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Recovery of aEEG Patterns at 24 Hours of Hypothermia Predicts Good Neurodevelopmental Outcome

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Abstract

Background: The clinical use of amplitude integrated electroencephalogram (aEEG) in the neonatal intensive care unit has largely increased. This method has been reported to have a very good predictive value for neurodevelopmental outcome in term neonates after perinatal asphyxia.

Aim: The aim of this study was to assess the recovery of aEEG patterns during hypothermic treatment in full term asphyxiated neonates. Our working hypothesis is that children with aEEG recovery within 24 h of therapeutic hypothermia will have a normal development outcome (i.e., no or mild neurological impairment).

Study design: We performed an observational prospective study on a group of asphyxiated patients admitted to our Neonatal Intensive Care Unit from April 2009 to April 2012. Results: 24 patients with moderate to severe perinatal asphyxia had an aEEG recorded for at least 72 h during hypotermia (at the beginning of the registration 13 patients presented moderate aEEG abnormalities and 11 severe aEEG abnormalities). Respectively 11 neonates with moderate aEEG abnormalities and 1 neonate with severe abnormalities normalized the aEEG pattern during the treatment. At the follow up 3 patients died during neonatal age, 5 babies developed cerebral palsy, 4 babies developed dyskinetic cerebral palsy and 12 babies did not develop any disability (babies with good outcome were those with normal aEEG pattern at 24 h).

Conclusion: Recovery to a normal aEEG background pattern within the first 24 h of hypothermia after perinatal asphyxia predicts a normal outcome. Abnormal aEEG pattern persisting after 24 h correlates with poor outcome (death or cerebral palsy).

Keywords: Amplitude integrated electroencephalogram; Perinatal asphyxia; Hypothermic treatment; Neurodevelopmental outcome

Abbreviations aEEG: Amplitude Integrated Electroencephalogram; NICU: Neonatal Intensive Care Unit; HIE: Hypoxic Ischaemic Encephalopathy; CNV: Continuous Normal Voltage; DNV: Discontinuous Normal Voltage; CLV: Continuous Low Voltage; BS: Burst Suppression; FT: Flat Trace; SE: Status Epilepticus; BSID: Bayley Scales of Infant Development; MDI: Mental Development Index; PDI: Psychomotor Developmental Index

Introduction

During recent years the clinical use of amplitude integrated electroencephalography (aEEG) in the neonatal intensive care unit has greatly increased. In the past aEEG was mainly used to evaluate neonatal brain activity or to select those infants who might benefit from neuroprotection treatment after birth asphyxia [1]. This early assessment has been used in many trials for selection of neuroprotective therapy. The entry criteria for hypothermia of the larger international trials (CoolCap and TOBY Trials) included abnormal aEEG in addition to evidence of birth asphyxia and moderate or severe encephalopathy [2]. This method has been noted to have also very good predictive value for neurodevelopmental outcome in term neonates after perinatal asphyxia especially in the first hours after birth [3]. We observed that the aEEG pattern at 24 h of hypothermia is a better predictor of neurodevelopmental outcome than the aEEG pattern in the first hours of life. The aim of this study was to assess the recovery of aEEG patterns during hypothermic treatment in full term asphyxiated neonates with an abnormal aEEG at admission to Neonatal Intensive Care Unit (NICU). We hypothesized that children in whom an abnormal background pattern rapidly recovered (within 24 h of treatment) would have an increased chance of normal neurodevelopmental outcome.

Methods

Patients

We performed an observational prospective study on a subgroup of asphyxiated patients enrolled for a registered multicenter pilot trial about topiramate/hypothermia co-treatment for neuroprotection (Current Controlled Trials ISRCTN62175998; ClinicalTrials.gov Identifier NCT01241019; EudraCT Number 2010-018627-25) [4].

Patients (n.24) were admitted to Neonatal Intensive Care Unit (NICU) of the Santa Chiara University Hospital of Pisa from April 2009 to April 2012 with the diagnosis of perinatal asphyxia and consecutively recruited. The infants had at least one sign of intrapartum fetal distress (abnormal cardiotocography, meconium stained amniotic fluid or low cord PH) caused by antepartum factors (e.g. maternal infection, chronic hypertension, bleeding in second or third trimester) or intrapartum factors (e.g. breech or other abnormal presentation, chorioamnionitis, precipitous or prolonged labor).

Inclusion criteria were the same reported in larger previous international trials on hypothermia: 1) gestational age ≥ 36 weeks and birth weight ≥ 1800 g, admitted to NICU within 6 h after birth; 2) metabolic criteria, i.e., Apgar score ≤ 5 at 10 min or persisting need for resuscitation, including endotracheal intubation or mask ventilation for more than 10 min after birth, or acidosis (pH ≤ 7.0 and/or base deficit ≥ −16 mmol/L in umbilical cord blood or arterial, venous or capillary blood) within 60 min from birth; 3) neurological criteria modified from Sarnat and Sarnat [5]: moderate to severe encephalopathy consisting of altered state of consciousness (irritability, lethargy, stupor or coma) and ≥ 1 of the following signs: hypotonia, or abnormal reflexes including oculomotor or pupil abnormalities, or absent or weak suctioning or clinical seizures; 4) moderately to severely abnormal aEEG pattern or seizures.

Exclusion criteria were: 1) gestational age<36 weeks or birth weight<1800 g or admitted at the NICU after 6 h of life; 2) major congenital abnormalities or other syndromes, including brain malformations, congenital viral infections or evidence encephalopathy other than hypoxic ischaemic encephalopathy (HIE); 3) informed consent refused.

All patients received moderate (33.5°C) whole-body hypothermia for 72 h, using a cooling servo controlled blanket with oesophageal and rectal temperature probes (Blanketrol III®, Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, Ohio). Subsequently, they were gradually re-warmed up to 36.5-37°C over the following 6–12 h (0.5°C/h). During the whole treatment, aEEG was continuously recorded by BrainZ® BRM3 Brain Monitor, Natus Medical Incorporated, San Carlos, CA USA.

We analyzed a subset of data collected for a registered trial, which was approved by the University of Pisa Ethics Committee. Informed consent was obtained from at least one parent prior to study entry. Parents received full verbal and written information regarding the objective and procedures of the study and the possible risks involved.

aEEG recording

A double-channel aEEG was continuously recorded by BrainZ® BRM3 Brain Monitor, Natus Medical Incorporated, San Carlos, CA USA. Brain monitoring started at admission to the NICU and lasted to the completed rewarming. Continuous visual validation of sensor contact quality was controlled through screen tinting. Nurses caring for patients were instructed and trained in marking events for capturing clinically relevant information during brain monitoring at bedside.

Thereafter, aEEG patterns were downloaded as digital files for offline analysis and archiving. Recorded data analysis was performed separately by a Neonatologist and a Development Neurologist. In particular, we compared aEEG pattern at admission in NICU (T0) and at 24 h of life (T1).

The aEEG background pattern (Figure 1) was classified as continuous normal voltage (CNV: continuous activity with voltage 10-25 μV), discontinuous normal voltage (DNV: discontinuous trace where the lower margin is <5 μV and the upper margin is >10 μV), continuous low voltage (CLV: continuous background pattern of very low voltage around or below 5 μV), burst suppression (BS: discontinuous background pattern; periods of very low voltage intermixed with burst of higher amplitude) and flat trace (FT: very low voltage, mainly inactive tracing with activity below 5 μV) [6]. Traces with CNV background pattern were classified as normal while DNV, CLV, BS and FT traces were classified as abnormal. Seizures were identified as periods of sudden increase in voltage, accompanied by narrowing of the band of aEEG activity and a subsequent brief period of suppression or a build-up of rhythmic activity of increasing amplitude and decreasing frequency. Repeated epileptic activity described status epilepticus (SE).The aEEG recordings were also assessed basing on voltage: normal (i.e., lower margin >5 μV and upper margin >10 μV) and abnormal (moderately abnormal, i.e., lower margin <5 μV and upper margin >10 μV or severely abnormal, i.e., lower margin <5 μV and upper margin <10 μV) [7].

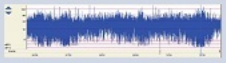
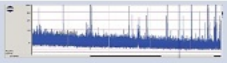
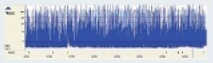
aEEG Pattern		Lower margin (μV)	Upper margin (μV)
Continuous normal voltage(CNV)		>5	>10
Discontinuous normal voltage (DNV)		<5	>10
Continuous low voltage (CLV)		<5	<10
Burst suppression (BS)		<5 (0-1)	>25
Flat Trace (FT)		<5	<5

Figure 1: aEEG patterns.

Neurodevelopmental outcome

Patients were evaluated during a specific neurodevelopmental follow up at 6, 12 and 18 months of age by examiners who were experienced clinicians specifically trained in test procedures.

We used standard series of measurements to assess the motor (fine and gross), language (receptive and expressive) and cognitive development. The test was administered on an individual basis. Raw scores of successfully completed items were converted to scale scores (Bayley Scales of Infant Development, BSID III) [8].

To our purpose, we specifically analyzed BSID data relating to mental scale and motor scale. Mental scale evaluated several types of abilities: sensory/perceptual acuities, discriminations, and response, acquisition of object constancy, memory learning and problem solving, vocalization and beginning of verbal communication, basis of abstract thinking, habituation, mental mapping, complex language, and

mathematical concept formation. This part of the evaluation yielded a score called the Mental Development Index (MDI).

Motor scale assessed the degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, dynamic movement, postural imitation, and the ability to recognize objects by sense of touch (stereognosis). The subsequent score is called Psychomotor Developmental Index (PDI). Both the mental and motor scales have reported high correlation coefficients (0.83 and 0.77, respectively) for test-retest reliability [9].

We classified poor outcome with MDI<70. Good outcome was defined with Mental Developmental Index and Psychomotor Developmental Index ≥ 70. Death prior to follow up ending was independently included in poor outcome.

Patient	Inclusion Criteria				
	A (history)			B (clinics)	C (aEEG)
	Apgar (10 min)	Cord blood gases	Resuscitation to 10 min	Examination at 60'	aEEG background
1	4	Not performed	Yes	Sarnat II	DNV
2	7	Not performed	Yes	Sarnat III	CLV
3	5	pH 6.88; BE-15.4	Yes	No	DNV
4	5	pH 7; BE-18.9	Yes	Sarnat III	CLV
5	2	pH 6.65; BE-29	Yes	Sarnat III	FT
6	6	pH 6.86; BE-18,7	Yes	Sarnat II	DNV
7	5	pH 6.82; BE-21,1	Yes	No	DNV
8	5	pH 6.96; BE-14.4	Yes	Sarnat III	FT
9	6	Not performed	Yes	No	DNV
10	4	Not performed	Yes	Sarnat III	SE
11	5	Not performed	Yes	No	DNV
12	4	pH 6.61; BE-23.9	Yes	Sarnat III	FT
13	4	Not performed	Yes	No	DNV
14	5	Not performed	No	No	DNV
15	3	pH 6.81; BE-22	Yes	No	BS
16	5	pH 7.06; BE-13.8	Yes	No	DNV
17	5	pH 6.79; BE-20.3	Yes	Sarnat III	BS
18	9	pH 6.94; BE -16.1	No	No	DNV
19	7	Not performed	Yes	No	BS
20	7	pH 6.77; BE-22	Yes	Sarnat II	DNV
21	6	pH 6.60; BE-30.9	Yes	Sarnat II	CLV
22	6	pH 6.79; BE: /	Yes	Sarnat III	FT
23	5	Not performed	Yes	No	DNV
24	7	pH 6.93; BE-14.4	No	No	DNV

Table 1: Patient clinical characteristics at the study enrollment.

Statistical analysis

Data were collected in a database and processed with statistical software MedCalc® Version 9.3.7. The comparison between groups for categorical variables was performed using Chi-squared test. P-value was considered significant as <0.05.

Results

According to the inclusion criteria, all recruited infants had moderate to severe perinatal asphyxia. At cord blood analysis median pH was 6.93 ± 0.14 and median BE -20.4 ± 5.04 (Table 1).

All newborns received the same analgesic therapy (fentanyl at the same dosage, 1 μg/kg/h) during hypothermic treatment. Five patients received also topiramate during hypothermia for neuroprotection co-treatment (three patients with moderate encephalopathy and two with severe encephalopathy). Most new-borns were out born so that admission to NICU (i.e., T0 for aEEG recording) was at an overall median age of 4 h after birth. At T0 13/24 neonates presented with a discontinuous aEEG pattern, i.e., moderately abnormal (group 1), while 11/24 showed severe aEEG abnormalities (group 2). Within group 2, 3/11 neonates had a BS background pattern (subgroup A), 3/11 neonates had CLV background pattern (subgroup B), 4/11 neonates had a FT background pattern (subgroup C) and 1/11 was suffering from a status epilepticus, SE (subgroup D) (Figure 2).

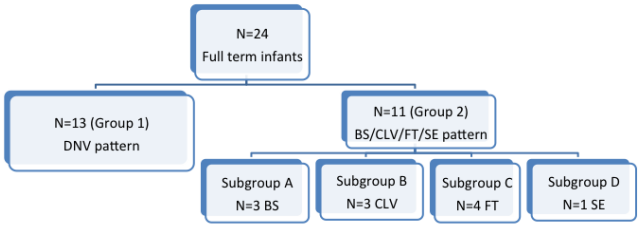


Figure 2: aEEG pattern at study enrollment.

In group 1, at T1 11/13 infants improved to CNV, while 2/13 worsened to a CLV pattern. In group 2, patients in subgroup A at T1 persisted BS (2/3) or turned to FT pattern (1/3). In subgroup B 1/3 infant showed the same CLV pattern at T1 instead 2/3 infant worsened to FT pattern. In subgroup C, at T1 1/4 neonate recovered to CNV while 1/4 was CLV and 2/4 persisted FT. The neonate with SE, at T1 changed to CLV.

As regards the outcome, aEEG pattern at T0 (i.e., belonging to group 1 or 2) did not correlate with MDI/PDI (p=n.s.). On the contrary, considering aEEG records at T1, data were statistically significant. All 11/13 patients who had CNV in group 1 had thereafter a normal neurodevelopmental outcome. That 2/13 with a CLV pattern developed a severe disability (i.e., dyskinetic cerebral palsy). Considering neonates in group 2 subgroup A had a poor outcome, developing severe disability (those 2/3 BS) or dying (1/3 FT). A similar outcome was verified for infants in subgroup B (2/3 cerebral palsy, 1/3 early death at 48 h).In subgroup C, 1/4 (CNV at T1) did not develop any disability while the other 3 had a poor outcome (2/4 cerebral palsy, 1/4 death).Finally, the only newborn with SE at T0 and CLV at T1 developed a dyskinetic cerebral palsy. Correlations between aEEG variations at T1 and outcome are shown in Figure 3. At an overall analysis, aEEG normalization at 24 h of life was associated with a good outcome (i.e., normal or mild impairment) at a 18 month follow up ($p<0.05$).

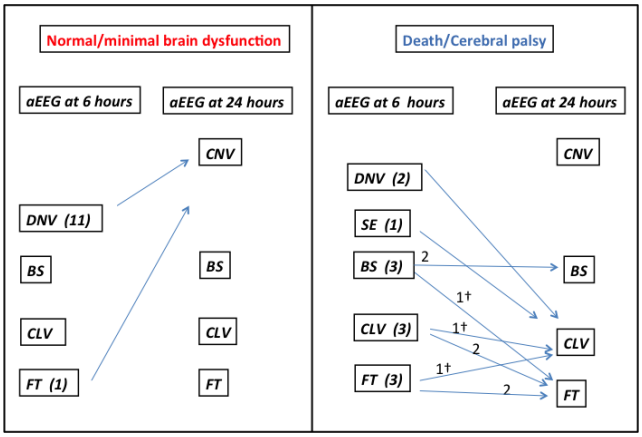


Figure 3: aEEG pattern variations from T0 to T1. Patients are divided in two groups, according to neurodevelopmental outcome.

Discussion

Previous studies demonstrated that the early aEEG background activity, recorded within 6 h after birth asphyxia, is a strong predictor of neurodevelopmental outcome [10]. Neonatologists assessed initial aEEG pattern to quantify the neurological damage and often considered brain activity of the first hours of life as a tool to decide the type of neonatal care. Subsequently other authors observed that the sensitivity of this tool increases if it is used during the first 72 h of life and that the modification of aEEG pattern within the third day of life correlates with the neurological outcome [11]. In fact an abnormal aEEG trace persisting during the first days of life after birth asphyxia correlates with a poor outcome. On the contrary a recovery of amplitude integrated electroencephalographic background correlates with a good outcome. In our study 11/24 patients were admitted to NICU with severe aEEG abnormalities but not all of them developed disability. One neonate at 4 h of life showed severe aEEG abnormalities (flat trace) but then at 24 h the trace improved to continuous normal voltage and he did not develop any disability. In this specific case an early assessment of the outcome at 4 or 6 h of life would have wrongly predicted the outcome. Instead 13/24 patients presented moderate aEEG abnormalities but two of them showed worsened traces at 24 h and developed disability. We observed that the aEEG pattern at 24 h of hypothermia is a better predictor of neurodevelopmental outcome than the aEEG pattern at 6 h. Patients that changed aEEG pattern from T0 to T1 did not receive topiramate. We can say that topiramate did not affect our results. The neuroprotection role of topiramate will be assessing at the end of a further study because some patients co-treated with hypothermia/topiramate are still in follow-up. Van Rooij et al. [3] confirmed that normalization of aEEG pattern within 24 h of perinatal asphyxia predicts a good neurodevelopmental outcome. Our data are in line with this previous study and stress the importance of continuous monitoring of brain activity, showing the importance of the modification of aEEG pattern. Thoresen et al. [12] demonstrated that in infants who were treated with hypothermia the predictive value of an early abnormal aEEG background is reduced. Hypothermia probably delays by itself the recovery. Infact they demonstrated that an infant who is cared for at normothermia can survive with a normal outcome if the aEEG recovers beyond 24 h after birth; however a hypothermia-treated infant could still develop normally as long as the

aEEG recovers before 48 h. Despite the small number of patients in our study we demonstrated that neonates who during hypothermia showed normalized aEEG background pattern until 24 h exhibit a good outcome at 18 months, while neonates who had abnormal aEEG at that time died or experienced a poor outcome.

Conclusion

This study confirms the prognostic value of aEEG patterns. Amplitude integrated electroencephalography (aEEG) is an easy tool that neonatologist can use to evaluate brain activity. Asphyxiated infants who present with a moderate to severe abnormal aEEG but who achieve a recovery to a normal aEEG background pattern within the first 24 h of life have a good chance of a normal outcome. In contrast, abnormal aEEG pattern persisting after 24 h of life correlates with poor outcome (death or cerebral palsy).

Limits of the Study

The limit of this work is that we enrolled only a limited number of patients (24) and the conclusions of the study cannot be generalized. Further studies on a larger cohort will be needed to confirm our data.

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