an uncooled cohort with HIE,[27] and Weeke et al. demonstrated that a Thompson score of ≥11 or a background pattern of continuous low voltage was associated with an adverse outcome.[18]

In our Ugandan cohort, prognostic accuracy of EEG for early childhood outcomes was higher at earlier timepoints and gradually decreased with time; consistent with other studies.[14] In Ireland, Murray et al. reported a gradual decrease in Spearman's correlation between 6 h (correlation coefficient 0.82, AUC 0.96), and 48 h (correlation coefficient 0.54, AUC 0.83).[4] Earlier EEGs predicted both neonatal death and early childhood NDI, whereas later EEGs predicted mostly NDI only (given the majority of neonatal deaths in NE occur in the first few days of life).[4] Reassuringly, we saw early resolution of EEG abnormalities to be associated with favourable outcome, although numbers were small. Similarly, De Wispelaere et al. reported EEG background normalisation within 48 h to be associated with favourable outcome amongst uncooled infants ($p < 0.001$).[14]

We did not examine associations between seizure burden and outcome due to delays in commencing EEG for many, and the high proportion of seizures commencing within the first hour of recording. In HICs, some studies have reported significant associations between seizures and adverse outcomes, independent of NE severity and therapeutic hypothermia[6,28]; however others have reported no significant association.[29,30] A seizure burden of over 40 min has been shown previously to increase the odds of abnormal outcome nine-fold; our cohort had a seizure burden over six times this figure.[6] As EEG is often unavailable in LMIC neonatal care settings, we assessed the prognostic accuracy of the clinical presentation (Thompson score) for adverse early childhood outcomes. Reassuringly, predictive performance was similar to EEG.

This study provides novel data on EEG findings amongst infants with NE from a LIC Sub-Saharan Africa setting, where therapeutic hypothermia is not available. We have shown that continuous video EEG is feasible in this setting with training and technical support where EEG data are lacking. Whilst differences in the definition of perinatal hypoxia-ischaemia exist between populations and settings, our NE study cohort may not be fully comparable to cohorts with HIE in HICs as we did not have access to gold standard modalities such as fetal monitoring and blood gas measurement. The EEG monitoring started at a median age of 21.2 h (IQR 12.6–28.9), due to time required for completing informed consent procedures with the research personnel available. Delays to consent arose due to time spent in tracing mothers within the hospital, unavailability of fathers at time of delivery and mothers being unwell after delivery. Additionally, we found that some caregivers expressed fear at the 'new technology' of EEG, and this sometimes led to delays in their decision making around participation in the study. This meant that we were not able to examine correlation of EEG and clinical neurological score during the neuroprotection window within 6 h of birth, which is important for identification of eligible neonates for neuroprotective agents. It also means that acute provoked seizures may have occurred before EEG monitoring was commenced meaning they were missed from our analysis. Seizure prevalence and burden may also have been modified by treatment administration or where medication was initiated before the monitoring started. In this study, as participants were cared for by a dedicated group of around-the-clock, trained neonatal research nurses, our findings may not be fully generalised to routine practice. Loss to follow-up of participants was higher than anticipated, largely due to travel restrictions related to the Covid-19 pandemic. Whilst we believe that these losses likely occurred at random, it is of course possible that they could have introduced some bias with respect to the

neurodevelopmental outcome findings. As the study site was an urban tertiary referral hospital, this may also have limited the generalisability of our findings. As this was a feasibility study, the sample size was relatively small, and a larger definitive study would be needed to confirm our findings.

Whilst EEG is considered the gold standard for monitoring of brain activity and detection of seizures in neonates, it is rarely available in LICs as part of routine clinical practice. EEG monitoring is feasible to use as a research tool in the sub-Saharan African setting and can provide unique insights into background brain activity, seizure prevalence and burden. Clinical assessment of newborns using an established scored neurological assessment can identify those with moderate to severe brain dysfunction. The seizure prevalence and burden, including status epilepticus, was high in this uncooled cohort with important potential implications for longer term outcomes amongst surviving children. Novel innovations to monitor brain dysfunction in diverse settings, could substantially improve our understanding of NE and support clinical management of seizures. More data is needed from LMIC settings to better understand the role of brain dysfunction and seizures, including the longer-term impacts for affected children and families, to support the identification of future potential neuroprotective strategies.

Contributors

The conceptualization and supervision of the EEG study was led by CT and GB. Literature search was conducted by SS and SM. EEG and all clinical data was collected by CN, NN, NS, MS, BM, ED, and IM and EEG reporting by SM and JC. The first draft of the manuscript was written by SM, SS and CT. Formal analysis was performed by SM and SS, EW and VL. EW and VL verified the underlying data. All authors contributed to editing and reviewing the final manuscript. All authors had access to all the data in the study and accept responsibility to submit for publication. All authors read and approved the final version of the manuscript.

Data sharing statement

Limited deidentified participant data and a data dictionary will be made available on request on publication.

Declaration of interests

Geraldine Boylan is director of Kephala Ltd and Cergenx Ltd. Sean Mathieson provides consultancy services to Kephala Ltd and Cergenx Ltd. No conflicts disclosed for all other authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102937.

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