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Outcome Prediction in Neonatal Hypoxic-Ischaemic Encephalopathy Using Neurophysiology and Neuroimaging

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Keywords
Amplitude-integrated electroencephalography · Magnetic resonance imaging · Near-infrared spectroscopy · Neonate · Neurodevelopment · Predictive power

Abstract
Objective: The aim of the study was to determine the predictive power of the combined use of neurophysiological (amplitude-integrated electroencephalography [aEEG], near-infrared spectroscopy [NIRS]) methods and neuroimaging (magnetic resonance imaging [MRI]) for long-term outcome prediction in neonates with hypoxic-ischaemic encephalopathy (HIE). ***Study Design:*** Prospective cohort study of 56 patients with moderate to severe HIE and hypothermia treatment at the Medical University of Vienna between 2008 and 2020. aEEG and NIRS were recorded continuously over a period of >4 days (102 h) starting at the initiation of hypothermia treatment, MRI was performed at a median age of 8 days. Receiver operating characteristic curves and area under the curve were calculated to evaluate the prognostic ability of aEEG, NIRS, and MRI parameters for outcome assessed via Bayley Scales of Infant Development 3rd edition at 2 years of age. ***Results:*** Combined aEEG and MRI parameters showed highest predictive power regarding long-term outcome. The highest area under the curve values (0.96–0.99) were obtained for aEEG (combination of background pattern and sleep-wake cycling) between 66 and 102 h after initiation of hypothermia in combination with MRI findings. NIRS parameters did not differ significantly between infants with favourable and adverse outcome. ***Conclusions:*** Combined aEEG and MRI parameter scores were more predictive than single parameter scores. No further improvement was observed when combining aEEG/MRI with NIRS data.

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Introduction

Hypoxic-ischaemic encephalopathy (HIE) due to perinatal asphyxia remains one of the leading causes of mortality and morbidity among newborns and is a significant cause of life-long disability and mortality in term-born neonates [1, 2]. Early classification of the degree of brain damage as well as outcome prediction remains challenging. Some observational data suggest that the combination of neurophysiological methods can improve the predictive power with regard to short-term outcome [1]. Also, many data were published on the use of neurophysiological assessment (amplitude-integrated electroencephalography [aEEG], near-infrared spectroscopy [NIRS]) and neuroimaging (magnetic resonance imaging [MRI]) for long-term outcome prediction in neonates diagnosed with moderate to severe HIE. However, there are no data on the predictive power of the combined use of those methods.

Our primary objective was to determine the predictive values and the optimal combination of aEEG, NIRS, and MRI for long-term outcome prediction in neonates with HIE. For this purpose, the predictive power of the available neurophysiological and neuroimaging data and different combinations of the latter were analysed.

Materials and Methods

All admissions due to perinatal asphyxia at the Department of Neonatology, Pediatric Intensive Care, and Neuropediatrics of the Medical University of Vienna, Austria, during June 2008 and February 2019 were reviewed. Term and near-term neonates diagnosed with moderate to severe HIE undergoing therapeutic hypothermia (TH) treatment were identified. Entry criteria for hypothermia were used as introduced by the CoolCap and TOBY trial [2]. Whole-body cooling to a rectal temperature of 33.5°C was sustained for 72 h with subsequent rewarming by 0.5°C per hour.

Only patients with available neurophysiology and/or neuroimaging data were prospectively included in this cohort study. Patients with congenital abnormalities and malformations were excluded, as were patients where TH had to be suspended due to clinical reasons.

Patient characteristics, clinical data, and laboratory parameters were manually extracted from our electronic documentation systems. The degree of HIE was determined using the modified Sarnat score.

Neurophysiology

aEEG and NIRS data were extracted from the respective devices (Olympic CFM TM 6000, BrainZ TM BRM3 Monitor, or Olympic Brainz Monitor/OBM TM, Natus Medical Incorporated; Invos TM 5100C Cerebral/Somatic Oximeter Monitor, Covidien). Cross-cerebral aEEG was applied to measure brain function continuously, raw EEG was available for review; NIRS was applied for non-invasive measurement of cerebral oxygenation, cerebral blood volume, and cerebral oxygen metabolism. Both methods were recorded continuously over a period of >4 days (102 h) starting at the initiation of hypothermia and included the 72 h of cooling, rewarming, and nearly 24 h after reaching normothermia. Recordings were divided into 6-h intervals for assessment.

The duration (hours) of the five different background patterns and sleep-wake cycling (SWC) were evaluated as previously described [1]. Time to normal trace (TTNT; i.e., >50% continuous normal voltage over two consecutive intervals) and time to mature SWC (TTMS; mature SWC for 6 consecutive hours) were assessed.

Next, the presence, type, and duration of electrographic seizures were analysed visually [1]. Total seizure burden (TSB; sum of all seizure episodes in minutes), maximum seizure burden (MSB; maximum hourly seizure burden during the recording in minutes per hour), and the seizure period (time from onset of the first to the end of the last seizure within the recording) were calculated. Furthermore, seizure onset (in hours after birth) and occurrence of MSB (in hours after birth) were assessed.

A previously applied scoring system [1] was used to translate results into numerical values. Adding the three subscores (BP score, SWC score, seizure score; ranging from 0 to 2) constitutes an aEEG summation score with a maximum value of 6.

Regional cerebral oxygen saturation ($rScO_2$) values were measured using the neonatal sensor (Invos Cerebral/Somatic Oximetry Infant-Neonatal Sensor, Covidien), and cerebral fractional tissue oxygen extraction (cFTOE) was calculated [1]. The time spent outside the validated normal $rScO_2$ ranging from 55 to 85% [3] during the entire study period was calculated. Furthermore, the occurrence of strong fluctuations in brain oxygenation, defined as the period of deviation of more than 10% from the hourly baseline of $rScO_2$, was calculated.

Neuroimaging

The standardized neonatal MRI protocol included the following sequences: T1 spin-echo (axial plane), T1 3D (sagittal plane), T2 turbo spin-echo (3 orthogonal planes), diffusion-weighted imaging (axial plane; *b* value = 0 and 700 s/mm^2), and single-voxel spectroscopy in the deep grey matter (echo time = 135 ams) on an Ingenia 1.5 Tesla MR system (Philips Healthcare). MRI was reviewed by GK with 15 years' experience in paediatric neuroradiology, blinded to the clinical history.

MRI findings were divided into three categories: normal MRI (score = 0), questionably abnormal MRI (score = 3 when there was no evidence for typical HIE lesions but the MRI presented slightly abnormal), and pathological MRI (score = 6; when typical HIE lesions according to the National Institute of Child Health and Human Development Neonatal Research Network score [4] and the Rutherford scoring [5] were detected).

Bayley Scales of Infant Development

Neurodevelopmental outcome was prospectively obtained via Bayley Scales of Infant Development 3rd edition (Bayley-III) using German norms by trained clinical psychologists. Delay was categorized using conventional standard deviation banded cut-offs as previously described by Johnson and Marlow [6]. Deceased infants received the minimum possible values. Disability was pooled into two groups; infants with normal outcome or mild disability (Bay-

Table 1. Patient characteristics

	Entire cohort	OCnorm	OCpath	*p* value
Descriptive data (*n* = 56)				
Sex male	25 (44.6)	20 (47.6)	5 (35.7)	0.542
Birthplace outborn	34 (60.7)	26 (61.9)	8 (57.1)	0.762
Birth mode				
Spontaneous delivery	14 (25.0)	12 (28.6)	2 (14.3)	0.478
Vacuum delivery	11 (19.6)	9 (21.4)	2 (14.3)	0.711
C-section	8 (14.3)	8 (19.0)	0 (0.0)	0.180
Emergency C-section	23 (41.1)	13 (31.0)	10 (71.4)	0.012
Gestational age, weeks^{+days}	39+1±2+0	39+2±1+6	38+5±2+2	0.331
Birth weight, g	3,366.0±680.2	3,397.5±617.5	3,271.5±861.2	0.478
Birth length, cm	50.9±2.7	50.9±2.3	50.6±3.7	0.864
Birth head circumference, cm	34.6±1.8	34.7±1.7	34.1±2.2	0.629
Observed complications leading to birth asphyxia (multiple complications can apply to one single patient; *n* = 56)				
Pathologic cardiotocography	25 (44.6)	16 (38.1)	9 (64.3)	0.123
Meconium aspiration syndrome	16 (28.6)	14 (33.3)	2 (14.3)	0.305
Difficult extraction	10 (17.9)	10 (23.8)	0 (0.0)	0.052
Placental abruption	8 (14.3)	7 (16.7)	1 (7.1)	0.664
Shoulder dystocia	5 (8.9)	3 (7.1)	2 (14.3)	0.590
Absent/reduced foetal movement	4 (7.1)	2 (4.8)	2 (14.3)	0.258
Umbilical cord compression/prolapse	3 (5.4)	3 (7.1)	0 (0.0)	0.565
Uterine rupture/haemorrhage	1 (1.8)	1 (2.4)	0 (0.0)	1.000
Maternal infection	1 (1.8)	1 (2.4)	0 (0.0)	1.000
Arm/foot protrusion	1 (1.8)	1 (2.4)	0 (0.0)	1.000
Postpartal asphyxia	1 (1.8)	1 (2.4)	0 (0.0)	1.000
Clinical data (*n* = 56)				
Apgar score at 1 min	3 (1–4)	3 (1–4)	2 (0–3)	0.163
Apgar score at 5 min	5 (3–7)	5 (4–7)	1 (1–6)	0.013
Apgar score at 10 min	7 (4–8)	7 (6–8)	3 (2–7)	0.009
Initial Thompson score	10 (8–15)	9 (8–12)	12 (9–17)	0.147
Maximum Thompson score	11 (8–15)	10 (8–13)	13 (9–17)	0.26
Cardiopulmonary resuscitation	22 (39.3)	11 (26.2)	11 (78.6)	0.001
Lab results (*n* = 56, except# – *n* = 49)				
Metabolic parameters				
pH umbilical artery[#]	7.07 (6.92–7.21)	7.07 (6.96–7.21)	7.06 (6.72–7.26)	0.507
First neonatal pH	6.90 (6.76–7.05)	6.90 (6.80–7.01)	6.97 (6.59–7.20)	0.902
First neonatal BE	−17.5 (−21.2 to −12.9)	−17.2 (−21.0 to −11.7)	−17.8 (−24.4 to −14.5)	0.215
First lactate, mmol/L	13.8 (8.0–16.9)	13.3 (6.9–15.0)	16.9 (13.6–19.9)	0.007
First LDH	835 (559–1,751)	758 (507–1,185)	1,783 (920–2818)	0.017
Inflammatory parameters				
Max. CRP, mg/dL	3.0 (2.1–4.3)	3.0 (2.0–3.8)	5.0 (2.0–7.7)	0.132
Max. interleukin, pg/mL	132.8 (70.5–324.6)	134.5 (70.5–324.6)	121.5 (63.5–387.0)	0.876
Max. leukocytes, g/L	22.4 (16.3–29.3)	20.8 (15.9–29.1)	24.5 (19.1–30.5)	0.188
Respiratory support (*n* = 56)				
Mechanical ventilation,	48 (85.7)	35 (83.3)	13 (92.9)	0.664
Ventilation with NO	12 (21.4)	9 (21.4)	3 (21.4)	1.000
Maximum FiO_2	55.5 (35–100)	54.0 (30–99)	70.0 (48–100)	0.093
Time until intubation, h	0.33 (0.17–0.85)	0.38 (0.25–1.05)	0.28 (0.23–0.46)	0.189
Duration of mechanical ventilation, days	5.3 (3.7–6.7)	4.6 (3.6–6.5)	6.7 (4.3–11.7)	0.038
Medication first 5 days (*n* = 56)				
Sedation/analgesia	46 (82.1)	35 (83.3)	11 (78.6)	0.698
Morphine, median dose[a]	9.38 (6.59–12.21)	9.38 (6.65–11.90)	8.90 (4.74–12.82)	0.387
Midazolam, median dose[b]	0.08 (0.05–0.14)	0.06 (0.04–0.09)	0.10 (0.06–0.34)	0.133
Fentanyl, median dose[c]	6.28 (4.54–9.08)	7.20 (3.56–9.68)	5.80 (4.40–9.85)	0.369
Circulatory support	43 (76.8)	31 (73.8)	12 (85.7)	0.480
Seizure treatment	17 (30.4)	11 (26.2)	6 (42.9)	0.317
Seizure treatment, number of administrations	0.0 (0.0–1.8)	0.0 (0.0–1.0)	0.0 (0.0–3.3)	0.218

Table 1 (continued)

	Entire cohort	OCnorm	OCpath	*p* value
Outcome data (*n* = 49 except# – *n* = 56)				
Died[#]	7 (12.5)	0 (0)	7 (50.0)	<0.001
Age at outcome, years	2.09 (2.01–2.40)	2.11 (2.01–2.46)	2.01 (1.95–2.11)	0.136
Bayley-III – Cognitive composite scale	102.5 (86.3–115.0)	105.0 (95.0–117.5)	55.0 (55.0–55.0)	<0.001
Bayley-III – Language composite scale	94.0 (73.3–106.0)	100.0 (86.0–109.0)	45.0 (45.0–47.8)	<0.001
Bayley-III – Motor composite scale	100.0 (76.0–110.0)	103.0 (97.0–113.5)	45.0 (45.0–46.0)	<0.001

Data are counts (percentages), mean ± SD or median (IQR) when appropriate. [a] Median dose of morphine in µg/kg/h. [b] Median dose of midazolam in mg/kg/h. [c] Median dose of fentanyl in µg/kg/h.

ley-III ≥70) were assigned to the "OCnorm" group and infants with moderate or severe disability (Bayley-III <70) and infants that died were assigned to the "OCpath" group.

Statistical Analysis and Ethics

Statistical analysis was performed using SPSS version 23 (IBM Corporation) and R studio (B Corporation). A two-sided *p* value <0.05 was considered significant. Differences between groups were compared using Mann-Whitney U and χ^2 test.

For outcome prediction, receiver operating characteristic curves and area under the curve (AUC) values were calculated to determine the prognostic ability of aEEG, NIRS, and MRI parameters and various combinations of the latter. Receiver operating characteristic analysis and 2 × 2 contingency tables were then used to identify the optimum cut-off points for the most powerful predictive parameter combinations. This study was approved by the Ethics Commission of the Medical University of Vienna (EK 369/11 and 1708/2020) and written informed consent was obtained.

Results

A total of 98 patients were diagnosed with HIE II-III during the study period. Three patients were excluded due to insufficient neurophysiological and neuroimaging data and 31 as no long-term outcome was available (no significant differences compared to study group in descriptive data, neurophysiology, and neuroimaging; data not shown). Another eight were excluded based on mentioned exclusion criteria, thus resulting in the final study cohort of 56 patients.

Forty-five (80.4%) patients were diagnosed with HIE II and eleven (19.6%) with HIE III. Target temperature was reached at a median age of 3.4 (1.9–5.8) hours. Detailed descriptive data are presented in Table 1 and online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000524751).

Bayley Scales of Infant Development

Thirty-one (55.4%) infants presented without any disability, eleven (8.9%) with mild disability, seven (12.5%) with severe disability, and seven (12.5%) died (median day of life 3 (1–18)). Therefore, the OCnorm group consisted of 42 (75.0%) patients, the OCpath group of 14 (25.0%). Median values are shown in Table 1.

Neurophysiology

All aEEG results are outlined in Table 2. Changes in the median percentage of each aEEG background pattern over time for both groups are demonstrated in Figure 1.

Electrographic seizures were detected in 50% of the neonates (*n* = 28). Changes in scoring over time are presented in Fig. 2a–d. Seventeen patients (30.4%) received antiepileptic drugs, eleven (26.2%) in OCnorm and six (42.9%) in OCpath. Phenobarbital was used as first-line treatment in all patients, followed by phenytoin (*n* = 5) and/or levetiracetam (*n* = 3) for refractory seizures.

NIRS results are shown in Table 2. In both groups, an overall increase in $rScO_2$ accompanied by a parallel decrease in cFTOE over the entire study duration was observed (Fig. 2e, f). The median values of $rScO_2$ and cFTOE did not differ significantly between the groups (Table 2). However, rScO2 fluctuation differed between the outcome groups. Patients in the OCpath group showed higher fluctuation in the entire measurement period, on day two of hypothermia and post-cooling.

Neuroimaging

A pathologic MRI was observed in ten (24.4%) infants in the OCnorm and twelve (92.3%) in the OCpath group ($p < 0.001$). MRI findings significantly differed between the groups: median MRI score was 0.0 (0.0–3.0) in the OCnorm and 6.0 (6.0–6.0) in the OCpath group ($p < 0.001$), see Table 2.

Table 2. Neurophysiology and neuroimaging results

	Entire cohort	OCnorm	OCpath	*p* value
aEEG (*n* = 56, except# – only neonates with seizures *n* = 28)				
CNV	44.0 (6.5–72.2)	58.5 (38.3–81.2)	0.5 (0.0–17.5)	**<0.001**
DNV	36.4 (13.1–53.0)	36.4 (15.1–52.7)	38.1 (0.0–63.1)	0.557
BS/CLV/FT	1.6 (0.0–26.7)	0.0 (0.0–5.9)	56.8 (16.4–100)	**<0.001**
TTNT, h	24.0 (12.0–58.5)	24.0 (12.0–37.5)	54.0 (27.0–93.0)	**0.034**
No SWC	29.0 (11.4–58.3)	24.3 (7.7–37.5)	93.9 (54.8–100)	**<0.001**
Immature SWC	36.9 (18.1–58.1)	50.2 (31.3–60.5)	6.1 (0.0–36.3)	**<0.001**
Mature SWC	19.1 (4.1–34.3)	23.6 (14.1–39.4)	0.0 (0.0–11.1)	**<0.001**
TTMS, h	69.0 (32.5–102)	47.5 (26.8–77.8)	102 (102–102)	**<0.001**
Seizures	28 (50.0)	19 (45.2)	9 (64.3)	0.355
Seizures	2.9 (0.0–24.0)	0.0 (0.0–20.9)	25.6 (0.0–43.4)	**0.047**
No seizure	97.1 (76.0–100)	100 (79.1–100)	74.4 (56.6–100)	**0.047**
Single seizure	0.0 (0.0–7.6)	0.0 (0.0–11.8)	0.0 (0.0–6.5)	0.614
Repetitive seizures	0.0 (0.0–11.8)	0.0 (0.0–7.6)	5.9 (0.0–18.1)	0.06
Status epilepticus	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–14.2)	**0.025**
Seizure characteristics[#, a]				
TSB, min	56.0 (18.3–154.3)	43.0 (18.0–79.0)	175.0 (30.0–440.5)	0.105
MSB, min/h	14.5 (10.0–37.5)	13.0 (10.0–25.0)	40.0 (14.5–60.0)	0.095
Seizure onset (hours after birth)	20.4 (9.0–50.6)	42.0 (11.2–52.7)	12.6 (5.8–18.8)	**0.028**
Seizure period, h	29.5 (12.3–55.3)	29.0 (7.0–53.0)	32.0 (14.5–68.5)	0.498
Time of MSB (hours after birth)	45.9 (13.9–73.0)	57.5 (17.1–73.1)	20.3 (12.9–59.4)	0.172
NIRS (*n* = 40)				
$rScO_2$ neonatal	80.7 (75.2–87.0)	80.1 (74.4–87.6)	83.8 (74.1–85.3)	0.668
cFTOE neonatal	0.16 (0.07–0.22)	0.16 (0.06–0.22)	0.11 (0.09–0.21)	0.553
$rScO_2$ adult[&]	72.2 (66.0–80.1)	71.6 (65.2–80.7)	76.3 (64.8–78.1)	0.668
cFTOE adult[&]	0.24 (0.15–0.31)	0.25 (0.14–0.31)	0.19 (0.16–0.31)	0.581
Time out of normal range*				
Total	36.0 (13.0–67.0)	31.0 (8.5–68.8)	47.0 (37.5–67.0)	0.355
Day 1 of TH	15.0 (3.0–39.5)	10.0 (1.5–51.5)	30.5 (27.0–31.8)	0.405
Day 2 of TH	44.0 (11.0–77.0)	34.0 (11.0–77.0)	71.0 (51.8–78.3)	0.203
Day 3 of TH	42.0 (4.5–88.0)	41.0 (3.5–84.0)	84.0 (32.3–96.0)	0.155
Post-cooling	26.0 (4.0–91.0)	21.0 (4.0–89.8)	60.0 (26.0)	0.250
rScO2 fluctuation				
Total	1.0 (1.0–2.0)	1.0 (1.0–2.0)	5.0 (1.5–5.5)	**0.013**
Day 1 of TH	1.0 (1.0–3.5)	1.0 (1.0–3.5)	3.0 (1.5–8.3)	0.175
Day 2 of TH	1.0 (0.0–2.0)	1.0 (0.0–2.0)	4.0 (1.3–7.5)	**0.046**
Day 3 of TH	0.0 (0.0–1.5)	0.0 (0.0–1.0)	2.5 (0.5–4.5)	0.081
Post-cooling	0.0 (0.0–0.0)	0.0 (0.0–0.0)	7.0 (0.0)	**0.028**
MRI (*n* = 54)				
Day of MRI	8.0 (4.0–9.0)	8.0 (6.0–10.0)	6.0 (4.0–8.3)	0.052
Normal MRI	32 (59.3)	31 (75.6)	1 (7.7)	**<0.001**
Pathologic MRI	22 (40.7)	10 (24.4)	12 (92.3)	**<0.001**
Posterior limb of the internal capsule injury	12 (22.2)	6 (14.6)	6 (46.2)	**0.027**
Basal ganglia and thalamic injury	16 (29.6)	6 (14.6)	10 (76.9)	**<0.001**
White matter injury	10 (18.5)	2 (4.9)	8 (61.5)	**<0.001**
Lactate peak in spectroscopy	6 (11.1)	1 (2.4)	5 (38.5)	**0.002**
Diffusion-weighted imaging abnormality	12 (22.2)	6 (14.6)	6 (46.2)	**0.027**
Scoring (*n* = 56)				
BP score	0.6 (0.3–1.1)	0.4 (0.2–0.7)	1.5 (0.9–2.0)	**<0.001**
SWC score	1.1 (0.7–1.4)	0.8 (0.6–1.2)	1.9 (1.5–2.0)	**<0.001**
Seizure score	0.6 (0.0–0.4)	0.0 (0.0–0.3)	0.4 (0.0–0.7)	**0.043**
aEEG summation score	1.8 (1.2–2.9)	1.5 (1.1–1.9)	3.8 (2.8–4.5)	**<0.001**
MRI score	0 (0–6)	0 (0–3)	6 (6–6)	**<0.001**

Footnote to Table 2

Data are counts (percentages) or median (IQR) when appropriate. aEEG, amplitude-integrated electroencephalography; BP, background pattern; BS, burst suppression; cFTOE, cerebral fractional tissue oxygen extraction; CLV, continuous low voltage; CNV, continuous normal voltage; DNV, discontinuous normal voltage; FT, flat trace; MRI, magnetic resonance imaging; MSB, maximum seizure burden; NIRS, near-infrared spectroscopy; OCnorm, favourable/normal outcome group; OCpath, adverse/pathological outcome group; $rScO_2$, regional cerebral oxygen saturation; SWC, sleep-wake cycling; TSB, total seizure burden; TTMS, time to mature sleep-wake cycling; TTNT, time to normal trace; TH, therapeutic hypothermia. [&] Adult values were calculated using the following equation: $rScO_{2\text{-adult}}=(rScO_{2\text{neonate}}-19.11)/0.8481$ (Alderliesten et al. Pediatr Res. 2016;79:55–64). * Normal $rScO_2$ range used was 55–85% (Hyttel-Sorensen et al. [3]). [a] Logistic regression analysis showed a significant relationship between early seizure onset, high TSB, high MSB, and adverse outcome at 2 years of age: the respective OR was 17.3 (95% CI: 1.8–171.7) for seizure onset <20.4 h after birth, 22.5 (95% CI: 2.0–249.2) for TSB ≥170 min, and 9.8 (95% CI: 1.5–63.9) for MSB >22 min per hour. For every hour that seizures started earlier, the odds of adverse outcome increased by 6.7% (OR 1.1, 95% CI: 1.0–1.1, $p = 0.039$). For every one-minute increase of TSB, the odds of adverse outcome increased by 0.4% (OR 1.0; 95% CI: 0.1–1.0, $p = 0.109$), and for every one-minute increase of MSB, the odds increased by 5.4% (OR 1.1; 95% CI: 1.0–1.1, $p = 0.030$).

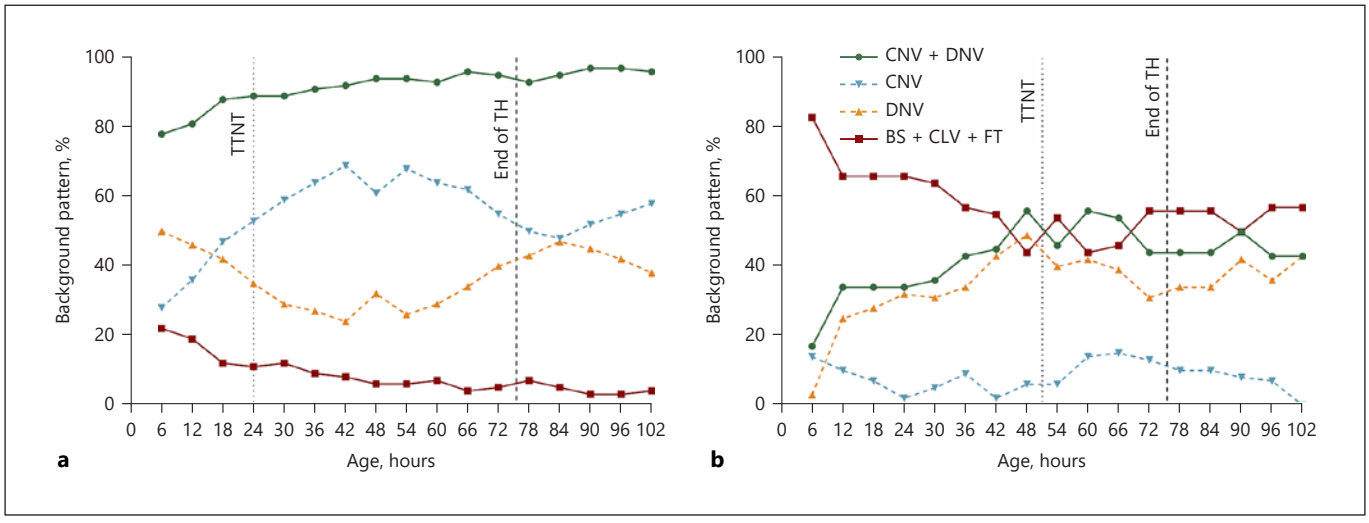

Fig. 1. Changes in aEEG background pattern over 102 h of recording in the OCnorm (**a**) and OCpath group (**b**). Mean percentages of each background pattern are provided to allow better illustration and are displayed for each 6-h interval. Continuous and discontinuous normal voltage (CNV + DNV) – green solid line, CNV – blue dotted line, DNV – orange dotted line, burst suppression, continuous low voltage, and flat trace (BS + CLV + FT) – red solid line, TTNT and end of TH – dotted vertical lines.

Prediction of Long-Term Outcome

AUC values are presented in Figure 3 in columns 1–20. The MRI score alone reached an AUC of 0.88. Combined aEEG and MRI parameter scores (12–15) attained equal or higher AUC values than single parameter scores (1–4 and 8), combined aEEG parameter scores (5–7), and aEEG/MRI and NIRS parameter scores (9–11 and 16–20). The highest AUC values were obtained between 66 and 102 h after initiation of hypothermia and during the post-cooling period.

The MRI score alone reached a sensitivity of 92.3%, a specificity of 85.4%, a PPV of 66.7%, and an NPV of 97.2%. These values improved when adding aEEG parameters. Between 66 and 102 h and during the post-cooling period, sensitivity and NPV were equal between BP + MRI, BP + SWC + MRI, BP + seizures + MRI, and aEEG SUM + MRI (100%). Specificity was similar between the four scores while PPV for adverse long-term outcome was highest for BP + SWC + MRI (range 63.6–88.9%). No further improvement in sensitivity, specificity, PPVs, and NPVs could be observed when combining aEEG/MRI with NIRS data (data not shown).

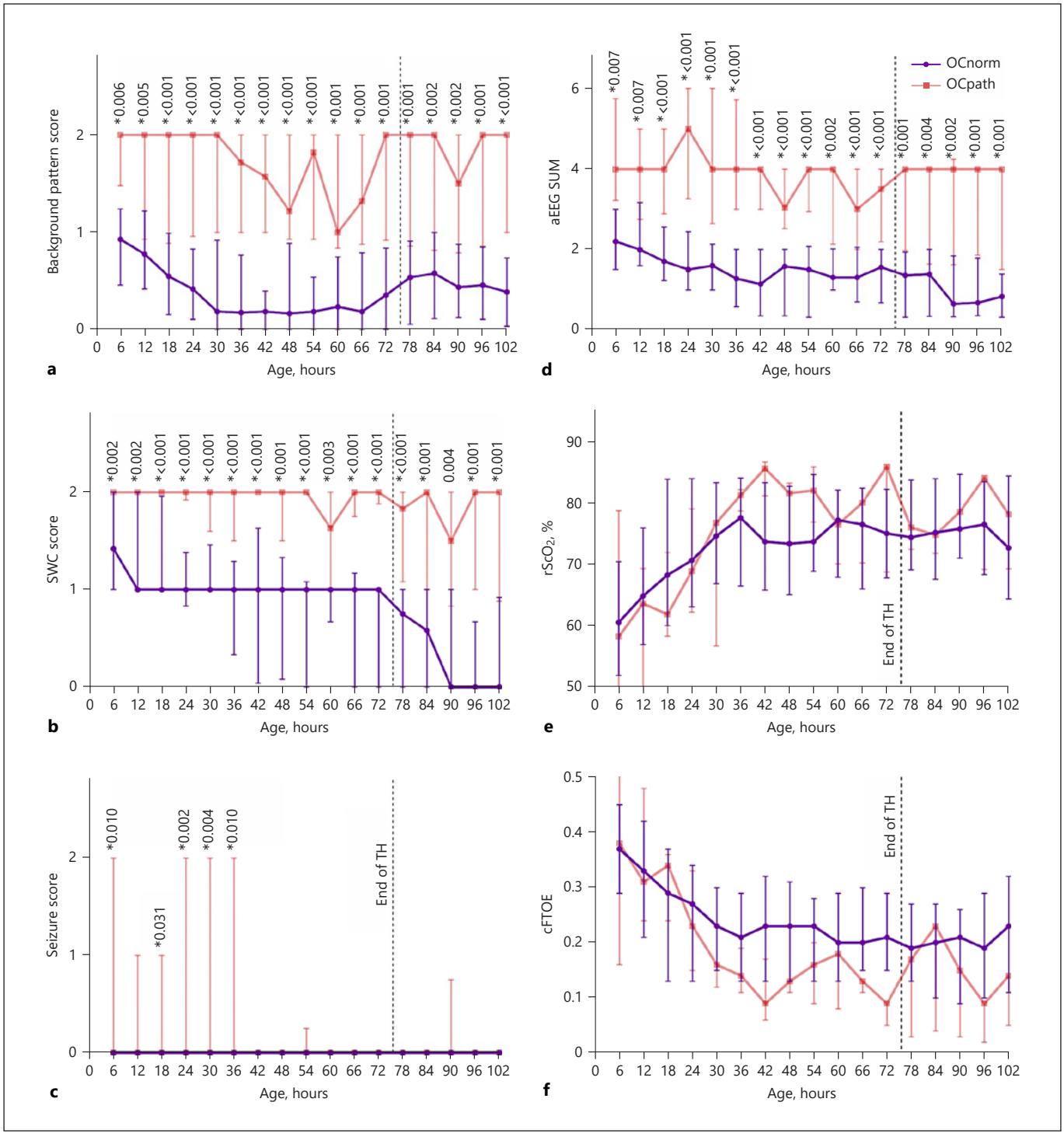

Fig. 2. Changes in aEEG: background pattern (**a**), SWC (**b**), seizures (**c**), aEEG summation score and NIRS (**d**), rScO2 (**e**), and cFTOE (**f**) in the 102 h of recording. Favourable/normal outcome group (OCnorm) – purple solid line, adverse/pathological outcome group (OCpath) – red solid line, end of TH – dotted vertical line. *p* values are displayed, if significant ($p < 0.05$).

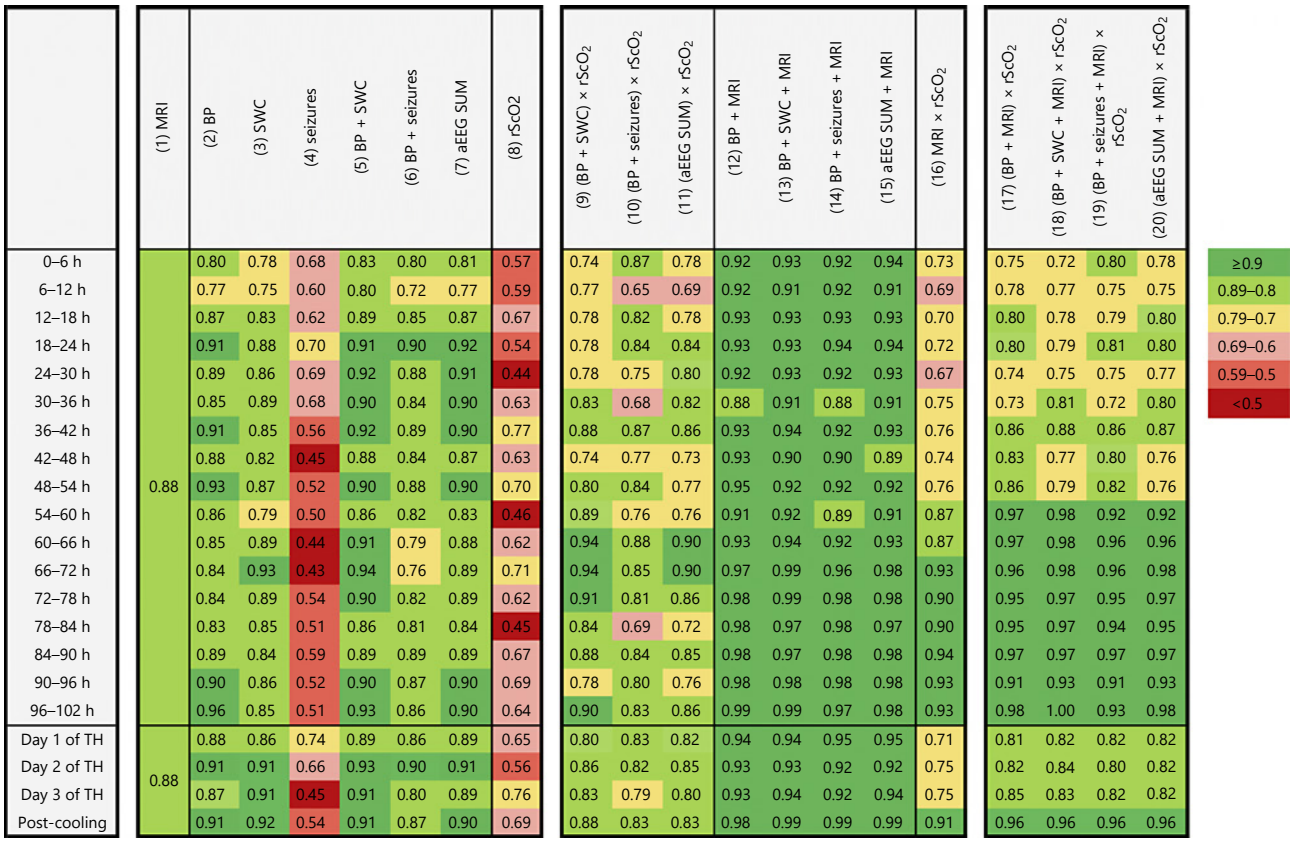

Fig. 3. AUC values from 0 to 102 h for several combinations of aEEG, NIRS, and MRI parameters: single methods 1–8, two methods combined 9–16, three methods combined 17–20. aEEG, amplitude-integrated electroencephalography; aEEG SUM, aEEG summation score; BP, background pattern; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; $rScO_2$, regional cerebral oxygen saturation; SWC, sleep-wake cycling.

Discussion

We analysed the prediction power of neurophysiological and neuroimaging techniques in asphyxiated newborns with respect to 2-year neurodevelopmental outcome. aEEG parameters and MRI results showed significant differences between the favourable and unfavourable outcome group. NIRS parameters did not differ significantly between the groups. Combined aEEG and MRI parameter scores were more predictive than single parameter scores. No further improvement regarding outcome prediction could be observed when combining aEEG/MRI with NIRS data. To our knowledge, this is the first study investigating the predictive value of the combined use of neurophysiological methods and neuroimaging with respect to the 2-year neurodevelopmental outcome in newborns undergoing TH after perinatal asphyxia.

The aEEG is considered to be of great prognostic utility for neonates with HIE, however, the predictive value is altered by TH [7–11]. In our study, background patterns differed significantly between the two outcome groups, which is in accordance with previous studies showing that infants with normal background patterns or rapidly normalizing patterns had at most mild neurodevelopmental deficits, whereas infants with severely abnormal background patterns suffered serious neurological impairment or death [7, 11–13]. Median TTNT differed by 30 h between the groups. These findings confirm previous results, showing that a background pattern that normalizes within 48 h in hypothermic infants correlates with favourable neurologic outcome [9, 12, 13]. The quality and time of SWC and the median TTMS as well as the occurrence of seizures showed significant differences between the groups, which is in agreement with previous

studies showing similar results regarding SWC [9, 14, 15] and electrographic seizures [16–18]. The occurrence of seizures per se was not associated with poor outcome at 2 years of age. However, median seizure onset in the OCnorm was significantly later than in the OCpath group and a seizure onset earlier than 20 h after birth was significantly correlated with adverse outcome at 2 years of age. Differences in TSB and MSB between the groups did not reach statistical significance, nevertheless, the OCnorm group had lower median TSB and MSB compared to the OCpath group (TSB: 43 vs. 175 min, MSB: 13 vs. 40 min per hour). These results suggest that early-onset and prolonged seizures may play a more important role in neurodevelopment than the sole occurrence of seizures [19].

Our NIRS results are in line with the findings of Shellhaas et al. [8, 20] reporting a limited prognostic ability of NIRS. Other publications demonstrating high $rScO_2$ values to be correlated with poor outcome are inconsistent with our results. Lemmers et al. [21] investigated 39 and 18 [22] infants with HIE. They found an association between an increase in $rScO_2$ and a parallel decrease in cFTOE values with adverse outcome at 18 months [21] and 5 years of age [22]. Ancora and colleagues [10] investigated twelve neonates treated with TH and observed significantly higher $rScO_2$ at 12 h of age in neonates with adverse outcome compared to those with normal outcome at 1 year of age. High cerebral oxygen saturation was presumed to mirror luxury reperfusion after suffering severe cerebral injuries and a reduced oxygen consumption by damaged neurons [10]. In our cohort, median $rScO_2$ values increased over the first 36 h of cooling in the OCnorm and over the first 42 h in the OCpath group with a parallel decrease in cFTOE. This observation may be due to the beneficial effects of hypothermia treatment, resulting in a reduced metabolic rate and thus a reduced energy and oxygen consumption [23]. As hypo- and hyperoxia increase the risk for adverse outcome, these conditions have to be kept to a minimum. In this context, it is important to note that median $rScO_2$ values of all patients in our cohort, irrespective of outcome, stayed within the normal range [3]. Nevertheless, both $rScO_2$ and cFTOE values of the OCpath group are subject to strong fluctuations. The same parameters remained relatively stable during the entire measurement period in the OCnorm group. Scarce data exist on fluctuations in brain oxygenation in asphyxiated term and near-term neonates. In our cohort, fluctuation in $rScO_2$ during the entire measurement period differed between the groups (1.0 vs. 5.0%), as well as on day two of hypothermia and in the post-cooling period. These data, however, should be interpreted with caution and larger studies are warranted to assess their potential clinical value.

MRI provides valuable information for early diagnosis and further treatment decisions and has shown to highly correlate with outcome at 12–24 months of age [24]. This is important considering parent counselling and the limited time frame for end-of-life decisions. The OCpath group showed a significantly higher percentage of pathologic MRI findings than the OCnorm group (92.3 vs. 24.4%). These findings agree with similar previously published data showing that neonates with normal MRI scans usually do not develop major motor and cognitive deficiencies [25]. As observed in our cohort, normal MRI scans do not always indicate normal long-term outcome, and developmental deficits presenting in early childhood are possible. Ten infants had normal outcome at 2 years of age despite pathologic MRI, whereas one infant with normal MRI had an adverse outcome. Therefore, prognosis should be made with caution and affected infants should be further evaluated by standardized neurodevelopmental follow-up.

Combined aEEG and MRI parameter scores led to an increase in sensitivity, specificity, PPV, and NPV for long-term outcome. AUC values, particularly for combined aEEG and MRI scores, were high throughout the entire measurement period. Nevertheless, the highest AUC values were obtained for aEEG between 66 and 102 h after initiation of hypothermia and during the post-cooling period combined with MRI (all ≥0.96). Sensitivity, specificity, and NPV were similar between those combinations, the highest PPV was observed for BP + SWC + MRI. Although NIRS data seemed to improve AUC values in individual time intervals, no overall improvement could be observed when combining aEEG/MRI with NIRS data. This is opposed to other studies showing an increase in predictive power using combined data [1, 10, 21, 22]. This may be explained by the relatively small number of neonates studied in the mentioned reports.

Strengths of our study include the large number of neonates investigated and the detailed analysis of aEEG and NIRS parameters over a period of >4 days starting at the initiation of hypothermia treatment, as opposed to shorter time and/or only selective time periods in previous reports [7–10, 12, 22]. The most important limitation is the use of 2-year outcome, similar to most hypothermia trials. Given the broad spectrum of impairments and heterogeneity following HIE, this might underestimate disability. Follow-up of affected neonates into later childhood is essential.

Conclusion

Infants with adverse outcome at 2 years of age presented with a higher percentage of abnormal background patterns and longer TTNT, a higher percentage of no SWC and longer TTMS, a higher percentage of electrographic seizures and pathologic MRI findings. NIRS parameters did not differ significantly between infants with favourable and adverse outcome.

Combined aEEG and MRI parameter scores were more predictive than single parameter scores. No further improvement regarding outcome prediction could be observed when combining aEEG/MRI with NIRS data. Based on our data, BP + SWC should be used to predict outcome in the first days after asphyxia, when only aEEG is available, and BP + SWC + MRI as soon as MRI results become available. Although NIRS is increasingly used as a monitor for cerebral oxygenation, cerebral blood volume, and cerebral oxygen metabolism, further investigation is required as its prognostic ability for neonates with HIE remains uncertain.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Commission of the Medical University of Vienna (EK 369/11 and 1708/2020). Written informed consent was obtained from parents. This study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose. The authors have no financial relationships relevant to this article to disclose.

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Author Contributions

Conceptualization/design and methodology: Katharina Goeral, Berndt Urlesberger, and Monika Olischar. Investigation: Mirjam Steiner, Vito Giordano, Gregor Kasprian, Sarah Glatter, Christiane Oberleitner-Leeb, Judith Rittenschober-Boehm, Tobias Werther, and Katharina Goeral. Supervision/oversight: Angelika Berger, Monika Olischar, and Katharina Goeral. Data curation: Mirjam Steiner, Vito Giordano, Gregor Kasprian, Sarah Glatter, Christiane Oberleitner-Leeb, and Katharina Goeral. Formal analysis: Mirjam Steiner, Berndt Urlesberger, Vito Giordano, Gregor Kasprian, Christiane Oberleitner-Leeb, Judith Rittenschober-Boehm, Tobias Werther, Angelika Berger, Monika Olischar, and Katharina Goeral. Resources: Angelika Berger.

Data Availability Statement

Additional anonymized data are available from the corresponding authors upon reasonable request.

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