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ABSTRACT

OBJECTIVES: Our objective was to evaluate the potential additional value of electroencephalogram (EEG) and evoked potentials in neonates with hypoxic-ischemic encephalopathy to predict their disability at 1 and 2 years old.

METHODS: 30 full-term infants after perinatal asphyxia who underwent therapeutic hypothermia were evaluated at 1 year and 2 years for disability using International Classification of Functioning, Disability and Health classification. Scores for EEG, sensory evoked potentials and brainstem auditory evoked potentials were evaluated after withdrawal of therapeutic hypothermia that lasted 72 hours. A regression approach was investigated to build models allowing to distinguish neonates according to their disability at 1 and 2 years. Two models were built, the first by considering the clinical data and EEG before and after therapeutic hypothermia and the second by incorporating evoked potentials recording.

RESULTS: Adding EEG and evoked potentials data after rewarming improved dramatically the accuracy of the model considering outcome at 1 and 2 years

INTERPRETATION: We propose to record systematically EEG and evoked potentials following rewarming to predict the outcome of neonates with hypoxic ischemic encephalopathy. Combination of altered evoked potentials with no improvement of EEG after rewarming appeared to be a robust criterion for a poor outcome.

KEYWORDS:

Perinatal asphyxia; hypoxic ischemic encephalopathy; neonatal EEG; Evoked potentials;

Highlights:

- Outcome of neonates with HIE remains uncertain
- Adding EEG and EP data after rewarming to clinical data improved the accuracy of a prediction model
- EEG and EP should be performed after withdrawal of TH to predict the outcome of neonates with HIE.

Abbreviations

BAEP: Brain auditory evoked potentials
EEG: electroencephalogram
EP: evoked potentials
HIE: hypoxic ischemic encephalopathy
ICF: International Classification of Functioning, Disability and Health
SEP: somatosensory evoked potentials

Introduction

Perinatal asphyxia is a common cause of neonatal death and long-term disabilities [1,2]. The degree of cerebral injury after perinatal hypoxia is commonly evaluated by clinical assessment, using scores such as the Sarnat score, which included electroencephalogram (EEG) in its original description [3]. Numerous studies have demonstrated that EEG provides an early and reliable evaluation of cerebral injury [4–6], also in neonates under hypothermia [5–7]. Indeed, the EEG background characteristics have a proven prognostic value after perinatal asphyxia [8–12]. This visual classification, adapted from Scavone and Pezzani [4,13], considers four severity grades (normal, mild, moderate and severe abnormalities) that correlates with long-term prognosis [14–16]. Burst suppression, low voltage and flat trace accurately predict neurodevelopmental outcome [17].

The use of multimodal evoked potentials (EP) in neonates with perinatal asphyxia to evaluate their future disability has already been addressed [18] but its additive value to EEG recordings remains subject to debate contrary to their use to evaluate outcome after cardiac arrest in adults [19]. Old studies as the one by Frank et al. 1985 [20] reported interest of EP in evaluating outcome in infants with hypoxia-ischemia. One of the advantages of EP is that they can be recorded at the bedside even in neonates and that they are minimally invasive[21]. Bilaterally absent somatosensory evoked potentials (SEPs) predict magnetic resonance imaging (MRI) injury and are associated with severe outcome in survivors of neonatal hypoxic ischemic encephalopathy (HIE)[22]. Even in the absence of MRI abnormalities, early neurophysiological recordings including EEG, SEPs and visual evoked potentials can predict neuropsychological outcome in HIE [23]. EP recorded with EEG predict outcome after perinatal asphyxia and have an additive value but the timing of the exams and the potential role of hypothermia were not addressed in this study.[18] Abnormal cortical N20 are present in up to 65 % of neonates with brain injury in HIE [24]. Neonates with HIE treated with TH with bilateral absent N20 may have a better prognosis with the use of TH according to Garfinkle et al [25]. However, SEPs are usually thought to be less reliable in neonates than in adults or in older children [26]. Cases of neonates without cortical SEPs without neurological disease have also been reported [27,28] and some methodological concerns should also be taken into account. Nevertheless, associated with short latency Brain auditory evoked potentials (BAEPs), SEPs are of additional value in comatose children with hypoxic insults [29]. Contrary to cortical SEPs, BAEPs are more reliable in neonates although they remain subject to interference with peripheral diseases affecting the VIIIth nerve and of course hypoxemia [30].

The aim of this study was to determine if the use of multimodal EP combined with EEG rating can better predict the outcome of neonates with HIE after rewarming. We expect an additive value of the use of EP to the EEG to determine outcome at 1 and 2 years.

Methods

Patients

Between 2013 and 2015, 45 neonates were placed under therapeutic hypothermia (TH) for HIE in our neonatal intensive care unit (NICU). In this study, we included 30 neonates placed under TH for HIE who all had multimodal EP (both SEP and BAEP) at the withdrawal of TH, following rewarming, associated with continuous EEG. Neonates who didn't have multimodal EP (for 7 neonates, no EP were performed, for 4 neonates, one modality, either SEP or BAEP wasn't performed for various reasons, mainly agitation with no sedation possible) or for who the outcome at 1 or 2 year was missing (4 neonates) were excluded.

TH criteria were as follows [31]: gestational age ≥ 36 weeks; birth weight > 1800 g; post-natal age ≤ H6; pH ≤ 7 or base deficit ≥ 16 mmol/L or lactate ≥ 11 mmol/L before 1 hour of life (measured in umbilical cord, capillary, venous or arterial blood); or Apgar score ≤ 5 at 10 minutes of life, or ventilatory support (intubation or mask ventilation) needed at birth and continued at 10 min of life, signs of moderate or severe HIE : stage 2 or 3 in Sarnat classification; initial EEG or aEEG (performed before H6 of life) grade 2 or 3 according to the French Classification(Annex 1). Newborns were excluded if another cause of metabolic acidosis or encephalopathy was suspected, such as congenital heart disease or inborn errors of metabolism. TH was maintained between 32 and 34°C for at least 72 hours. Initial EEG was recorded within 6 hours of life and then continuously during TH. EP were performed after discontinuation of TH (minimum: 6 hours, maximum: 24 hours) after rewarming (SEP and BAEP were performed at the same time). Indeed, although TH is not supposed to alter EP[32,33], a few examples of a possible influence of TH on EP is present[34]. Light sedation (morphine or sufentanyl IV) was accepted.

Outcome

Clinical follow-up was systematically proposed and clinical data were collected from medical visits reports. Neurological assessment was graded from 0 to 4 at one and two years of age using a score adapted from the ICF (International Classification of Functioning, Disability and Health) classification (Annex 2). For the analyses, children were separated into two groups of good and poor outcomes, the latter being defined as significant sequelae (score ≥ 3) or death (grade 5).

The study has been previously declared to the National Commission of Information Technology and Liberties. The parents were informed by a written document of the anonymized use of data and non-opposition consent was obtained.

EEG recordings

EEGs were recorded, using the Micromed EEG System®. Initial EEG was recorded in the first 6 hours of life, before the initiation of controlled TH, then the recording was continuous during TH and until 6 hours after rewarming. Grades of initial EEG and EEG after 6 hours after rewarming were taken into account for this study. Eight scalp electrodes (F4, C4, T4, O2, F3, C3, T3, O1), one ground electrode and one reference electrode were positioned according to the international 10:20 electrode placement system, modified for neonates. After scalp cleaning, cup electrodes were fixed using adhesive tape and secured by a net. The electrode impedance was maintained below 5 kOhm. The EEG signals were digitized at a sampling rate of 256 Hz and stored on a computer hard drive and read on the System Plus Evolution Software® (Micromed SAS, Mâcon, France). EMGs and ECGs were concomitantly recorded and stored on the same disk.

EEG classification

The visual analysis of initial EEG was conducted on a bipolar display montage, with 0.53–70 Hz digital filters, an amplitude of 100 µV/cm and a display of 30 mm/sec. HIE severity grade from 0 to 3 was assessed using the French classification (Annex 1). Grades 0 and 1 were respectively normal or subnormal EEGs, grades 2 and 3 corresponded respectively to moderate and severe anomalies. Spikes and seizures (defined as a sudden, repetitive, stereotyped discharge lasting at least 10 seconds [35]) were also noted. EEGs were graded before TH and after discontinuation of TH.

Evoked potentials recording

SEPs were recorded by stimulating the median nerves at wrist at supra-motor threshold. For the median nerve, active surface electrodes were placed at the Erb's point, fifth cervical vertebra level and at the contralateral parietal level at Pi or Pc, 2 cm behind C3 and C4 as defined by the 10-20 international system. The reference electrode was placed at FPz (scalp electrodes) and/or contralateral ear. Three series of up to 300 traces were recorded (frequency 1.1 Hz).

BAEPs were recorded using supra-aural earphones at 80 dB. Three series of 1000 clicks were recorded. They were read on the System Plus Evolution Software® (Micromed SAS, Mâcon, France).

Evoked potentials classification

To analyze SEP responses, we considered the integrity of peripheral (N9), cervical (N13) and cervico-bulbar junction (P14) components before further analysis. The amplitude of N20 wave was calculated on the signal obtained from the off-line subtraction of Pi-earlobe from Pc-earlobe recordings, to avoid the influence of subcortical potentials including the widespread N18 component. We measured peak-to-peak amplitudes of the N20 component. For the latter measurement, we used the peak of the first positivity following the N20 peak. We adapted the classification proposed by Logi [36]: Grade 1.

Normal cortical SEP (amplitude and latency), Grade 2. Increased latency of N20 component (bilateral). Grade 3. Reduced amplitude. Grade 4. Absent (bilateral). For BAEP: Grade I. Normal, Grade 2. Increased latency of wave V or increased interpeak delay I-V or III-V, Grade 3. Decreased V/I < 0.5, Grade 4. V waves absent. See annex 3 for an example of grading.

Statistical analyses

Demographic, clinical as well as EEG and EP characteristics were described by the mean and standard deviation. Differences between the characteristics at the two outcomes: one year and two years, were tested using one –way ANOVA or chi-squared test for categorical data. Performance of each individual electrophysiological exam was assessed using receiver operating characteristic (ROC) curves, the following metrics were derived: sensitivity measured as the percentage of true positives, the specificity measured as the percentage of true negatives, the negative predictive value (NPV) computed as the ratio of negative results and true negative results and lastly the positive predictive value (PPV) defined as the ration of positive results and true positive results.

In order to investigate the predictive abilities of the EP characteristics, logistic regression models were built for each outcome, two models by outcome. The first included as covariables, the gestational age, the weight, the Sarnat's and the Apgar's scores and the EEG grades at day 1 and following rewarming, while the second added to these variables the EP characteristics (SEP and BAEP). Performances of each model were assessed using confusion matrices and ROC curve and the area under the curve (AUC).

All the analyses were done using the XLStat software (Addinsoft (2019). XLSTAT statistical and data analysis solution. Long Island, NY, USA. https://www.xlstat.com.)

Results

Characteristics of the population

The demographic and perinatal characteristics of the 30 infants were not different (including for laboratory results). No differences existed between the different outcomes in terms of perinatal characteristics. Considering ICF score at 2 years, in score 0: 73 % of neonates were sedated during the exams; in score 1: 50 %; in score 2: 48 %; in score 3: 91 % and in score 4-5: 60 % (chi square, no differences). The most severe outcomes at 1 and 2 years differed in EEG grades, EP grades following rewarming (Table 1).

AUC were > 0.7 to predict a bad outcome only for Grade EEG >2 after withdrawal of TH (AUC=0.838, outcome at 1 year; AUC=0.822 outcome at 2 years) and Grade SEP > 2 (AUC=0.868, outcome at 1

year and AUC=0.905, outcome at 2 years). PPV and NPV are reported in Table 1b. Specificity of Grade EEG > 2 after TH was poor.

Predictive values of the models including EEG and the combination EEG and EP

Performances of the model built using the demographic, clinical and EEG characteristics are summarized by the confusion matrices and the derived metrics represented in table 2 and the ROC curves in Figure 2.

When the EP characteristics were embedded in the modelling (SEP and BAEP after TH), the model was able to correctly classify all the infants (AUC= 1, specificity = 100% and sensibility = 100 %) for both prognostic models (1 and 2 years).

Discussion

Clinical characteristics, and in particular the Sarnat scores, of neonates at birth with signs of HIE who underwent TH, didn't differ between neonates with future good or bad outcome. Adding EEG (before and after TH) and EP data following rewarming improved accuracy with the best prediction of combination of clinical and neurophysiological data for all grades of disability.

It is recommended to combine clinical markers and initial EEG to evaluate the severity of HIE and to induce TH. However, performing an EEG after discontinuation of TH associated with EP gave additional information for further outcome at 1 and 2 years since neonates with a good outcome presented a dramatic improvement of EEG grade after TH. EEG has been scored to evaluate outcome of neonates[6,9,10]. We here confirmed that an initial grade 3 (severe abnormalities) alone was not sufficient to fully predict a poor outcome and that an improvement of EEG following TH was a criterion for a better outcome. This was in line with previous studies [6,9,10].However, specificity of EEG after TH remains low making this exam alone insufficient to predict outcome.

We used a very simple method to evaluate the grade of the EP in line with what has been proposed in adults to evaluate the severity of hypoxic encephalopathy [36]. However, neonates are not adults and one should be very cautious with the interpretation using this exam alone to predict future outcome. Absence of cortical N20 component after median nerve stimulation is considered in adults as a criterion of poor outcome (death or vegetative state) with a good sensitivity and an excellent specificity close to 100%. This is not the case in neonates who can have no N20 component and good outcome, even in absence of HIE[26]. We should first mention methodological reasons for no detection of cortical SEP response in normal neonates. The detection rate of SEPs, even in healthy neonates, is dependent of the number of stimulations (a lower number of stimulations could result in higher amplitudes of SEP[37,21]) and a smaller number of stimulations should be performed in some neonates if a gradual decrease of the amplitude is observed during the averaging. Other parameters should be taken into account, such as band-pass filtering, and a lower stimulation rate than in adults is

recommended [38]. Arousal state of neonates also modifies amplitude/latency of SEPs[39,26,37] and is more difficult to control in an ICU. Moreover, latency of the component is very variable in neonates and increased latency should not be interpreted as abnormal. BAEP are more robust in neonates but appear less sensitive to detect abnormalities. Previous literature showed that the predictive values of abnormal BAEP was poor[40]. Reliability of BAEPs is reduced in NHIE also by the susceptibility of the cochlea to the hypoxic ischemic insult. Moreover, the cochlea has higher susceptibility than central auditory pathways at the brainstem level generating the central BAEP components and to conductive hearing loss frequent in neonates during intensive care. Thus BAEPs are only reliable in neurological prognostication if the first peak is present, confirming the "peripheral integrity". However, combination of altered BAEP (absent or decreased V wave) and N20 (absent or decreased) with concordant EEG (Grade 2-3) after TH appeared to be a robust criterion for a poor outcome. Indeed, neonates with initial EEG Grade 2 or 3 and final EEG grade 2 were not classified adequately for 3 neonates at 1 year and for 4 additional neonates at 2 years using only EEG. All these neonates presented clearly abnormal multimodal EP.

We should acknowledge several limitations in our study: EEG and EP were performed after discontinuation of TH (at least 4-6h) and rewarming but some neonates were still under light sedation (IV morphine or sufentanyl) during the exams facilitating their realization. These drugs are known to have very little to no effect on EP amplitude or latency [41] but could have influenced the results. The absence of differences of sedated neonates between Grade 0 and 3 (chi square, p=0.18) was not in favor of a strong influence. Finally, the main problem was the possibility of recording these neonates after TH in the best conditions (no important sedation, possibility of coupling both exams, EEG and EP) knowing that an MRI was also frequently performed and required a sedation. We acknowledge that it could be difficult in centers that did not have a neurophysiological platform dedicated for children and neonates. Finally, some neonates were excluded of the study. Initial Grade 0 on EEG were not under TH and no follow-up with EEG or EP was proposed in these neonates. With these results, we recommend the systematic evaluation of EEG and EP in neonates with HIE after withdrawal of TH and rewarming to better predict outcome.

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Table 1a. Outcome of neonates at 1 and 2 years according to perinatal characteristics, EEG performed before and after therapeutic hypothermia (TH), after rewarming, sensory evoked potentials (SEP) and brainstem evoked potentials (BAEP) after TH. Mean ± standard deviation. GA: gestational age. ICF: International Classification of Functioning, Disability and Health

Table 1b. Predictive values of electrophysiological exams for bad outcome at 1 and 2 years.

a.

	Good at 1 year	Poor at 1 year	F	p		Good at 2 years	Poor at 2 years	F	p
GA (AW)	39.5 ± 1.0	39.5 ± 1.0	0.01	0.91	**GA (AW)**	39.4 ± 1.0	39.7 ± 1.0	0.5	0.49
Apgar	4.2 ± 2.7	4.9 ± 2.5	0.41	0.52	**Apgar**	4.4 ± 2.8	4.4 ± 2.4	0.0	0.95
Weight (mg)	3298 ± 702	3298 ± 508	0.11	0.74	**Weight (mg)**	3264 ± 703	3280 ± 548	0.0	0.94
Sarnat	2.2 ± 0.6	2.4 ± 0.7	0.64	0.42	**Sarnat**	2.2 ± 0.6	2.4 ± 0.7	1.1	0.30
Grade EEG day 1	2.5 ± 0.5	2.9 ± 0.3	3.9	0.06	**Grade EEG day 1**	2.5 ± 0.5	2.8 ± 0.4	2.5	0.12
Grade EEG day 3	1.6 ± 0.5	2.5 ± 0.5	19.1	<0.001	**Grade EEG day 3**	1.6 ± 0.5	2.4 ± 0.5	18.2	<0.0001
Grade SEP day 3	1.8 ± 0.9	3.6 ± 1.0	22.9	<0.0001	**Grade SEP day 3**	1.7 ± 0.8	3.6 ± 0.9	39.1	<0.0001
Grade BAEP day 3	2 ± 0.9	2.5 ± 0.8	2.1	0.16	**Grade BAEP day 3**	2.1 ± 0.9	2.25 ± 1.0	0.2	0.69
ICF 1 year	0.5 ± 0.8	4.4 ± 0.8	163.2	<0.0001	**ICF 2 years**	0.4 ± 0.7	4.2 ± 0.9	154.2	<0.0001

b.

Outcome at 1 yr	Threshold >	Sensitivity	Specificity	PPV	NPV	Outcome at 2 yrs	Threshold >	Sensitivity	Specificity	PPV	NPV
Grade EEG before TH	2	90%	45%	45%	90%	**Grade EEG before TH**	2	1	44%	50%	80%
Grade EEG after TH	2	50%	100%	100%	80%	**Grade EEG after TH**	2	0	100%	100%	72%
Grade SEP after TH	2	90%	85%	75%	94%	**Grade SEP after TH**	2	1	94%	92%	94%
Grade BAEP after TH	2	70%	60%	47%	80%	**Grade BAEP after TH**	2	1	56%	47%	67%

Table 2. Confusion matrices and the evaluation metrics of the predictive models built using the combination of EEG, demographic and clinical characteristics. (a) Model for the prognosis at 1 year and (b) model for the prognosis at 2 years.

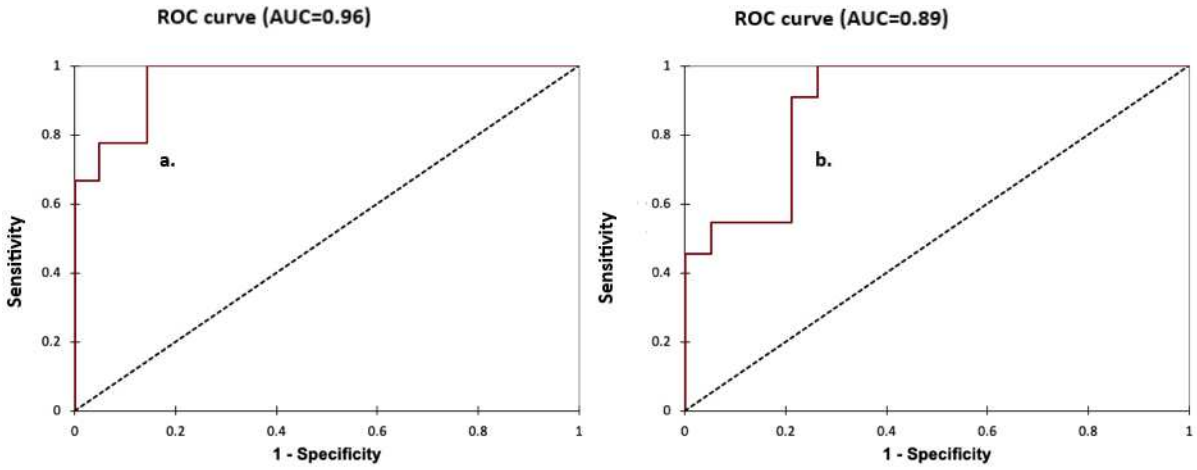
(a)

	Good outcome	**Poor outcome**
Good outcome	20	1
Poor outcome	2	7
Specificity	78%	
Sensitivity	95%	
Negative predictive value	88%	
Positive predictive value	91%	

(b)

	Good outcome	**Poor outcome**
Good outcome	17	2
Poor outcome	5	6
Specificity	55%	
Sensitivity	89%	
Negative predictive value	75%	
Positive predictive value	77%	

Figure 1. Receiver operating characteristic curves for the predictive models built using the demographic, clinical and EEG characteristics. (a) Prognosis at 1 year and (b) prognosis at 2 years.



(a) (b)

Annex 1

French classification of HIE EEG grades after perinatal asphyxia (Lamblin 2013)

HIE grade	EEG	Description
0	Normal for gestational age	"Activité moyenne" (continuous background pattern) or "tracé alternant" (during quiet sleep) with physiological figures ("encoches frontales", "dysrythmie lente antérieure"), temporo-spatial organisation with sleep-wake cycling (SWC) and reactivity.
1	Mild abnormalities	Frequent spikes or mild amplitude depression (30–50 µV) or transitory discontinuity with conserved organisation, SWC and reactivity.
2	Moderate abnormalities	**Discontinuous tracing type A**: burst (physiological amplitude and morphology) for 10–30 sec, IBI (< 10 µV) for < 10 sec, with conserved spatial organisation, lability and reactivity but no identifiable SWC. **Discontinuous tracing type B**: burst (30–50 µV) for 10–30 sec, IBI (< 10 µV) for < 10 sec, no physiological element or organisation, lack of lability. **Hyperactive rapid tracing**: continuous background activity with physiological features intermingled with abundant ample and diffuse waves of 4–12 Hz. Lack of lability and reactivity, no SWC. **Slow EEG**: continuous background activity with diffuse delta waves of 0.5–1.5 Hz in wakefulness and sleep, amplitude < 50 µV. Lack of lability and reactivity, no SWC.
3	Severe abnormalities	**Paroxysmal tracing**: burst (spikes with theta and delta

	waves) for 1–10 sec, IBI (< 5 μV) for 10–60 sec without physiological figures. No temporo-spatial organisation, no lability, no SWC. **Low voltage plus theta tracing**: burst of theta frequencies (5–15 μV) of varying length, background activity with very low amplitude of < 15 μV, without physiological figures. No temporo-spatial organisation, no lability, no SWC. **Inactive tracing:** very depressed continuous background activity with amplitude of < 5 μV or IBI (< 5 μV) for > 60 sec, without physiological figures. No temporo-spatial organisation, no lability, no SWC.

cEEG: conventional EEG; IBI: interburst interval; SWC: sleep-wake cycles

Annex 2

ICF score – This clinical score (0–4) is adapted from the International Classification of Functioning, Disability and Health (World Health Organization Geneva, 2002). 1 point is assigned for each category of impairment.

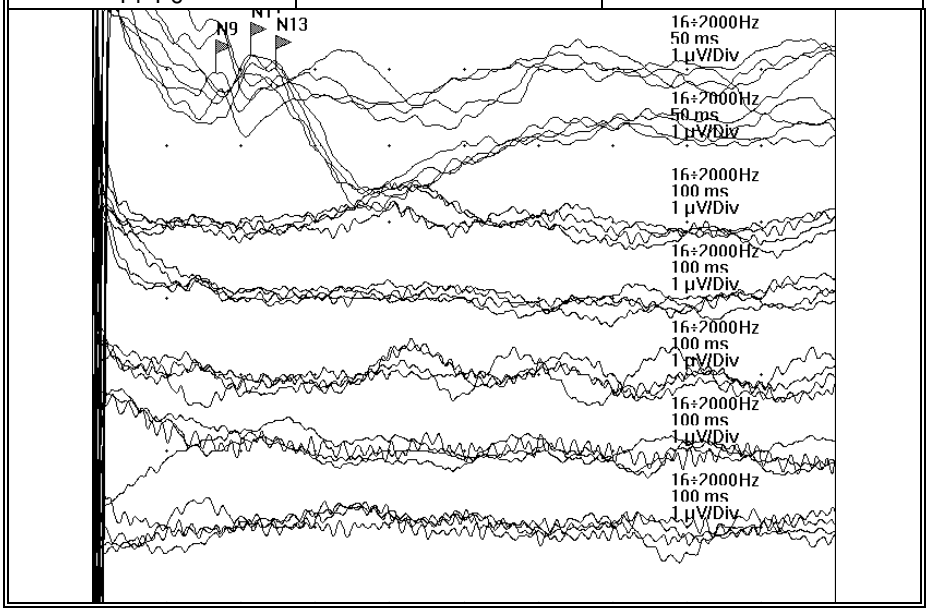
Scoring	Category of impairment	Example
1 point	Body structure or function impairment*	Axial hypotonia or hypertonia, paresis, spasticity, ataxia, sensory loss, etc.
1 point	Activity limitation	At 1 year: lack of head control, sitting posture not acquired At 2 years: inability to walk, no language
1 point	Participation restriction	Impact on family life

**If several body structures or functions are impaired, the sum of impairment is listed in the "amount" category. If the amount is ≥ 4, 1 point is added to the final score.*

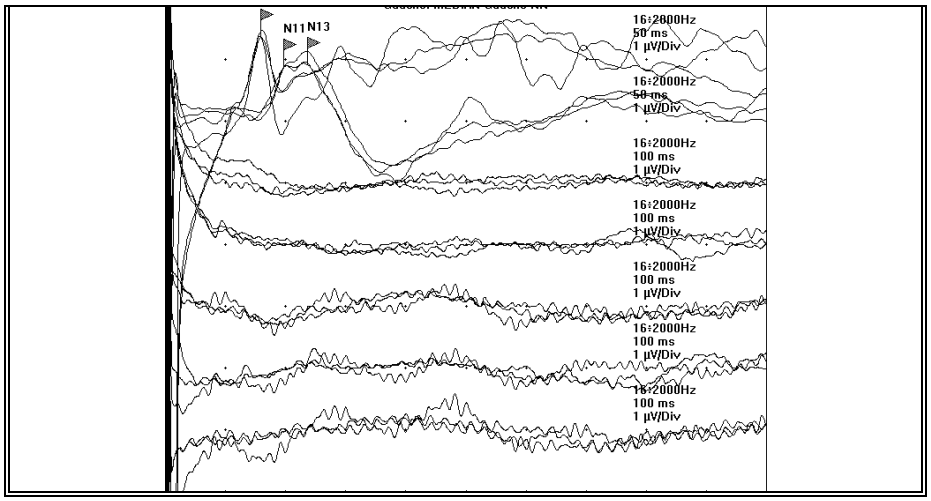
Annex 3

Example of somatosensory evoked potentials, stimulation of right and left median nerves at the wrist, intensity: 11mA right, 13mA left in a neonate after withdrawal of therapeutic hypothermia. Peripheral N9 and cervical N13 components were present bilaterally. No contralateral cortical component was observed. It was considered as a Grade 4. Brain evoked potentials (90dB) were also recorded, only waves I were recorded. It was considered as a Grade 4. Pi: parietal ipsilateral, Pc: parietal contralateral.

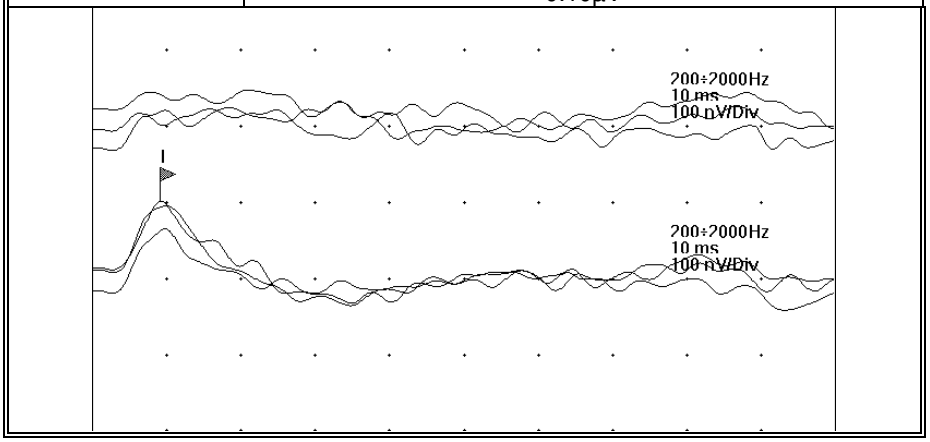
Right Median	Latency Amplitude	Latency Amplitude
A1 Erb	N9 8,30ms 0.50 µV	
A1 C5	N11 10.68ms 1.18µV	N13 12.33ms 1.01µV
Fz Pc		
A1 Pi		
Fz Pc		
A2 Pi		
Pi Pc		



Left Median	Latency Amplitude	Latency Amplitude
A2 Erb	N9 7.93ms 0.38µV	
A2 C5	N11 9.89ms 0.89µV	N13 11.84ms 0.92µV
Fz Pi		
A1 Pi		
Fz Pc		
A2 Pc		
Pi Pc		



Left BAEP	Latency Amplitude
Cz A2	
Cz A1	I 0.92ms 0.10µV



Right BAEP	Latency Amplitude
Cz A2	I 0.98ms 0.12µV
Cz A1