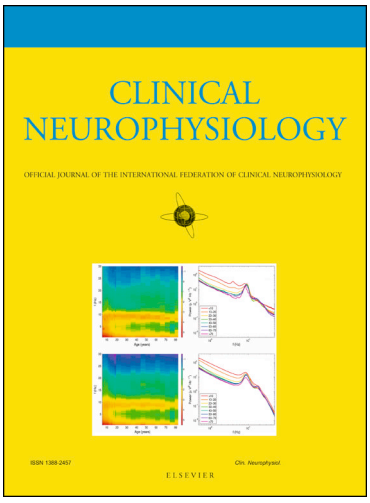


Bilateral loss of cortical SEPs predict severe MRI lesions in neonatal hypoxic ischemic encephalopathy treated with hypothermia

Agnese Suppiej, Ambra Cappellari, Giacomo Talenti, Elisa Cainelli, Matteo Di Capua, Augusta Janes, Daniela Longo, Rodica Mardari, Cristina Marinaccio, Stefano Pro, Paola Sciortino, Daniele Trevisanuto, Roberta Vittorini, Renzo Manara

PII: S1388-2457(17)31115-X
DOI: https://doi.org/10.1016/j.clinph.2017.10.020
Reference: CLINPH 2008311

To appear in: *Clinical Neurophysiology*

Accepted Date: 27 October 2017

Please cite this article as: Suppiej, A., Cappellari, A., Talenti, G., Cainelli, E., Di Capua, M., Janes, A., Longo, D., Mardari, R., Marinaccio, C., Pro, S., Sciortino, P., Trevisanuto, D., Vittorini, R., Manara, R., Bilateral loss of cortical SEPs predict severe MRI lesions in neonatal hypoxic ischemic encephalopathy treated with hypothermia, *Clinical Neurophysiology* (2017), doi: https://doi.org/10.1016/j.clinph.2017.10.020

Bilateral loss of cortical SEPs predict severe MRI lesions in neonatal hypoxic ischemic encephalopathy treated with hypothermia

Agnese Suppiej[a], Ambra Cappellari[a], Giacomo Talenti[b], Elisa Cainelli[a], Matteo Di Capua[c], Augusta Janes[d], Daniela Longo[e], Rodica Mardari[b], Cristina Marinaccio[f], Stefano Pro[c], Paola Sciortino[g], Daniele Trevisanuto[h], Roberta Vittorini[f], Renzo Manara[i].

[a] Child Neurology and Clinical Neurophysiology, Pediatric University Hospital of Padova, Italy

[b] Neuroradiology Unit, University Hospital of Padova, Italy

[c] Neurophysiology Unit, Department of Neuroscience, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

[d] Terapia intensiva Neonatale Azienda Sanitaria Unica Integrata SMM Udine, Italy

[e] Neuroradiology Unit, Ospedale Pediatrico Bambino Gesù - IRCCS – Roma, Italy

[f] SC Neuropsichiatria Infantile Dipartimento di Pediatria e Specialità Pediatriche, A.O.U. Città della Salute e della Scienza Torino,Presidio OIRM, Italy

[g] SC Neuroradiologia, Dipartimento di Diagnostica per Immagini e Radioterapia, A.O.U. Città della Salute e della Scienza Torino, Presidio CTO, Italy

[h] Neonatal Intensive Care Unit, Pediatric University Hospital of Padova, Italy

[i] Neuroradiology, University of Salerno, Italy

Corresponding author:

Agnese Suppiej

Child Neurology and Clinical Neurophysiology,

Paediatric University Hospital

Via Giustiniani, 3 35128 Padova, Italy

Tel.: +39 49 8218094

E-mail: agnese.suppiej@unipd.it

Highlights

1. Bilaterally absent SEPs predict MRI injury in infants cooled for hypoxic ischemic encephalopathy.
2. Normal MRI is usually associated with normal SEPs.
3. Therapeutic hypothermia does not seem to affect prognostic reliability of SEPs.

Abbreviations: SEP, somatosensory evoked potentials; NE, neonatal encephalopathy; MRI, magnetic resonance imaging; EEG electroencephalogram; TH, therapeutic hypothermia; HIE, hypoxic-ischemic encephalopathy; WS, watershed; BG/T, basal ganglia/thalamus.

Abstract

Objective. The introduction of therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy calls for reevaluation of the prognostic role of somatosensory evoked potentials (SEPs).

Methods. Among 80 consecutive neonates undergoing hypothermia for hypoxic-ischemic encephalopathy, 58 performed SEPs and MRI at 4-14 days of life and were recruited in this multicenter study. SEPs were scored as: 0 (bilaterally/unilaterally recorded N20) or 1 (bilaterally absent N20). The severity of brain injury was scored using MRI.

Results. Bilaterally absent N20 was observed in 10/58 neonates (17%); all had moderate/severe MRI abnormalities; 36/48 neonates (75%) with score 0 at SEPs had normal MRI. The positive predictive value of SEPs on MRI outcome was of 1.00, while the negative predictive value 0.72, sensitivity 0.48, specificity 1.00, with an accuracy of 0.78 ($p<.001$).

Conclusions. Bilateral absence of cortical SEPs predicts moderate/severe MRI pattern of injury.

Significance. Therapeutic hypothermia does not seem to significantly affect prognostic reliability of SEPs.

Keywords: perinatal asphyxia, cooled infants, evoked potentials, neonatal encephalopathy.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) in term neonates is a significant cause of infant mortality and morbidity. As a routine, early assessment of neonatal encephalopathy is based on clinical observation (graded by Sarnat and Sarnat, 1976), MRI and EEG recordings of brain electrical activity while the acquisition of somatosensory evoked potentials (SEPs) in the neonatal period is often hampered by logistic reasons. After moderate whole-body hypothermia (therapeutic hypothermia- TH) proved its efficacy and safety in reducing death and cerebral palsy and improving neurological outcome (Azzopardi et al, 2009), clinicians and researchers needed to test its influence on the most widely used prognostic tools.

Several MRI based severity scores have been repeatedly demonstrated to be strong predictors of outcome severity (Barkovich et al., 1998; Rutherford et al., 2010; Glass et al., 2011; Martinez-Biarge et al., 2012; Cheong et al., 2012) both in normothermic and hypothermic patients, even when the follow-up is extended until childhood (Natarajan et al., 2016). According to these studies TH reduces the rate of lesions in any cerebral area and increases the number of negative scans. However, the predictive value of both early and late scans remains unaffected and neonatal MRI is an accepted surrogate outcome measure in neurophysiological studies (Glass et al, 2011).

In contrast, a few recent studies showed that the EEG predictive value after birth is negatively influenced by TH (Hallberg et al., 2010; Thoresen et al., 2010; Gucuyener et al., 2012), suggesting the need for alternative tools to complement clinical and imaging scores, in prognostic assessment.

SEPs are an extension of the clinical examination and complementary to neuroimaging since they inform on functional integrity of structures vulnerable to asphyxia. In adult survivors after cardiopulmonary arrest, SEPs have shown a major prognostic role (Robinson et al., 2003; Grippo et al., 2016) ensuing their inclusion in the practice parameters of the American Academy of Neurology (Wijdicks et al., 2006; 2010; Sandroni et al., 2014). The bilateral absence of cortical SEPs at 24 hours has an unfavorable prognostic significance since all patients die or remain in vegetative state. The prognostic role of SEPs in neonatal HIE has been less investigated but is supported by several studies (for a review see van Laerhoven et al., 2013). In particular, bilateral absence of cortical SEPs was shown to predict cerebral palsy, the most severe outcome among survivors (Suppiej et al., 2010). However, these data were obtained before TH became a standard of care in neonatal HIE (Azzopardi et al., 2009). After the advent of TH, the prognostic role of neonatal SEPs is still under investigated (Garfinkle et al., 2015).

Based on these observations, we conducted a multi-center prospective study aimed to test the prognostic value of SEPs in neonatal HIE treated with TH, correlating SEP data with previously validated neuroradiologic severity scores.

2. Materials and methods

2.1 Subjects

Neonates suffering from HIE and eligible for TH from four Italian Centers (Padova, Roma, Udine, Torino) during the period 1st March 2012 - 31 December 2015 were recruited if they had SEPs recordings and MRI between 4-14 days of life. Selection for TH included: 1) gestational age at birth ≥ 36weeks, 2) any of the following: arterial umbilical cord or first blood gas analysis (within 1 postnatal hour) with pH ≤ 7.0, cord and base excess <12, or 10-minute Apgar score < 5, or need for respiratory support at 10 minutes of life, and 3) moderate to severe encephalopathy within 6 hours of birth. Neonatal encephalopathy was graded according to Sarnat and Sarnat criteria (Sarnat and Sarnat, 1976).

Exclusion criteria were suspected or known congenital malformations and inborn errors of metabolism. TH was initiated as soon as possible after birth or at the time of referral from other hospitals and consisted of whole-body moderate hypothermia (target temperature 33.0-34.0°C) for 72 hours followed by a rewarming rate of approximately 0.5°C/h. All patients received Fentanil infusion throughout TH to prevent discomfort and shivering (1-2 microg/kg/h, with boluses as needed). All infants had attained normothermia at the time of SEPs recordings.

Ethics committees of each participating hospital approved the protocol, and the review of the clinical records, PE, and imaging data for this study.

2.2 Neurophysiological data

Methodology for SEP recordings was previously agreed between centers according to consensus obtained within the Pediatric Neurophysiology Study Group of the Italian Society of Clinical Neurophysiology. In brief, SEP responses were elicited by right and left median nerve stimulation with electrical pulses at motor threshold intensity, rate 0.5 Hz, duration 0.2 ms, time window 100 ms. We used a "Galileo NT" system (EBNeuro/Florence Italy) and recorded with Ag/AgCl cup electrodes secured with paste and gauze. The N13 spinal component was recorded at the 7th cervical vertebra with Fz reference. The cortical N20 component was recorded at the central location contralateral to stimulation (C3 or C4 of the International 10-20 System). We choose central locations (instead of centro-parietal locations used at older ages) to take into account anatomical data reporting that in the neonatal period the of posterior movement of the central sulcus due to increasing size of association areas of the frontal lobe has not yet occurred (Karniski 1992, Karniski et al 1992). For best identification of the N20 cortical component we used both C3-C4 and C3-Fz or C4-Fz montages and three filter settings 10–1,000 Hz, 5–5,000 Hz and 1–100 Hz since

filter setting may variably affect responses (Bongers-Schokking et al., 1989). The number of sweeps used varied depending on signal to noise ratio during recordings in the hostile NICU environment, usually 30–40 responses with a maximum of 100 responses, to take into account habituation, were averaged and repeated two to four times to ensure reproducibility (Bongers-Schokking et al., 1989). Curarization was not used.

Recordings were done in active sleep or awake state (Suppiej et al., 2010). The behavioral state of the neonate was monitored by behavioral scoring (Suppiej et al., 2010). Only the N20 component in the presence of a normal cervical potential N13 was considered for analysis and scored as follows: bilaterally/unilaterally recorded (score 0); bilaterally absent (score 1). It is known that unilaterally present neonatal SEP has a prognostic value lower than bilaterally absent N20 or normal SEP (Suppiej et al 2010). Since our focus was on the more severe outcome measure i.e the bilaterally absent N20 pattern, and our population did not allow separate analysis, we choose to include unilaterally recorded SEP in score 0. All evoked potentials recordings were interpreted by the same neurophysiologist (A.C.) and agreed independently by a second neurophysiologist (A.S.), both blind to the clinical history and MRI data.

2.3 Neuroradiological data

Infants underwent MRI using a specialized neonatal head coil on 1.5-T SignaEchoSpeed system (GE Medical Systems, Waukesha, Wisconsin) or 1.5 T Achieva scanner (Philips, Best, The Netherlands), at a median age of 6 days (range 4-14 days).

Imaging sequences, including spoiled gradient echo volumetric T1-weighted, axial spin-echo T2-weighted and Diffusion-Weighted Imaging MRI (DWI), were optimized for the neonatal brain, as described previously. The severity of brain injury was assessed on all available sequences. Two pediatric neuroradiologists (R.M. and G.T.) who were blinded to the clinical history evaluated the MRIs. We used a previously validated MR scoring system (Barkovich et al., 1998; Bonifacio et al., 2011) for acute and subacute signal abnormalities, evaluating the extent of injury in the basal ganglia/thalami (BG/T) region (scored from 0 to 4) and watershed (WS) region (scored from 0 to 5). Each sequence (T1, T2 and DWI) was assigned a BG/T and WS score and eventually a global score was assigned to each patient after combining the information from DWI (acute changes) and T1/T2 sequences (acute and chronic changes). Scores represent the extent of injury observed, and were used to categorize images into two additional outcome measures based on the predominant pattern of injury: WS predominant, or BG/T predominant. The WS pattern was assigned when the WS region scores were higher than the BG/T scores. The BG/T pattern was assigned when the BG/T scores were higher or as high as the WS region scores. Neonates with total brain injury

(maximum BG/T and WS scores) were assigned to the BG/T pattern. A dichotomous outcome of normal-mild injury (normal imaging or WS score of ≤ 2 or BG/T score of ≤ 1) vs. moderate-severe brain injury (WS score of ≥ 3 or BG/T score of ≥ 2) was modeled after a similar classification scheme was found to be highly predictive for neurologic disability at age 18 months in neonates treated with hypothermia (Rutherford et al., 2010).

2.4 Statistical analysis

Pearson's Chi-Square and Fisher Exact test were used for dichotomous variable. The sensitivity and specificity of the used tests were also considered. All analyses used STATISTICA 6.0 for Windows (StatSoft, Tulsa, OK).

3. Results

Twenty-two out of 80 eligible patients were excluded from analysis because of death or transfer in other hospitals before MRI (3 patients) and SEPs (9 patients) or because of artefactual and non-interpretable SEP traces (10 patients).

Thus, 58 neonates were finally included in the analysis.

Clinical characteristics of the patients are summarized in Table 1.

The N20 component of SEPs was bilaterally absent in 10/58 (17%) HIE neonates, all had moderate/severe MRI abnormalities. The N20 was at least unilaterally detected (score 0) in 48/58 (83%) of whom 36/48 (75%) had normal MRI. Considering the 12/48 infants with SEP score 0 and abnormal MRI, 6/12 did not have a normal SEP since they had the N20 component that was absent unilaterally, while the other six had bilaterally present N20. Figure 1 represents, as an example, the N20 cortical response of upper limb SEPs recorded on day 7 in a neonate affected by moderate post asphyxia encephalopathy in whom the the MRI was normal on day 6.

Cross tabulation of SEPs scores (bilateral + monolateral presence *vs* bilateral absence) and the dichotomous outcome of normal-mild injury (normal imaging or WS score of ≤ 2 or BG/T score of ≤ 1) *vs* moderate-severe brain injury (WS score of ≥ 3 or BG/T score of ≥ 2) MRI results are listed in Table 2.

SEPs showed a positive predictive value for moderate-severe MRI abnormalities of 1.00 and a negative predictive value of 0.72, sensitivity 0.48 and specificity 1.00, with an accuracy of 0.78 ($p<.001$).

Table 3 reports the summary frequencies of SEP score (0: bilateral + monolateral presence; 1: bilateral absence) and MRI localization of lesions (no injury, injury in BG/T, injury in WS, injury in BG/T and WS. It can be seen that the prevalent pattern of injury in our population is the occurrence

of both BG/T and WS abnormalities (11/22 patients); in the majority of them (7/11), the N20 component was bilaterally absent. This pattern occurred also in the two patients with isolated BG/T involvement. The group of infants with SEP score 1 was too small and the confidence intervals too large to reach statistical significance.

4. Discussion

The present multicenter study showed that, in infants cooled for neonatal asphyxia, bilateral loss of the median nerve SEPs N20 cortical component reliably predicts the presence of severe HIE-related parenchymal brain changes.

Several studies before the advent of TH reported the efficacy of SEPs in predicting extreme clinical outcomes in HIE neonates (i.e. death and surviving with cerebral palsy) (De Vries et al., 1991; Majnemer and Rosenblatt, 1995; Scalais et al., 1998; Suppiej et al., 2010). Specificity of abnormal SEPs has been reported to vary from 73% to 85% (Gibson et al., 1992; Taylor et al., 1992; Eken et al., 1995; Swarte et al., 2012; Julkunen et al., 2014) increasing above 90% when cortical SEPs are bilaterally absent (Mandel et al., 2002; Suppiej et al., 2010; Bouwes et al., 2012). Since the introduction of TH, only two studies investigated the role of bilaterally absent SEPs in the management of HIE neonates. One of these studies (Garfinkle et al., 2015) disclosed a strikingly decreased predictive value for poor clinical outcome suggesting a negative effect of TH on SEP findings, while the other did not reveal significant differences when the predictive role of SEPs was compared between the populations of treated and not treated infants (Nevalainen et al., 2017). Differences in methodology might account for results variability as observed in previous studies; specific frequencies of electrical stimulation filter settings and accurate monitoring of the clinical state of the neonate are needed to take into account receptor, peripheral and central nervous system immaturity. Particularly important is to take into account the habituation phenomena. One possible explanation of the better positive predictive value of SEP in the present study, compared to Garfinkle et al (2015) may be methodology. We used a lower stimulation rate 0.5 Hz versus 4 Hz. The detection rate of SEPs, even in healthy neonates, is dependent on the stimulation rate and other parameters (Bongers-Schokking et al 1989; De Vries, 1993). Studies using a stimulation rate of ≤2 Hz and a high-pass filter ≤10 Hz have reported a success rate of 100% for recording cortical SEPs in healthy neonates, whereas a stimulation rate of >2 Hz and a high-pass filter of ≥20 Hz yielded SEP success rates as low as 66%–87% (Suppiej 2007 for a review). Also important is to reduce as much as allowed by signal to noise ratio, the number of averaged traces (Bongers-Schokking et al., 1989; Pressler et al., 2003); however, the use of low number of averages adopted in the present study does not seem to explain the better predictive role of SEPs. In fact, Nevalainen et al, 2017

obtained results similar to ours using a higher number of averaged traces; these authors suggest that a higher number of averages yield a better signal-to-noise ratio in the unfavourable NICU environment. The issue of being able to avoid artefacts in neonatal SEP recordings in of sick neonates in NICU is important. Indeed, ten out of sixty-eight neonates recruited in the present study had to be excluded from analysis because of unreliable traces due to artefacts. Possibly, this limitation could be avoided increasing the number averaged traces. Differences in predictive value of SEPs after TH might also depend on the number of patients with abnormal outcome, since limited numbers may lead to its underestimation and may explain the discrepancies between ours and other studies. The adoption of TH hypothermia for HIE had a positive effect on asphyxia-related brain damage at MRI (Bednarek et al., 2012) in line with improvement of long-term prognosis. But, it is difficult to recruit cases with severe SEP abnormalities. To overcome this problem, we underwent a multi-center study but despite of being the present study among the largest cohorts published so far, the still limited number of subjects, particularly those with severe outcome, compromised the possibility to carry out a more extensive statistical analysis.

The present study is in line with knowledge in adults with post anoxic coma (Tiainen et al., 2005; Rossetti et al., 2010; Bouwes et al., 2012) and seems to extend to post cooling era the high predictive value of bilaterally absent cortical SEPs *vs* moderate/severe outcome, in neonatal HIE.

On the other hand, this study disclosed a decreased sensitivity of SEPs after TH towards the presence of MRI abnormalities as less than half of neonates harboring MRI changes were identified by bilaterally absent cortical SEPs. In pre-TH studies, abnormal SEPs had a sensitivity ranging from 0.85 to 1.00, with respect to clinical outcome (deVries, 1991; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998). According to our findings, TH seems to have an effect on the electrical activity of neurons, reducing demyelination and/or axon loss and thus preserving detection of N20 also in the presence of structural parenchymal changes particularly if due to tissue edema shown at MRI. On the other hand, 12/80 neonates were excluded from the study because of death occurring before undergoing SEPs or MRI. The inclusion of this subgroup, affected by a more severe form of HIE, most likely would have improved the global sensitivity of SEPs as these neonates have an increased probability of abnormal SEP and MRI. As pointed out by Nevalaien et al. (2017), much of the variability of predictive values of SEP reported in previous studies, could arose from different definitions of a SEP abnormality. The definition of SEP abnormalities adopted in the present study can partly explain our SEP/MRI incongruences. Indeed, based on our previous finding of best prediction of severe neurological outcome using bilaterally absent N20 (Suppiej et al 2010), for analysis we merged bilaterally and unilaterally recorded N20 component in one single group. Thus,

SEP score 0 subgroup included patients with unilaterally absent N20 that could show unilateral or less extended MRI parenchymal lesions. Preliminary follow up data are available, at 24 months, for seven patients of the present study having SEP/MRI incongruences (personal communication). All five patients with neurological sequelae, MRI abnormalities and SEP score 0, had monolateral SEP abnormality. By contrast, in the remaining two patients with normal neurological outcome and abnormal MRI, the SEP score 0 included bilaterally recorded N20 in one and unilaterally recorded N20 in the other one. The 23 patients with concordant SEP and MRI and available follow up data at 24 month all had coherent clinical outcome, confirming the complementary role of functional and anatomic diagnostics.

The use of MRI as a surrogate marker of neurological outcome is a limitation of the present study since MRI-specificity may be about 82% regarding 18-month clinical outcome (Rutherford et al., 2010). However, several studies, based on large populations of cooled and non-cooled neonates, have extensively confirmed the predictive value of different MR imaging patterns particularly for late scans (> 7 days), being the lesions in a more advanced state of evolution (Barkovich et al., 1998; Shankaran et al., 2012). Furthermore, for infants imaged earlier than 7 days of life, the use of DWI sequences allows the highest sensitivity, before pseudo-normalization occurs. In the present study, infants were imaged between 4 and 14 days, allowing a good sensitivity. Abnormalities in the acute phase may, however, transiently occur and resolve without sequelae, as observed in our two patients where the clinical outcome was more adherent to electrophysiological than imaging findings. This issue needs to be further investigated on a wider cohort. One other limitation of the present study is the use of only two scalp locations for recording the N20 component. The use of more electrodes better takes into account variability in scalp distribution of the N20, however, none of our patients with bilaterally absent SEP had normal outcome on MRI showing that this possibility did not occur in our study, possibly because we used central locations rather than centro-parietal, taking into account the differences in the scalp to brain relationships of the immature brain (Karniski 1992a; 1992b). The choice of electrodes location for recording cortical SEP is one other methodological issue. We recorded at C3 and C4 locations, but other authors suggest the optimal site to be behind the interauricular line (Desmedt et al., 1976) and the majority of SEP studies have been performed with the posterior location. Nevertheless, with sufficiently high intensity stimuli, N20 is clearly seen at C3 and C4 too (Hashimoto et al., 1983).

In HIE neonates, MRI patterns of injury, depend on the duration and severity of hypoxic-ischemic insult, which are different from those of adult post-anoxic coma because of selective age-dependent vulnerability (DeVries and Groenendaal, 2010; Rutherford M et al., 2010; Barkovich et al., 1998).

Considering the different location of MRI abnormalities found in this study, the majority of patients with bilaterally absent SEPs were in the most severe subgroup showing coexistence of both WS and BG/T patterns of abnormalities. Differently from adults, in whom it is generally assumed that bilaterally absent cortical SEP reflect mainly severe widespread irreversible cortical damage, we found bilaterally absent cortical SEP pattern also in two patients with isolated BG/TA involvement, suggesting that absence of N20 cortical response in these cases was probably due to interruption of afferent somatosensory volley. Unfortunately, the number of cases with abnormal MRI was insufficient to analyze SEPs in different subgroups.

5. Conclusions

In asphyxiated term neonates, bilateral absence of cortical SEPs seems to be associated with moderate/severe MRI patterns of injury, which are known to correlate with cerebral palsy, the most severe outcome in survivors of neonatal HIE. SEPs should be included in the workup of HIE undergoing TH since their prognostic role is confirmed also in the population of neonates undergoing this therapeutic treatment, particularly when SEP and MRI give coherent results. Data on the clinical follow up, at present on the way, are needed to clarify the prognostic role of SEPs in patients with discrepant SEP/MRI findings.

Acknowledgments

The authors thank all the children and their families who participated in the Study.

Funding sources

This research was partially supported in the collection of the data by the MURST Project RF-2009-1511075.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

References

Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E et al.; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361(14):1349-58.

Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. AJNR Am J Neuroradiol 1998;19(1):143–9.

Bednarek N, Mathur A, Inder T, Wilkinson J, Neil J, Shimony J. Impact of therapeutic hypothermia on MRI diffusion changes in neonatal encephalopathy. Neurology 2012;78(18):1420-7.

Bongers-Schokking CJ, Colon EJ, Hoogland RA, Van den Brande JL, De Groot KJ. The somatosensory evoked potentials of normal infants: influence of filter bandpass, arousal state and number of stimuli. Brain Dev 1989;11(1):33-9.

Bonifacio SL, Glass HC, Vander Pluym J, Agrawal AT, Xu D, Barkovich AJ et al. Perinatal events and early MRI in therapeutic hypothermia. J Pediatr 2011; 158(3):360-5.

Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, ToornvlietAC, et al. Prognosis of Coma After Therapeutic Hypothermia: A Prospective Cohort Study. Ann Neurol 2012;71:206–12.

Cheong JL, Coleman L, Hunt RW, Lee KJ, Doyle LW, Inder TE et al.; Infant Cooling Evaluation Collaboration. Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy: substudy of a randomized trial. Arch Pediatr Adolesc Med 2012;166(7):634-40.

Desmedt JE, Brunko E, Debeker J. Maturation of the somatosensory evoked potentials in normal infants and children, with special reference to the early N1 component. Electroencenphalogr Clin Neurophysiol 1976; 40:43-58.

De Vries LS, Pierrat V, Eken P, Minami T, Daniels H, Casaer P. Prognostic value of early somatosensory evoked potentials for adverse outcome in full-term infants with birth asphyxia. Brain Dev 1991;13(5):320– 5.

De Vries LS. Somatosensory evoked potentials in term neonates with postasphyxial encephalopathy. Clin Perinatol 1993;20(2):463-82.

DeVries LS, Groenendaal F. Patterns of neonatal hypoxic–ischemic brain injury. Neuroradiology 2010;52:555–66.

Eken P, Toet MC, Groenendaal F, de Vries LS. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 1995;73(2):F75–F80.

Garfinkle J, Sant'Anna GM, Rosenblatt B, Majnemer A, Wintermark P, Shevell MI. Somatosensory evoked potentials in neonates with hypoxic-ischemic encephalopathy treated with hypothermia. Eur j paediatr neurol 2015;19:423-8.

Gibson NA, Brezinova V, Levene MI. Somatosensory evoked potentials in the term newborn. Electroencephalogr Clin Neurophysiol 1992;84(1):26-31.

Glass HC, Nash KB, Bonifacio SL, Barkovich AJ, Ferriero DM, Sullivan JE et al. Seizures and magnetic resonance imaging-detected brain injury in newborns cooled for hypoxic-ischemic encephalopathy. J Pediatr 2011;159(5):731-5.

Grippo A, Carrai R, Scarpino M, Spalletti M, Lanzo G, Cossu C et al. Neurophysiological prediction of neurological good and poor outcome in post-anoxic coma. Acta Neurol Scand 2016 Aug 1. doi: 10.1111/ane.12659.

Gucuyener K, Beken S, Ergenekon E, Soysal S, Hirfanoglu I, Turan O, et al. Use of amplitude-integrated electroencephalography (aEEG) and near infrared spectroscopy findings in neonates with asphyxia during selective head cooling. Brain Dev 2012;34:280–6.

Hallberg B, Grossmann K, Bartocci M, Blennow M. The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment. Acta Paediatr 2010;99:531–6.

Hashimoto T, Tayama M, Hiura K, Endo S, Fukuda K, Tamura Y, Mori A, Miyao M. Short latency somatosensory evoked potential in children. Brain Dev. 1983;5(4):390-6.

Karniski W. The late somatosensory evoked potentials in premature and term infants. I. Principal component topography. Electroencephalogr Clin Neurophysiol 1992a;84:32–43.

Karniski W, Wyble L, Lease L, Blair RC. The late somatosensory evoked potential in premature and term infants. II. Topography and latency development. Electroencephalogr Clin Neurophysiol 1992b;84: 44–54.

Kontio T, Toet MC, Hellström-Westas L, van Handel M, Groenendaal F, Stjerna S et al. Early neurophysiology and MRI in predicting neurological outcome at 9–10 years after birth asphyxia. Clinical Neurophysiology (2013)124:1089–94.

Julkunen MK, Himanen SL, Eriksson K, Janas M, Luukkaala T, Tammela O. EEG, evoked potentials and pulsed Doppler in asphyxiated term infants. Clin Neurophysiol 2014;125:1757-63.

Majnemer A, Rosenblatt B. Prediction of outcome at school entry in neonatal intensive care unit survivors, with use of clinical and electrophysiologic techniques. J Pediatr 1995;127:823–30.

Mandel R, Martinot A, Delepoulle F, Lamblin MD, Laureau E, Vallee L, et al. Prediction of outcome after hypoxic-ischemic encephalopathy: a prospective clinical and electrophysiologic study. J Pediatr 2002;141:45–50.

Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop JM, Rutherford MA et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology 2011;76:2055.

Natarajan G, Pappas A, Shankaran S. Outcomes in childhood following therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy (HIE). Semin Perinatol 2016;40(8):549-55.

Nevalainen P, Lauronen L, Metsäranta M, Lönnqvist T, Ahtola E, Vanhatalo S. Neonatal somatosensory evoked potentials persist during hypothermia. Acta Paediatr. 2017 Mar 4. doi: 10.1111/apa.13813.

Pressler R, Bady B, Binnie CD, Boylan GB, Connell JA, Lütschg J, et al. Neurophysiology of the neonatal period. In: Binnie C, Cooper R, Mauguière F, Osselton JW, Prior PF, Tedman BM, editors. Clinical neurophysiology, Volume 2. EEG, paediatric neurophysiology, special techniques and applications. Amsterdam: Elsevier; 2003. p. 450–506.

Robinson LR, Micklesen PJ, Tirschwell DL, Lew HL. Predictive value of somatosensory evoked potentials for awakening from coma. Crit Care Med 2003;31(3):960-7.

Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67:301–7.

Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol 2010;9(1):39–45.

Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation 2014;85(12):1779-89.

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinicaland electroencephalographic study. Arch Neurol 1976;33(10):696–705.

Scalais E, Francois-Adant A, Nuttin C, Bachy A, Guerit JM. Multimodality evoked potentials as a prognostic tool in term asphyxiated newborns. Electroencephalogr Clin Neurophysiol 1998;108:199–207.

Shankaran S, Barnes PD, Hintz SR, Laptook AR, Zaterka-Baxter KM, McDonald SA et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2012;97(6):F398-404.

Suppiej A. General characteristics of evoked potentials. In: Pressler R, Binnie CD, Cooper R, Robinson R, editors. Neonatal and paediatric clinical neurophysiology. Edinburgh: Churchill Livingstone, Elsevier; 2007. p. 111–54.

Suppiej A, Cappellari A, Franzoi M, Traverso A, Ermani M, Zanardo V. Bilateral loss of cortical somatosensory evoked potential at birth predicts cerebral palsy in term and near-term newborns. Early Hum Dev 2010;86:93–8.

Swarte RM, Cherian PJ, Lequin M, Visser GH, Govaert P. Somatosensory evoked potentials are of additional prognostic value in certain patterns of brain injury in term birth asphyxia. Clin Neurophysiol 2012;123:1631-8.

Taylor MJ, Murphy WJ, Whyte HE. Prognostic reliability of somatosensory and visual evoked potentials of asphyxiated term infants. Dev Med Child Neurol 1992;34(6):507–15.

Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics 2010;126:131-9.

Tiainen M, Kovala TT, Takkunen OS, Roine RO. Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. Crit Care Med 2005;33:1736–40.

van Laerhoven H, de Haan TR, Offringa M, Post B, van der Lee JH. Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review. Pediatrics 2013;131(1):88-98.

Wijdicks EF, Varelas PN, Gronseth GS, Greer DM; American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74(23):1911-8.

Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice Parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcom-mittee of the American Academy of Neurology. Neurology 2006;67:203-10.

Tables

Table 1. Clinical characteristics of the population

	Neonates (n=58)
Male	30 (51.7%)
Birth weight, g	3228 ± 450
Gestational age, weeks	39.1 ± 1.8
pH < 7.0	36 (62%)
Base deficit >12	37 (63.7%)
Severe encephalopathy (Sarnat 3)	19 (32.8%)
10 min. Apgar score < 5	9 (15.5%)
Respiratory support at 10 min.	51 (87.9%)

Table 2. Cross tabulation of SEPs score (0: bilaterally/unilaterally recorded; 1: bilaterally absent) and the dichotomous outcome of MRI

MRI	SEP score 0	SEP score 1	Total
Normal-mild	**36**	**0**	**36**
Moderate-severe	**12**	**10**	**22**
Total	**48**	**10**	**58**

Table 3. Summary frequencies of SEP score (0: bilateral + monolateral presence; 1: bilateral absence) and MRI score (no injury, injury in BG/T, injury in WS, injury in BG/T and WS).

SEP	**Normal/mild MRI**	**BG/T**	**WS**	**WS+BG/T**	**Total**
Score 0 (%)	36 (75%)	4 (8,3%)	4 (8,3%)	4 (8,3%)	48
Score 1 (%)	0 (0%)	2 (20%)	1 (10%)	7 (70%)	10
Total	36	6	5	11	58

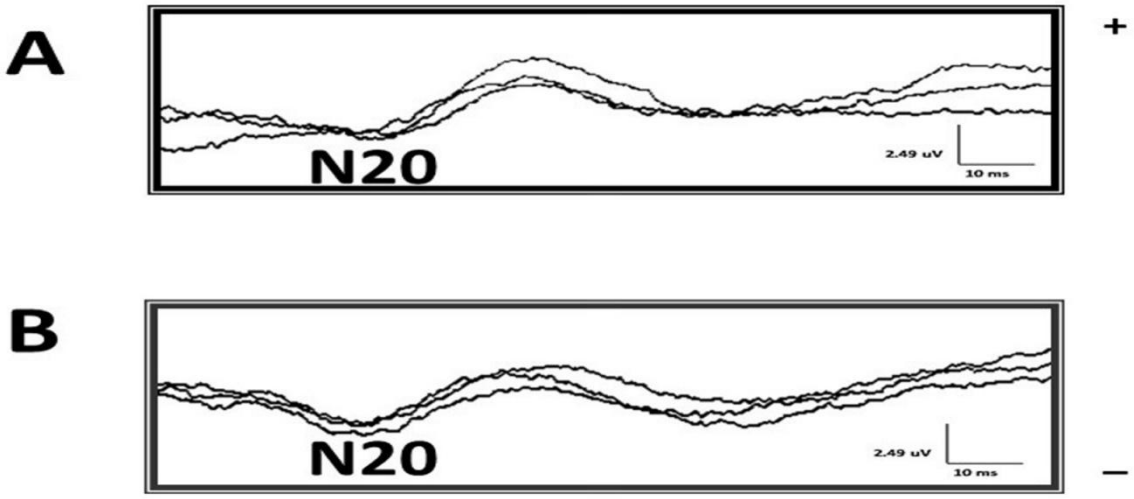
Legend: BG/T: basal ganglia/thalami region; WS: watershed region

Figure Legend

Figure 1. The N20 cortical response of upper limb SEPs recorded on day 7 in a neonate affected by moderate post asphyxia encephalopathy. The MRI was normal on day 6.

Traces recorded with C3-C4 montage following right median nerve stimulation at wrist (A) and with C4-C3 montage following left median nerve stimulation at wrist (B).

Bandpass 10 Hz-1.000 Hz.


A
N20
2.49 uV
10 ms
+
B
N20
2.49 uV
10 ms
–