ARTICLE

Amplitude-integrated EEG recorded at 32 weeks postconceptional age. Correlation with MRI at term

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OBJECTIVE: The study aims to establish the role of late aEEG (scored by Burdjalov) in predicting brain maturation as well as abnormalities evaluated at term equivalent age (TEA) by brain MRI.
METHODS: 91 infants born before 30 wks gestation underwent an aEEG monitoring at 32 wks postconceptional age (PCA). aEEG, was correlated with TEA MRI, scored by Kidokoro.
RESULTS: A significant correlation between the aEEG score and the MRI scores was found. The same results were obtained for the aEEG continuity score; cyclicity and bandwidth scores were associated with grey matter and cerebellar MRI items. Moreover, a correlation between aEEG and cEEG recorded both at 32 and 40 wks PCA, was found.
CONCLUSIONS: aEEG monitoring can be predictive of MRI findings at TEA, suggesting that it could be implemented as a useful tool to support ultrasound to help identify neonates who will benefit from early intervention services.

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INTRODUCTION

Brain development protection is a primary objective in the neonatal intensive care unit (NICU), mainly because the survival of preterm babies has grown in the last years. Preterm babies have an increased risk of neurodevelopmental disorders such as cerebral palsy and intellectual disabilities. Neonatal brain injury occurs between 24 and 40 weeks, that is a period of extraordinarily rapid and complex events in human brain development [1–3]. It includes not only major lesions, i.e., cystic periventricular leukomalacia or hemorrhages, but also more subtle brain abnormalities that can be more important than the simple loss of tissue in determining the neurological outcome [1–3]. Brain lesions are traditionally diagnosed in preterm infants, during their NICU stay, by cranial ultrasound (CUS) whereas Magnetic Resonance Imaging (MRI) is mainly performed in selected cases or at term equivalent age to assess white matter injury in relation to neurodevelopmental outcomes [4, 5]. Evaluation of brain function and maturation and the effects of therapies administered during hospitalization, have been instead provided by the conventional electroencephalography (cEEG) [6] and recent advances in neonatal care emphasized the need for improved tracking of brain maturation. Recently, some studies have reiterated the importance of EEG as a sensitive method for assessing neuromotor and cognitive prognosis [7–9].

Prognostic information have been traditionally based on MRI at term equivalent age (TEA) [5, 10–12]. Nevertheless, debate still exists on the appropriateness of executing a brain MRI as a routine screening in preterm infants at discharge. Indeed, this examination is expensive, requires infant sedation and specialist pediatric neuroradiologist for evaluation [13, 14].

Moreover, infants can have neurodevelopmental impairments even in the absence of major neuroimaging abnormalities. The importance of exploring other measures that can give a prediction of outcome is a clear consequence. The possibility to detect brain anomalies or delayed brain maturation earlier on, during the NICU stay, may help to promote early preventive and rehabilitative strategies to improve later outcome [7–9]. In the last years, simplified monitoring has been increasingly used in NICUs. The amplitude integrated electroencephalogram (aEEG), recorded during the first 72 h of life, when preterm infants are at high-risk of most intracranial lesions, has shown an excellent diagnostic and prognostic value [15–17]. However, little is known on the diagnostic role of aEEG performed at later stages, to detect subtle lesions or developmental abnormalities traditionally diagnosed by TEA-MRI [15–17].

The present study aimed to establish the role of aEEG, performed at 32 weeks postconceptional age (PCA), in predicting brain maturation evaluated at term equivalent age with brain MRI.

Since the evaluation of cerebral maturity has always been provided by the cEEG, the secondary aim of the present study was to compare information obtained from aEEG with those obtained from cEEG.

PATIENTS AND METHODS

This was a prospective monocentric observational study carried out in the third level neonatal center of Rimini, Italy, from April 2015 to April 2018. It was approved by the local Ethics Committee.

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Table 1. Clinical characteristics of the studied population.

VARIABLES	COHORT ($n = 91$)
GA (mean ± sd)	27 + 6/7 weeks ± 2 weeks
Birth Weight (mean ± sd)	1035 g ± 330 g
Antenatal corticosteroid prophylaxis (*n*, %)	10 incompletes (10.9%) 81 completes (89%)
Chorioamnionitis (*n*, %)	35 (38%)
Magnesium Solfate prophylaxis	50 (54.9%)
CRIB-II score (mean ± sd)	8.5 ± 3.6
Days of mechanical ventilation (mean ± sd)	6.5 ± 14.4
Days of nasalCPAP (mean ± sd)	9.1 ± 11.9
Days of high flow nasal canula (mean ± sd)	19.1 ± 17.9
Days of oxygen therapy (mean ± sd)	32 ± 37
Post-natal steroids (*n*, %)	28 (30.7%)
Sepsis (*n*, %)	37 (40.6%)
Necrotizing enterocolitis (*n*, %)	11 (12%)
Patent ductus arteriosus (*n*, %)	42 (48.3%)
Intraventricular hemorrhage grade 3–4(*n*, %)	10 (10.9%)
Cystic periventricular leukomalacia	2 (2.2%)
Retinopathy of prematurity 1st and 2nd stage 3rd and 4th stage	16 (17.5%), 5 (5.5%)
Oxygen supplementation at 36 wks PCA (*n*, %)	24 (26.3%)

GA gestational age, *CRIB-II* Clinical Risk Index for Babies score, *nCPAP* nasal Continuous Positive Airway Pressure, *PCA* postconceptional age.

Study population

The study cohort comprised all infants, inborn or outborn, born before 30 weeks (0/7–6/7) gestational age (GA), admitted consecutively to our Institution, in which a written parental informed consent was obtained at 32 weeks PCA. Infants were excluded if they showed signs of severe illness that could contraindicate electrode placement (e.g., septic or cardiovascular shock) at that time of aEEG recording.

Standard practice for neuromonitoring in infants with GA < 30 weeks at our center includes serial CUS, neurological and physical examination during the NICU stay and TEA MRI, regardless of CUS results.

Study phase

aEEG, cEEG, and brain MRI were recorded during the study phase.

aEEG: was recorded at 32 weeks PCA (32 + 0/7–32 + 6/7) for at least 4 h. Needle electrodes were placed in the C3-P3 and C4-P4 positions on the newborn's head, according to the International 10–20 system. Pain control before electrodes placement was done according to the Italian Guidelines for procedural pain in the newborn [18]. Tracings were recorded by Brainz Olympic® monitor-Natus and were analyzed in double-blind by two specialized neonatologists. The aEEG recordings were evaluated using the Burdjalov score [1], based on the four main components of aEEG tracing: continuity, bandwidth, sleep-wake cycles and amplitude of the low border.

cEEG: in order to compare the prognostic value of aEEG with cEEG, a conventional electroencephalogram was recorded at the same weeks of the aEEG (32 weeks PCA: 32 + 0/7–32 + 6/7) and, a second one was performed at TEA for at least 30 min. At least eight electrodes were placed at F3, F4, C3, C4, O1, O2, T3, and T4, in accordance with the international 10 to 20 system, modified for newborns, and traces were recorded by Micromed PC® with system plus software. All the traces were analyzed by one expert pediatric neurologist, and EEG background activity was scored as 1(normal); 2 (mildly abnormal): excess sharp activity, absence or decreased frequency of normal patterns, excessively long low-voltage periods or overall slightly decreased voltage; 3 (moderately abnormal): asymmetries in voltage or frequencies; asynchrony for age; 4 (severely abnormal): isoelectric or low voltage invariant activity; burst-suppression pattern; permanent discontinuous activity [19, 20].

Brain MRI: was performed at term equivalent age to evaluate white matter, cortical and deep grey matter and cerebellum. An MRI scoring system, adapted from Kidokoro et al. [21] was used which combines quantitative and qualitative measurements of brain abnormalities in preterm infants, at term equivalent age (See Appendix). Sedation was achieved thorough the administration of intranasal midazolam, 0.2–0.3 mg/kg; the dosage was repeated as necessary. A specialized pediatric neurologist analyzed the images.

Perinatal and neonatal clinical data extracted from the Vermont Oxford Network Register and from the electronic medical records are reported in Table 1.

ANALYSIS OF DATA

All data were recorded in a specific Excel Database. Normally and not normally distributed variables were analyzed by parametric and nonparametric statistics, respectively. Univariate analyses were conducted to evaluate the effect of perinatal variables on the Burdjalov score. Variables that showed a statistically significant correlation in the univariate analysis were inserted as independent variables in a logistic regression model to evaluate the independent effect on the categorized Burdjalov score (normal score ≥9, abnormal score <9). The Burdjalov score, obtained by the aEEG analysis at 32 weeks PCA, was correlated both with the cEEG scores at 32 and 40 weeks PCA and the Kidokoro score for brain MRI at TEA. Data were considered statistically significant if the error alpha was lower than or equal 5%. The SPSS 13.0 statistical package for the statistical analysis was used.

RESULTS

One hundred and seven consecutives eligible newborns were referred to the NICU from April 2015 to April 2018. Parental informed written consent was not obtained in four cases; other two more newborns died before study entry and two were transferred to another region before term equivalent age; moreover, eight newborns were not enrolled due to the low enrollment activity.

Nobody was excluded because of severe illness at the time of the CFM study. Therefore, the study population included 91 infants born before 30 weeks GA and surviving at TEA.

Obstetric and neonatal data are reported in Table 1.

aEEG

The Burdjalov score at 32 weeks PCA was assessed for all the studied infants. Inter-rater agreement for qualitative aEEG scoring was excellent (Cronbach's alpha 0.985). When scores differed between the two neonatologists, an agreement was reached.

Seventy-four percent (67/91) newborns obtained a normal Burdjalov score of 9–11; a Burdjalov score <9 was found in 26% (24/91) infants. Results on the univariate correlation between the Burdjalov score and perinatal variables are available in the supplemental Table 1.

A logistic regression analysis model, including as the dependent variable the categorized Burdjalov score (normal ≥ 9 and abnormal <9) and as independent variables those statistically significant at the univariate analysis, showed that severe CUS abnormalities -severe IVH and cPVL- ($p < 0.01$) and a treated Patent ductus arteriosus ($p < 0.01$) had a statistically significant negative impact on the Burdjalov score.

cEEG

cEEG scores were obtained in 86 and 84 patients at 32 and 40 weeks PCA, respectively.

Brain MRI

A modified Kidokoro score was obtained in the all the studied population and is reported in Table 2.

Table 2. MRI Kidokoro score TEA.

	White matter (=*n*)	Cortical gray matter (=*n*)	Deep gray matter (=*n*)	Cerebellum (=*n*)	Total (=*n*)
Normal	32	5	12	23	5
Mild	35	3	11	6	17
Moderate	11	14	30	36	31
Severe	13	69	38	26	38

Table 3. Correlation between aEEG and MRI performed at 40 weeks of GA.

	Total		Continuity		Cyclicity		Bandwidth	
	p value	Spearman	*p* value	Spearman	*p* value	Spearman	*p* value	Spearman
WM Cysticlesions	***	−0.4814	***	−0.4932	***	−0.3483	***	−0.4056
WM Focalsignalabnormality	*	−0.2456	**	−0.2753		−0.2021		−0.17010
Myelination delay	*	−0.2235	*	−0.2096		−0.1733		−0.1708
Thinning of the corpus callosum		−0.0739		−0.0692		−0.1083		−0.0175
Dilatedlateralventricles	**	−0.3406	*	−0.2506	*	−0.2534	**	−0.3153
WM Volume reduction		−0.1108	**	−0.2842		−0.0156		−0.1600
Cortical GM abnormality	*	−0.2535	*	−0.2341	**	−0.2943		−0.1418
Delayedgyration	**	−0.3178	**	−0.3350	**	−0.3135	*	−0.2598
Dilated extra cerebral CSF space		−0.0238		−0.0067		0.00464		0.0438
Deep GM signal abnormality	***	−0.3844	**	−0.3328	**	−0.3173	**	−0.2953
Deep GM volume reduction	**	−0.2939	***	−0.3660	*	−0.2587	*	−0.2548
Cerebellum signal abnormality	*	−0.2557	**	−0.3080	*	−0.2446		−0.1660
Cerebellum volume reduction	***	−0.3903	***	−0.4725	*	−0.2342	***	−0.3823
MRI tot	**	−0.2925	***	−0.3508	*	−0.2565		−0.2044

WM white matter, *CSF* Cerebrospinal fluid, *GM* grey matter, *MRI* magnetic resonance imaging
Spearman rho correlation, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Correlation among aEEG, cEEG, and MRI

Analysis of data showed a good correlation between aEEG recorded at 32 weeks PCA and cEEG, recorded at both 32 (Spearman rho −0.342, $p < 0.01$) and 40 weeks PCA (Spearman rho −0.259, $p = 0.01$).

Table 3 shows the correlation between aEEG component variables recorded at 32 weeks PCA and TEA brain MRI abnormalities, with the exclusion of the low border score that did not show any statistically significant correlation with any MRI patterns. Fourteen infants showed both a normal aEEG and normal MRI, and 43 both pathological aEEG and MRI. On the other hand, 10 babies with abnormal aEEG score at 32 weeks PCA had a normal or mild-moderate MRI and 24 babies with Burdjalow score >9 at 32 weeks, had severe abnormalities at TEA MRI. Supplementary Table 2 reports number of infants with or without MRI anomalies at TEA according to the categorized Burdjalov score (normal score ≥9, abnormal score <9) evaluated on the aEEG at 32 weeks PCA.

DISCUSSION

Literature reports a good predictive value of brain MRI performed at TEA on long term outcome in infants who were born very preterm [22]. Indeed, MRI allows an accurate prediction of neurological outcome by detecting better minor lesions and reduction of brain volume [5, 10–12, 15–17, 21–23].

aEEG has recently been demonstrated to be a less expensive and more simplified tool to explore brain function, for the assessment of brain maturation and anomalies [24]. Hellstrom-Westas affirms that the simplicity of aEEG makes it possible to apply and interpret around the clock by the neonatal staff, and the interrater reliability is usually excellent [25]. Some scoring systems have been developed to classify aEEG traces. The Burdjalov score was primarily designed to describe the physiological maturation of electrocortical activity, whereas the Hellström-Westas classification was designed to distinguish between pathological and physiological patterns rather than to describe maturational changes over time. For the purposes of the present study, we were more interested in preterm brain maturation so we chose the Burdjalov score over other grading systems [26].

Although the aEEG has not been evaluated in preterm babies as extensively as in term infants, several studies have shown its utility in this population [25–27].

The absence of cyclicity in the first 24 h of life in preterm infants appears to be a marker for brain injury and predicts intraventricular hemorrhages and white matter damage [28]. Early detection of continuity, cyclicity and background activity at aEEG correlates with short and long-term neurobehavioral and motor outcomes. Moreover, early signs of dysmaturity in brain activity have been associated with later neurodevelopmental impairments [28–35].

Few data are available on the prognostic value of the aEEG recorded at late postnatal ages, when morbidities have shown their impact and the brain maturation, together with the effect of cerebral plasticity, are ongoing. In a study published by Reynolds at al., aEEG, recorded during the first six weeks of life in preterm newborns, can predict neurodevelopmental outcome at two years of age. In this study, the Burdjalov score correlates with neonatal factors, i.e., sepsis and prolonged mechanical ventilation, but not with GA at birth, suggesting that cerebral electrophysiological function may be more affected by postnatal events rather than by the age of prematurity itself [29].

In the present study, aEEG was performed at the PCA of 32 weeks to evaluate the infants outside of the immediate acute

phase of the neonatal stay, at the time of the expected appearance of maturational processes, i.e., definite cycling.

A good correlation between the total Burdjalov score and all the considered MRI items, except for the dilatation of extracerebral CSF spaces and the thinning of the corpus callosum, was found. The same results were obtained when the continuity score was analyzed; cyclicity and bandwidth scores were more consistently associated with grey matter and cerebellar MRI items; instead, the score of the lower border did not show any significant association with any of the MRI items.

Results from the present study show that aEEG monitoring, beyond the acute phase of the brain damage, can be predictive of MRI findings at TEA. Recently, the American Academy of Pediatrics, in the "Choosing Wisely in Newborn Medicine", stated that there is insufficient evidence for the routine use of TEA MRIs in preterm infants as it does not improve long-term outcome [36].

However, developmental alterations are already present by term equivalent age, which warrants intervention during NICU hospitalization. Early detection of brain dysmaturity provides the clinicians with an instrument to identify preterm infants at risk for abnormal cortical development and unfavorable outcome. cEEGs surveillance during NICU stay, showed to be useful in this regard [37]. However, a continuous conventional EEG has both interpretative and recording issues in the NICUs due to the environmental noise and to the high number of electrodes that need to be positioned on the patient. Moreover, cEEG requires qualified and trained technicians and neurophysiologists. A bedside, simplified recording, that can be read by neonatologist, such as the aEEG, can provide information similar to those obtained from cEEG [6–9, 38, 39], allowing to design an individualized developmental rehabilitative program to sustain brain maturation and plasticity during the NICU stay. The good correlation between aEEG at 32 weeks PCA and cEEG, both at 32 and 40 weeks PCA, is also confirmed in our study.

aEEG monitoring can be considered time-consuming and sometimes conflicting with principles of minimal handling, because of the application of needle electrodes. However, studies from literature did not confirm these concerns, demonstrating feasibility and safety profile of aEEG monitoring, with few adverse events, even in this fragile population of preterm infants [40]. In the present study, no adverse events occurred due to scalp electrodes and oral glucose solution or breast milk administration was feasible in all cases to control pain [18].

The main limitation in the interpretation of data from the present study is the lack of long-term data on development. A psychomotor follow-up is ongoing and data at two years of corrected age will be reported at the end of the observational period.

CONCLUSIONS

The results from the present study show that aEEG monitoring in preterm infants, recorded at 32 weeks of PCA, may anticipate results obtained later by a more complex tool such as brain MRI.

aEEG could be used to support CUS to early identify neonates who will benefit from early intervention services and to provide management plans with occupational and physical therapies after discharge.

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AUTHOR CONTRIBUTIONS

AT conceptualized and designed the study, participated in data acquisition, interpreted aEEG traces and wrote the manuscript. MN participated in acquisition of data and revised the article critically for content. JS interpreted brain MRI scans and participated in acquisition of data. AA interpreted conventional EEG traces and participated in acquisition of data. PP conceptualized the study, supervised data collection, and reviewed the manuscript. GA conceptualized and designed the study, interpreted aEEG traces, analyzed and interpreted data, wrote the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

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

ADDITIONAL INFORMATION

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