

Amplitude-Integrated EEG Pattern Predicts Further Outcome in Preterm Infants

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ABSTRACT: Changes in EEG background activity are powerful but nonspecific markers of brain dysfunction. Early EEG and amplitude-integrated EEG (aEEG) pattern predict further neurodevelopmental outcome in term infants; however, sufficient data for prognostic value of aEEG in preterm infants are not available so far. The aim of the study was to evaluate whether aEEG predicts further outcome and to compare it to cerebral ultrasound assessment. In 143 preterm infants, aEEG within the first 2 wk of life and outcome data at 3 y of age (Bayley Scales) could be obtained. aEEG was classified into a graded score according to background activity, appearance of sleep-wake cycling, and occurrence of seizure activity. In preterm infants, aEEG was significantly associated with further outcome. Specificity was 73% for assessment within the first and increased to 95% in the second week of life, whereas sensitivity stayed nearly the same 87% (first week) to 83% (second week). Cerebral ultrasound showed a specificity of 86% within the first and second week, sensitivity also stayed nearly the same (74 and 75%). aEEG has a predictive value for later outcome in preterm infants and can be used as an early prognostic tool. (*Pediatr Res* 70: 102–108, 2011)

Despite recent advances in perinatal care, the incidence of impaired outcome in preterm infants has not decreased. Rates of CP and overt cerebral lesions [*e.g.* cystic leukomalacia and intraventricular hemorrhage (IVH)] are decreasing, but the incidence of neurodevelopmental impairment stays high in preterm infants. This is due to different mechanisms in brain injury (*e.g.* inflammation, oxidative stress, impaired connectivity) and result in mainly cognitive impairment (1–3). Extensive studies have demonstrated the usefulness of cerebral ultrasound (CUS) in detecting cerebral lesions and predicting neurological outcome (4–7). Also conventional EEG is proven to be useful in evaluating brain function and in predicting further development (8). On the background of an acute brain insult, EEG activity shows various degrees of depression and its severity parallels the magnitude of the brain lesion. These “acute-stage” abnormalities gradually improve with time and are replaced by “chronic-stage” abnormalities such as dysmaturity and disorganization. Several studies suggest that acute changes in the EEG background are powerful but nonspecific markers of brain dysfunction (8,9). In addition, a correlation between chronic-stage abnormalities and

cognitive impairment is suggested (10–13). Although early postnatal EEG has been used increasingly in preterm infants during the last years, there is no clear evidence to confirm its prognostic value in preterm infants of <30 wk GA (9).

The most dominant feature of the extremely preterm infants’ EEG is discontinuity, making a “grading” and “severity-scoring” in terms of depression in these infants difficult. Furthermore validated reference criteria with regard to maturation and appearance of sleep-wake cycling (SWC) to score “disorganization” and/or “dysmaturity” are still scarce.

Recording full conventional EEG continuously or at least repeatedly during the first days and weeks of life in very premature infants is technically difficult. Therefore, a more easily applicable trend-monitoring—the amplitude-integrated EEG (aEEG)—is now increasingly used in NICU. The aEEG background pattern correlates well with conventional EEG, and the method has been found to have very good predictive value for neurodevelopmental outcome in term neonates after perinatal asphyxia (14–17).

The aim of this study was to evaluate first whether aEEG-pattern within the first weeks of life predict further outcome in preterm infants of <30 wk GA. Second, we aimed to assess the optimal time point for assessment of aEEG and to compare its sensitivity and specificity to CUS.

PATIENTS AND METHODS

All infants born between January 1, 2000, and December 31, 2002, with a GA of <30 wk were prospectively included into the study after parental consent was obtained. The study was approved by the local ethics committee (Austria Ethikkommission) and the study protocol was registered (Clinical-Trials NCT00728234).

Amplitude-integrated EEG. The aEEG was recorded as a single channel EEG from biparietal surface disk electrodes using a CFM (CFM 5330; Lectromed Devices Ltd., UK) or the CFM 6000 (Natus Medical Incorporated, San Carlos, CA). The technique of aEEG has been described in detail elsewhere (18). In brief, the obtained signal is filtered, rectified, smoothed, and amplitude-integrated before it is written out or digitally available on the monitor at a slow speed (6 cm/h), directly at the bed side.

Cerebral ultrasound. CUS scans were performed on d 1, 3, 5, 7, and 10 of life and then once a week, using an Acuson 128XP (Mountain View, CA) with a 7.5-MHz transducer. IVH and periventricular leukomalacia were classified according to Papile *et al.* (19) and de Vries *et al.* (20), respectively. Normal CUS was defined when no white matter abnormality and no sign of IVH or

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Abbreviations: aEEG, amplitude-integrated EEG; CUS, cerebral ultrasound; IVH, intraventricular hemorrhage; MDI, mental development index; NPV, negative predictive value; PDI, psychomotor development index; PPV, positive predictive value; SWC, sleep-wake cycling

other abnormality was detected. Mildly, abnormal CUS was defined when there were persistent periventricular echodensity or mild IVH (I + II). Severely abnormal CUS was defined when there were focal and multifocal cystic lesions, ventriculomegaly or severe grade IVH (III + IV) or any other parenchymal bleeding/infarction. For comparison with aEEG only one recording per week (obtained nearest to the recording day of the aEEG; e.g. within the first week d 5, in second week d 12) was taken into account. CUS scans were also reevaluated by one of the authors.

Patients. Recording time and impedance of the aEEG tracing, birth weight, GA at birth and postnatal age at the time of the recording, medication, CUS findings, and clinical condition were recorded in all patients. GA was determined according to antenatal ultrasound scans.

Evaluation of aEEG tracings. Tracings were evaluated visually and classified according to the method previously described by Hellström-Westas *et al.* (21). Descriptive analysis of the background activity of the aEEG tracings was done by dividing each trace in 10-min epochs. These 10-min epochs were classified into five pattern categories (continuous pattern, discontinuous pattern, burst suppression pattern, low voltage activity, and flat trace).

Then appearance of SWC and seizure activity was noted within the entire recording. Referring to seizure activity only saw-tooth pattern or repetitive seizure activity was taken into account (21). aEEG pattern was then scored according to the following:

1. Background activity [age-adequate distribution of pattern (given in percentages) was classified according to reference values previously published; a value within 25th and 75th percentile for every pattern was classified as "age-adequate"] (22).
2. Appearance of SWC.
3. Presence or absence of seizure activity (21).

"Normal aEEG-pattern" was defined when all three categories were classified as normal, "moderately abnormal aEEG-pattern" was defined when 1/3 categories were classified as abnormal, and "severely abnormal aEEG-pattern" was defined when 2 to 3/3 categories were classified as abnormal as shown in Figure 1.

aEEG recordings were planned to be obtained once a week for a minimum of 4 h recording time, starting from the first week of life. To minimize influence of sedative medication, data of the first 2 wk were analyzed together and the one recording without sedative medication or the one obtained earlier (=within the first week of life) was taken into account for statistical analysis. An additional analysis was done using only recordings obtained within the

first 2 wk of life where no sedative medication was used at all. Classification of the aEEG was done by two of the authors and interrater reliability was determined.

Assessment of outcome. Assessment of neurodevelopmental outcome was done by an experienced staff (developmental psychologist and pediatrician) unaware of the aEEG-findings at 3 y of age using the Bayley Scales of Infant Development II (23) and a standardized neurological examination (24). Normal outcome was defined as none of the following: death, CP, neurosensory impairment, and mental developmental index (MDI) or psychomotor developmental index (PDI) score of <85.

Statistical analysis. The effect of the following items: "aEEG-pattern" (summed score), "SWC," "CUS," "percentage of continuous pattern," "percentage of burst suppression pattern," "seizure activity on aEEG," "chronological age (CA)," "GA," and "sedative/analgetic/anticonvulsant medication" on outcome were estimated in a multinomial regression mode in SAS (SAS/STAT User's Guide, version 9, 2002–2003; SAS Institute Inc., Cary, NC).

The diagnostic accuracy of aEEG-score and CUS were compared by computing the sensitivity and specificity indexes (and the 95% CIs) from χ^2 analysis tables. A *p* value of <0.05 was considered significant.

ORs were calculated for appearance of "CP," "severe impairment" (=MDI/PDI < 70), "death" and "abnormal outcome at 3 y" (summed score = occurrence of death, CP, neurosensory impairment, and MDI/PDI score < 85) for "abnormal aEEG" (=moderately and severely abnormal as defined above), "appearance of SWC," "abnormal background activity," "occurrence of seizure activity at aEEG," and "abnormal CUS" (=mildly and severely abnormal as defined above). For statistical analysis data for aEEG-pattern (summed score), CUS and neurodevelopmental outcome were stratified. Mildly and severely abnormal data were put together and only "normal *versus* abnormal" was analyzed.

RESULTS

During the study period, 247 preterm infants born <30 wk GA were included. Outcome data in our hospital could be obtained in 143/247 infants. Ninety-six of 247 patients were transferred during their initial stay on NICU to other hospitals (nine different), 17 patients were excluded from the study (dropout during follow-up). Outcome data were available in 56/96 of the transferred infants at the age of 3 y, obtained with different developmental tests. For further statistical analyses only the standardized data of our (not transferred) patients were taken into account.

Median GA was 26 wk [mean: 25.9 wk (23.1–29.8 wk)], median birth weight was 800 g [mean: 832 g (421–1646 g)], 82 patients were male and 66 female. Median duration of the recordings were 250 min [mean: 379 min (50–1440 min)], median impedance of the tracings was 2 kOhm [mean: 2.8 kOhm (0–11 kOhm)].

Thirty-seven infants died (25.8%), 24 (16.7%) showed severe impairment (=MDI/PDI < 70), and 23 (15.5%) showed mild impairment (MDI/PDI, <85 >70); CP was found in 34 (22.9%) infants. Sixty-one infants (41.2%) showed normal outcome at the age of 3 y. Epidemiological data of our study group are shown in Table 1.

aEEG evaluation and results. Classification of the aEEG was done by two of the authors (K.K and M.O.) for measurement of agreement and to proof interrater reliability Cohen's Kappa was determined, which was 0.77.

In 38/143 patients (26.5%), the CFM 6000 (Olympic Medical) was used; in 105/143 (73.5%), the CFM 5330 (Lectromed Devices Ltd., UK) was used. Within the first week of life one aEEG recording was obtained in 132/143 patients on median d 5; 72/132 (54.5%) stayed under sedative/analgetic/anticonvulsive medication. Within the second week of life, one aEEG recording was obtained in 106/143 patients on median d 12; 45/106 (42.4%) stayed under sedative/analgetic/

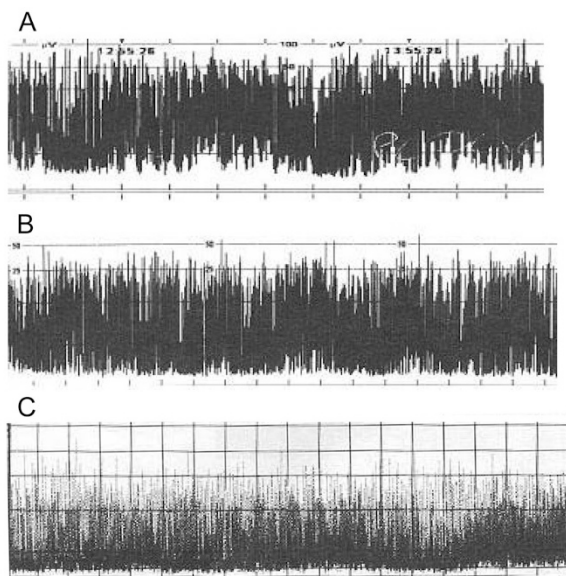


Figure 1. (A) 24 + 5 wk GA, 1 wk CA: normal aEEG (age-adequate background activity, presence of SWC, and no seizure activity). (B) 25 + 2 wk GA, 2 wk CA: moderately abnormal aEEG [background pattern not age-adequate (increased percentage of burst suppression and discontinuous pattern), presence of SWC, and no seizure activity]. (C) 26 + 1 wk GA, 2 wk CA: severely abnormal aEEG [background pattern not age-adequate (increased percentage of burst suppression), absence of SWC, and no seizure activity].

Table 1. Epidemiological data of the study group

	All patients		Patients with normal outcome		<i>p</i>	Patients with abnormal outcome	
Male	82/148	55.40%	28/64	43.80%	0.03	54/84	64.30%
Weight (g)	832 (421–1646)		892 (585–1524)		NS	786.01 (421–1646)	
Gestation (wk)	26 (23–29)		26.5 (24–29)		NS	25.49 (23–29)	
Apgar 1 min	6.14 (1–10)		6.5 (1–10)		NS	5.8 (1–10)	
Apgar 5 min	7.9 (2–10)		8 (4–10)		0.03	7.82 (2–10)	
IVH	70/148	47.30%	15/64	23.50%	<0.001	55/84	65.50%
IVH 3 + 4	28/148	18.90%	1/64	1.60%	<0.001	27/84	32.10%
PVL	20/128	13.50%	4/64	6.30%	<0.001	16/84	19%
Length of stay (d)	78.74 (2–270)		76.11 (18–125)		<0.001	80.75 (2–270)	
Antenatal steroids	137/148	92.60%	64/64	100%	<0.001	74/84	87.10%
RDS	112/148	75.70%	43/64	67.20%	<0.001	69/84	82.10%
Ventilation (d)	12.54 (0–120)		3.34 (0–45)		<0.001	19.55 (0–120)	
CLD	40/148	27%	8/64	12.50%	<0.001	32/84	38.10%
NEC	24/148	16.20%	5/64	7.80%	<0.001	19/84	22.60%
AIS	80/148	54.10%	24/64	37.50%	NS	56/84	66.70%
ROP	17/148	11.50%	4/64	6.30%	<0.001	13/84	15.50%
Shunt	13/148	8.80%	0	0%	<0.001	13/84	15.50%
Seizures	51/148	34.50%	7/64	10.90%	<0.001	44/84	52.40%
Visual impairment	17/148	11.50%	1/64	1.60%	<0.001	16/84	19%
CP	35/148	23.70%	0	0.00%	<0.001	34/84	40.50%
Death	38/148	25.60%	0/64	0%	<0.001	38/84	45.2%

Data were given as total numbers and percentages or median with given range of each value. A *p* value of <0.05 was considered significant.

PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; CLD, chronic lung disease; NEC, necrotizing enterocolitis; AIS, amniotic infection syndrome (=chorioamnionitis); ROP, retinopathy of prematurity; Shunt, necessity of ventriculoperitoneal shunt implantation; Seizures, seizures during hospital stay.

Table 2. aEEG pattern (summed score), appearance of SWC, occurrence of seizure activity, background activity, and CUS data in association to outcome analyzed for the first 4 wk of life

Outcome 3 y	aEEG-score		SWC	Seizures	Background		CUS		Sed.	day	Wk
	normal	abnormal			normal	abnormal	normal	abnormal			
Normal = 46	36	10	39	1	41	5	40	6	11	5	1
Abnormal = 86	13	73	24	19	16	70	22	64	61	4	1
Normal = 45	43	2	45	1	43	2	39	6	4	12	2
Abnormal = 61	10	51	32	7	19	42	15	46	41	11	2
Normal = 33	29	4	32	3	31	2	29	4	3	18	3
Abnormal = 45	10	35	29	18	22	23	15	30	23	18	3
Normal = 37	36	1	37	0	36	1	31	6	2	26	4
Abnormal = 38	10	28	27	12	19	19	12	26	19	25	4
Normal = 61	57	4	60	2	59	2	53	8	5	6	1 + 2
Abnormal = 82	15	67	29	26	20	62	26	56	46	6	1 + 2
Normal = 56	55	3	55	2	55	1	50	6	0	6.5	1 + 2 no sed .med.
Abnormal = 36	14	22	12	7	19	17	19	17	0	6	1 + 2 no sed. med.

aEEG-score, summed score; seizures, appearance of repetitive seizures on aEEG; background, background activity according to reference values (22); Sed., number of patients with sedative/analgetic/anticonvulsant therapy; day, median day of obtained aEEG recording; wk, wk of life (CA); normal outcome was defined as none of the following: CP, neurosensory impairment, MDI, and PDI (Bayley Scales) <85; normal aEEG was defined as age-adequate background activity, presence of SWC and no occurrence of seizure activity; normal CUS was defined as no signs of IVH and white matter abnormality. 1 + 2, data of the first 2 wk were analyzed together and the one recording without sedative medication or the one obtained earlier was taken into account. 1 + 2 no sed. med., data obtained within the first 2 wk of life and only recordings obtained without any sedative/analgetic/anticonvulsive medication were taken into account.

anticonvulsive medication. Within the third week of life, one aEEG recording was obtained in 78/143 patients on median d 18; 26/78 (33.3%) stayed under sedative/analgetic/anticonvulsive medication. Within the fourth week of life, one aEEG recording was obtained in 75/143 patients on median d 25; 21/75 (27.9%) stayed under sedative/analgetic/anticonvulsive medication.

The number of patients per week with further normal or abnormal outcome, the number of patients where normal or abnormal (stratified as defined above) aEEG pattern (summed score), normal or abnormal background activity, SWC within

aEEG and where seizures on aEEG could be found and the number of patients with normal or abnormal CUS within this week are presented in Table 2.

To minimize influence of sedative medication, data of the first 2 wk were analyzed together and the one recording without sedative medication or the one obtained earlier within this first 2 wk of life was taken into account. aEEG recordings of all 143 patients could be used; still 51/143 (35.6%) patients stayed under sedative/analgetic/anticonvulsive medication. Therefore, an additional analysis was done for one aEEG-recording, obtained within the first 2 wk of life, without any

Table 3. ORs for abnormal outcome at the age of 3 y, occurrence of CP, severe impairment and death for aEEG score, appearance of SWC, abnormal background activity, CUS, and occurrence of seizure activity within aEEG obtained within the first 2 wk of life without any sedative medication

OR (95% CI)	CP	Death	Severe impairment (MDI/PDI < 70)	Abnormal outcome at 3 y
Abnormal aEEG score	14.7 (4.3–50.3)	8.1 (1.4–45.1)	16.9 (3.9–72.4)	27.7 (7.2–106)
Abnormal background	12.4 (3.3–45.3)	6.7 (1.3–33.5)	13.2 (3.2–52.8)	49.2 (6.1–395.1)
Appearance of SWC	0.03 (0.006–0.16)	0.37 (0.06–2.1)	0.04 (0.009–0.19)	0.03 (0.004–0.29)
Seizures in aEEG	6.5 (0.9–42.3)	21.3 (3.7–122.5)	11.8 (1.7–80.6)	6.5 (1.2–33.4)
Abnormal CUS	13.4 (3.9–46.0)	9.3 (1.6–51.9)	7.8 (2.1–29.3)	7.4 (2.5–21.7)

Abnormal CUS: mildly and severely abnormal CUS; abnormal aEEG score: moderately and severely abnormal; abnormal background, not age-adequate background activity referring to reference values (<25th or >75th percentile) (22). Abnormal outcome at 3 y was defined as one or more of the following: CP, neurosensory impairment, MDI, and PDI (Bayley Scales) <85.

Table 4. Sensitivity, specificity, positive, and negative predictive value for abnormal outcome at the age of 3 y for aEEG pattern (summed score) and all its components (background activity, SWC, and occurrence of seizure activity) and CUS in relation to CA

	aEEG (summed score)	Background activity	SWC	Seizures	CUS
Wk 1					
Sensitivity (95% CI)	0.87 (0.78–0.94)	0.81 (0.71–0.88)	0.72 (0.61–0.81)	0.22 (0.13–0.32)	0.74 (0.63–0.83)
Specificity (95% CI)	0.73 (0.58–0.85)	0.89 (0.76–0.96)	0.84 (0.71–0.93)	0.97 (0.88–0.99)	0.86 (0.73–0.95)
PPV (95% CI)	0.84 (0.75–0.91)	0.93 (0.85–0.97)	0.89 (0.80–0.95)	0.95 (0.75–0.99)	0.91 (0.82–0.96)
NPV (95% CI)	0.78 (0.66–0.89)	0.71 (0.58–0.83)	0.61 (0.48–0.73)	0.40 (0.31–0.49)	0.64 (0.51–0.76)
Wk 2					
Sensitivity (95% CI)	0.83 (0.71–0.91)	0.68 (0.55–0.80)	0.47 (0.34–0.60)	0.11 (0.04–0.22)	0.75 (0.62–0.85)
Specificity (95% CI)	0.95 (0.84–0.99)	0.95 (0.84–0.99)	0.96 (0.84–0.99)	0.98 (0.90–0.99)	0.86 (0.73–0.94)
PPV (95% CI)	0.96 (0.87–0.99)	0.95 (0.84–0.99)	0.96 (0.82–0.99)	0.87 (0.47–0.99)	0.88 (0.76–0.95)
NPV (95% CI)	0.81 (0.68–0.90)	0.69 (0.56–0.80)	0.50 (0.37–0.62)	0.50 (0.40–0.59)	0.72 (0.58–0.83)
Wk 3					
Sensitivity (95% CI)	0.77 (0.62–0.88)	0.51 (0.35–0.66)	0.35 (0.21–0.51)	0.40 (0.25–0.55)	0.66 (0.51–0.80)
Specificity (95% CI)	0.87 (0.71–0.96)	0.90 (0.70–0.98)	0.97 (0.84–0.99)	0.90 (0.75–0.98)	0.87 (0.71–0.96)
PPV (95% CI)	0.89 (0.75–0.97)	0.92 (0.73–0.99)	0.94 (0.71–0.99)	0.85 (0.63–0.96)	0.88 (0.72–0.96)
NPV (95% CI)	0.74 (0.57–0.86)	0.47 (0.32–0.65)	0.52 (0.39–0.65)	0.52 (0.38–0.66)	0.65 (0.50–0.79)
Wk 4					
Sensitivity (95% CI)	0.73 (0.56–0.86)	0.50 (0.33–0.66)	0.28 (0.15–0.45)	0.31 (0.17–0.48)	0.68 (0.51–0.82)
Specificity (95% CI)	0.97 (0.85–0.99)	0.97 (0.85–0.99)	0.97 (0.86–0.99)	0.97 (0.86–0.99)	0.66 (0.40–0.86)
PPV (95% CI)	0.96 (0.82–0.99)	0.95 (0.75–0.99)	0.91 (0.61–0.99)	0.92 (0.63–0.99)	0.81 (0.63–0.92)
NPV (95% CI)	0.78 (0.63–0.89)	0.65 (0.51–0.77)	0.57 (0.44–0.70)	0.58 (0.45–0.70)	0.50 (0.29–0.70)

aEEG-score, summed score; seizures, appearance of repetitive seizures on aEEG; background activity, age adequate according to reference values (22).

sedative/analgetic/anticonvulsive medication; data of 92 patients (=92 recordings) could be used, aEEG was obtained on median d 6.5. Data were presented as the last two paragraphs of Table 2.

ORs for having an abnormal outcome at the age of 3 y (summed score defined as above), severe impairment (MDI/PDI <70), CP and death for abnormal aEEG-score (summed score), abnormal background activity, appearance of SWC and occurrence of seizure activity (calculated from the 92 recordings obtained on median d 6.5 without any sedative/analgetic/anticonvulsive medication), and abnormal CUS (also obtained on median d 5) were evaluated and are presented in Table 3.

From all variables, the multinomial regression model revealed a significant correlation to outcome at 3 y of age (stratified as described above) only for “aEEG-pattern” (summed score) ($p = 0.0003^*$), “CUS” ($p = 0.0005^*$), and appearance of “SWC” ($p = 0.037^*$) (again calculated from recordings obtained within the first 2 wk of life, on median d 6); all other did not reach significance.

The further aim of this study was to find the optimal time point for best sensitivity and specificity of aEEG when it comes to prognosis prediction. Sensitivity, specificity, positive

predictive value (PPV), and negative predictive value (NPV) for aEEG-score (summed score), background activity, appearance of SWC, occurrence of seizure activity, and CUS in relation to CA in weeks are shown in Tables 4 and 5.

A subgroup analysis by GA for associations of aEEG-score (summed score), background activity, appearance of SWC, occurrence of seizure activity, and CUS (again obtained within the first 2 wk of life) to outcome to evaluate whether there is a difference in the associations to later outcome in different GA groups was done. Infants were divided in three GA groups [group I = infants of 24 + 0 – 25 + 6 wk of GA ($n = 50$); group II = infants of 26 + 0 – 27 + 6 ($n = 61$); and group III = infants of 28 + 0 – 29 + 6 wk of GA ($n = 32$)]. All variables showed sensitivities to be the lowest in the more mature infants with similar or slightly increased specificities when compared with the youngest age group (Table 6).

DISCUSSION

In this study, we can show that aEEG pattern (a summed score) and its three components alone, background activity, the appearance of SWC, and the occurrence of seizure activity and CUS, were correlated to later outcome among preterm

Table 5. Sensitivity, specificity, PPV, and NPV for aEEG pattern (summed score) and all its components (background activity, appearance of SWC, occurrence of seizures on aEEG) and CUS in relation to outcome at 3 y of age in aEEG recordings obtained within the first 2 wk of life in recordings with and without sedative/analgetic/anticonvulsive medication

	aEEG	Background activity	SWC	Seizures	CUS
Wk 1 + 2					
Sensitivity (95% CI)	0.81 (0.71–0.89)	0.75 (0.64–0.84)	0.64 (0.53–0.74)	0.31 (0.21–0.42)	0.68 (0.57–0.78)
Specificity (95% CI)	0.93 (0.84–0.98)	0.96 (0.88–0.99)	0.98 (0.91–0.99)	0.96 (0.88–0.99)	0.86 (0.75–0.94)
PPV (95% CI)	0.94 (0.86–0.98)	0.96 (0.89–0.99)	0.98 (0.90–0.99)	0.92 (0.76–0.99)	0.87 (0.76–0.94)
NPV (95% CI)	0.79 (0.67–0.87)	0.74 (0.63–0.83)	0.67 (0.56–0.76)	0.51 (0.41–0.60)	0.67 (0.55–0.77)
Wk 1 + 2 no sed. med.					
Sensitivity (95% CI)	0.61 (0.43–0.76)	0.47 (0.30–0.64)	0.50 (0.35–0.64)	0.19 (0.08–0.36)	0.47 (0.30–0.64)
Specificity (95% CI)	0.98 (0.90–0.99)	0.98 (0.90–0.99)	0.92 (0.63–0.99)	0.96 (0.87–0.99)	0.89 (0.78–0.95)
PPV (95% CI)	0.95 (0.78–0.99)	0.94 (0.72–0.99)	0.96 (0.79–0.99)	0.77 (0.39–0.97)	0.73 (0.62–0.81)
NPV (95% CI)	0.79 (0.68–0.88)	0.74 (0.62–0.83)	0.33 (0.18–0.50)	0.65 (0.53–0.75)	0.72 (0.60–0.82)

aEEG-score, summed score; seizures, appearance of repetitive seizures on aEEG; background activity, age adequate according to reference values (22); wk 1 + 2, data of the first 2 wk were analyzed together and the one recording without sedative medication or the one obtained earlier was taken into account. Wk 1 + 2 no sed. med., data obtained within the first 2 wk of life and only recordings obtained without any sedative/analgetic/anticonvulsive medication were taken into account.

Table 6. Association of aEEG-pattern, background activity, appearance of SWC, occurrence of seizure activity, and CUS to outcome in different GA groups

Wk 1 + 2	n	aEEG score (summed score)	Background activity	SWC	Seizures	CUS
Group I (24 + 0–25 + 6 wk)	50					
Sensitivity (95% CI)		0.85 (0.68–0.95)	0.76 (0.58–0.89)	0.61 (0.43–0.77)	0.26 (0.12–0.44)	0.77 (0.60–0.89)
Specificity (95% CI)		0.87 (0.61–0.98)	0.93 (0.69–0.99)	0.93 (0.69–0.99)	0.87 (0.61–0.98)	0.81 (0.51–0.95)
PPV (95% CI)		0.93 (0.78–0.99)	0.96 (0.81–0.99)	0.95 (0.77–0.99)	0.81 (0.48–0.97)	0.90 (0.74–0.97)
NPV (95% CI)		0.73 (0.48–0.90)	0.65 (0.42–0.83)	0.53 (0.33–0.72)	0.35 (0.21–0.52)	0.60 (0.36–0.80)
Group II (26 + 0–27 + 6 wk)	61					
Sensitivity (95% CI)		0.80 (0.65–0.91)	0.78 (0.63–0.89)	0.57 (0.40–0.72)	0.23 (0.12–0.39)	0.67 (0.50–0.80)
Specificity (95% CI)		0.95 (0.73–0.99)	0.95 (0.74–0.99)	0.95 (0.73–0.99)	0.95 (0.73–0.99)	0.90 (0.66–0.98)
PPV (95% CI)		0.97 (0.85–0.99)	0.97 (0.84–0.99)	0.96 (0.79–0.99)	0.90 (0.58–0.99)	0.93 (0.77–0.99)
NPV (95% CI)		0.69 (0.48–0.85)	0.66 (0.46–0.83)	0.50 (0.32–0.67)	0.36 (0.22–0.50)	0.54 (0.36–0.72)
Group III (28 + 0–29 + 6 wk)	32					
Sensitivity (95% CI)		0.55 (0.21–0.86)	0.44 (0.13–0.78)	0.44 (0.13–0.78)	0.11 (0.02–0.48)	0.33 (0.07–0.70)
Specificity (95% CI)		0.93 (0.68–0.99)	0.94 (0.68–0.99)	0.94 (0.69–0.99)	0.94 (0.69–0.99)	0.86 (0.59–0.98)
PPV (95% CI)		0.83 (0.35–0.99)	0.80 (0.28–0.99)	0.80 (0.28–0.99)	0.50 (0.01–0.98)	0.60 (0.14–0.94)
NPV (95% CI)		0.77 (0.52–0.93)	0.73 (0.48–0.90)	0.75 (0.50–0.91)	0.65 (0.42–0.83)	0.68 (0.43–0.87)

aEEG-score, summed score; seizures, appearance of repetitive seizures on aEEG; background activity, age adequate according to reference values (22); wk 1 + 2, data of the first 2 wk were analyzed together and the one recording without sedative medication or the one obtained earlier was taken into account.

infants born <30 wk GA. The presence of an abnormal aEEG-pattern-score within the first 2 wk of life was highly predictive for adverse outcome (defined as death, MDI/PDI < 85, CP, neurosensory impairment at the age of 3 y; $p = 0.0003$). The aEEG-pattern-score as proposed in this study can therefore be used as predictive and prognostic tool in preterm infants with a specificity of 94% and sensitivity of 81%.

Similar to previous studies (25,26), neurodevelopmental impairment was common in our cohort. Thirty-eight infants died (25.7%), 26 (17.5%) showed severe impairment (MDI/PDI < 70 and neurological/neurosensory impairment), 23 (15.5%) showed mild impairment (MDI/PDI < 85 > 70), and 34 (22.9%) infants developed CP. Sixty-one infants (41.2%) showed normal outcome at the age of 3 y. These high rates of neurodevelopmental impairment within this group underline the importance of early identification of infants who are at greatest developmental risk.

In term infants, prior studies have demonstrated associations between aEEG abnormalities and neurodevelopmental outcome (14,17,27) after hypoxic-ischemic insult. A meta-analysis showed sensitivities between 73 and 100% and spec-

ificities between 73 and 100% for aEEG recordings within hours after hypoxic-ischemic encephalopathy (14).

EEG activity of preterm infants is variable because of maturational changes reflecting the rapid evolutionary changes in brain development in this time period. Developmental changes of normal EEG features in the preterm infant have been reviewed previously (10–13,28), but there are only few reports of EEG findings on infants <30 wk GA. Additionally, there are other confounding factors on brain morbidity and activity in preterm infants when compared with their term peers such as perinatal infection and inflammation, lacking cerebral autoregulation, arterial hypotension, metabolic, and/or respiratory acidosis, medications—just to name a few of them.

We expected not only to find acute (perinatally acquired) abnormalities in our cohort but also abnormalities that dated back several weeks, and also some infants were supposed to suffer from later—postnatally acquired—brain damage. Thus, we reasoned, that longitudinal recordings of aEEG would be essential to assess changes and their association to outcome and to find out, whether there is an optimal time point in

assessing aEEG pattern for best predictive value. One recording from the first week of life was good in predictive value but not as good as a recording from the second week of life. Thereafter predictive power was decreasing with each post-natal week. This reflects that many of these infants do have acute perinatal brain damage, but some of them only develop abnormalities, which require more time to be assessed. In the first week of life of a premature infant, many changes in respiratory and hemodynamic status are occurring and sedative medication is used more often than in the following weeks. Therefore, the false positive rate of aEEG assessment can be higher early after birth. Assessing aEEG within the first 2 wk of life using the earliest tracing without sedative or analgetic medication provides the strongest association to later outcome with a specificity of 98%, sensitivity of 61%, PPV of 96%, and NPV 79%.

Infants of higher GA or CA showed lower sensitivities for predicting outcome. This was true for aEEG-pattern score and all its components seen alone. SWC did also appear in infants with brain lesions but usually emerged later when compared with healthy infants. There is evidence that appearance of SWC and their time of onset is of prognostic value in term infants (29), and this seems to be even more true for preterm infants. The absence of SWC remains a very specific sign of brain damage, with a specificity of 97% after 4 wk.

The same is true for aEEG-background pattern, because this is also “normalizing” in infants with brain damage—the older the infant gets or the higher its GA was at birth. The proposed summed aEEG-score in this study combines features that reflects acute changes of brain activity (mostly seen as an increase of all discontinuous background pattern) and chronic abnormalities, which stay longer (as later onset of SWC). With its reference to age-dependent values, its classification becomes more objective and therefore even more helpful in the assessment of preterm infants, independent of their GA.

Reports on sensitivity and specificity of CUS for predicting neurodevelopmental outcome in preterm infants range from 45 to 90% (30–33). In our cohort, a specificity of 87% and a sensitivity of 68% was found; sensitivity was clearly lower than the assessment by aEEG.

Recently, MRI has shown to be of increasing value in evaluation of brain damage of preterm infants and offers high predictive values (sensitivity 84%, specificity 89%) when performed at term equivalent (26). This might be also true when performed earlier, although it is a current matter of discussion whether its value stands above assiduous ultrasound scans (4,31).

The strengths of our study include its prospective design and the large size of the study population and the assessment of neurodevelopmental outcome by independent observers unaware of the aEEG findings. The limitation of this study is the low rate of standardized neurodevelopmental follow-up because of logistic reasons as our hospital is under a lot of pressure to transfer a high rate of our patients to other level II units including especially the most stable patients. That might have introduced a selection bias in our cohort to higher morbidity and mortality.

We are also well aware that still quite a high number of our patients were receiving analgetic and/or sedative and/or anti-convulsant medication (mainly morphine, midazolam, and phenobarbitone). The analysis summarizing the assessment of the first and the second week of life together (as shown in Table 3) was done to minimize the influence of sedative medication as much as possible. Additional analysis of the recordings without any sedative/analgetic/anticonvulsive medication showed the same trend of correlation to outcome parameters.

We also would like to declare, that the accuracy of outcome prediction by aEEG assessed by non experts might be less than as reported in this study, because even interobserver agreement within the two authors of this study was not excellent. Problems occurred especially referring to definition of “age-adequate” normality of background activity. Hence, we especially recommend to use the percentages of the different background pattern and the percentiles of reference values already published.

We only analyzed aEEG obtained once a week (because of staff and machine resources), within the first week of life (on median d 6). With the data of this study, it can be hypothesized that earlier and longer recordings would even more improve the prognostic value of this method.

In conclusion, our data show that one aEEG recording obtained within the first 2 wk of life (optimally obtained without any sedative/analgetic/anticonvulsive medication) predicts further outcome in preterm infants with a specificity of 98%, sensitivity of 61%, PPV of 96%, and NPV of 79%. Thus, we can underline the usefulness of this method also for preterm infants born <30 wk GA and enhance early functional neurophysiological assessment.

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