Motor nerve conduction velocity and somatosensory evoked potentials in the newborn and young child in relation to thyroid function

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Chapter 5

Somatosensory evoked potentials in very preterm infants

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Submitted
Abstract

Sufficient reference values of cortical N\textsubscript{1} peak latency of the median nerve SEP in very preterm infants are not yet available. In the placebo treated infants within an L-thyroxine supplementation trial, born at less than 30 weeks' gestation, cortical N\textsubscript{1} peak latency was measured at two weeks, at term, and at six months corrected age. Cross-sectional cortical N\textsubscript{1} peak latency values obtained in 50 infants and complete series of longitudinal values obtained in 15 infants were analyzed in relation to postmenstrual age (PMA). Mean cortical N\textsubscript{1} peak latency decreased from 66 to 20 ms. Longitudinal cortical N\textsubscript{1} peak latency values decreased as well and were consistent with cross-sectional cortical N\textsubscript{1} peak latency values. Possible confounding factors did not have any significant effect on cortical N\textsubscript{1} peak latency at two weeks or at term age except cranial ultrasound abnormalities at two weeks of age. The observed cortical N\textsubscript{1} peak latencies at term and at six months corrected age suggest that extrauterine maturation of the somatosensory pathway in infants born at less than 30 weeks' gestation, is delayed by extrauterine life.

Key words electrophysiology, evoked potentials, preterm infant, somatosensory.
In recent years, median nerve somatosensory evoked potentials (SEPs) in newborns have received increased attention. Sufficient reference values of peak latencies of the first cortical potential (N) in infants born at less than 30 weeks’ gestation are not yet available. Moreover, the validity of median nerve SEPs as a prognostic test to predict neurodevelopmental outcome especially in preterm infants is not yet fully established.

To determine whether L-thyroxine supplementation improved neurodevelopmental outcome at the age of two years, we recently carried out a randomized, double-blind, placebo controlled trial in 200 very preterm infants, irrespective of their clinical condition and thyroid hormone levels, who were born at less than 30 weeks’ gestation. SEP recordings were obtained at two weeks, at term and at six months corrected age. The present paper describes cross-sectional and longitudinal reference values of the first cortical peak latency (N) after stimulation of the median nerve based on data obtained in the placebo group. Because cortical peak N latency reflects the functional integrity of the somatosensory pathway in the nervous system, it can be abnormal due to intracerebral hemorrhages, periventricular leucomalacia and ventriculomegaly. All of these conditions are not infrequently occurring in very preterm infants. Therefore, we examined all cranial ultrasound examinations of the infants during admission. Other possible confounding factors were also analyzed. Moreover, cortical peak N latency values were studied in relation to neurologic development at two years of age.

Patients and Methods

Between January 1991 and July 1993, 200 very preterm infants were enrolled in the thyroxine supplementation trial. The study was approved by the Research and Ethics Committee of the Academic Medical Center in Amsterdam. Criteria for inclusion were birth at a gestational age of 25 to 30 weeks and admission to our neonatal intensive care unit within the first 24 hours after birth. Exclusion criteria were severe congenital malformations, maternal endocrine disease and maternal illicit drug dependency. After informed consent by at least one parent, each infant was randomly and blindly assigned to receive either L-thyroxine or a placebo. For the purpose of the study presented here
cortical $N_1$ peak latency values of median nerve SEPs obtained in the placebo group were analyzed.

**SEP measurement**

SEPs were recorded after stimulating the median nerve with a mobile SEP recording machine (Neuropack Four Mini, model MEB-5304K - Nihon Kohden, Tokyo, Japan). A hand-held device was placed at the wrist overlying the median nerve and 0.5 Hz electrical pulse stimuli of 0.1 ms duration were given. The intensity of the stimulus used was set at a level that was necessary to produce a minimal thumb twitch. The skin temperature was guaranteed to be above 36° C. Recordings were obtained from the left somatosensory cortex, following stimulation of the right median nerve. Only in case of an infusion line in the right arm or left-sided brain lesions, recordings were obtained from the right somatosensory cortex, following stimulation of the left median nerve. Recordings were done using 10 mm diameter silver-silverchloride disk electrodes. The negative electrode was placed over the primary somatosensory area for the upper extremities, i.e. two cm posterior to C3/C4 (C3'/C4'), according to the international 10 - 20 electrode system. The reference electrode was placed in midfrontal position (Fz) and one electrode was placed on the lower arm as ground. The skin-electrode resistance was usually kept under 5 kΩ. The analysis time was 200 ms. Thirty to fifty cortical potentials were averaged through a bandpass of 2-100 Hz. For reproducibility, each recording was duplicated. After stimulating the median nerve, the latency to the peak of the first negative wave ($N_1$), i.e. the first cortical potential was measured according to the criteria of Desmedt et al. When a bilobed $N_1$-wave was present the latency to the first prominent peak was determined. All infants were tested without sedation. At two weeks of age, the infant's behavioral state during recording was noted according to Prechtl. At term and at the corrected age of six months, the behavioral state of the infant was classified as awake or asleep. Furthermore, actual medication was recorded. Each SEP recording took about 45 minutes to complete. All potentials were stored on a disk. Later on they were reassessed and classified for quality according to predefined criteria with respect to configuration and reproducibility. If both configuration and reproducibility were good, the quality was considered good. If the configuration was good, but lacked good reproducibility, i.e. two cortical $N_1$ peak latencies with a difference more than 10 % of the largest value, the quality was considered moderate. If neither configuration nor reproducibility were good, the quality of the potentials was considered poor. In cases of good or moderate quality the mean value of the two cortical $N_1$ peak latencies was
used for the analyses. Potentials of poor quality were excluded from statistical analyses. In each patient SEPs were obtained at two weeks (14-17 days), at term (37-43 weeks postmenstrual age [PMA]) and at six months corrected age (63-69 weeks PMA). PMA is defined as gestational age at birth plus postnatal age. Corrected age is defined as age corrected for preterm birth, i.e. age from the expected date of birth. Figures 1a, 1b, and 1c provide examples of good, moderate and poor quality SEPs and cortical N1 peak latency measurements.

Cranial ultrasound
We analyzed all cranial ultrasound examinations of the infants during admission using a mechanical sector scanner (ATL Ultramark 4) with a 7.5 MHz transducer. Ultrasound scan results on day 14 and the final results on day 42 were used for statistical analysis. We classified hemorrhage according to Volpe (grade 1: germinal matrix hemorrhage with no or minimal intraventricular hemorrhage, grade 2: intraventricular hemorrhage to 50% of ventricular area, grade 3: intraventricular hemorrhage above 50% of

![Fig. 1. Median nerve SEPs of good (a), moderate (b) and poor (c) quality and cortical N1 peak latency measurement in very preterm infants](image-url)
ventricular area, usually with distention of lateral ventricle and grade 4: hemorrhagic intracerebral involvement or other parenchymal lesion), and periventricular leucomalacia according to De Vries et al. (grade 1: transient periventricular densities, persisting for ≥7 days, grade 2: transient periventricular densities, evolving in small localized fronto-parietal cysts, grade 3: periventricular densities, evolving into extensive periventricular cysts and grade 4: densities extending into deep white matter evolving into extensive cystic lesions). Ventriculomegaly was classified according to Levene (ventricular index > P_{97} or > P_{97} + 4 mm).

Follow up with respect to neurologic development at two years
In this study, in contrast to the few earlier studies in low-risk preterm infants, a group of high-risk preterm infants for abnormal neurologic development was investigated. Therefore, we studied whether latency values of median nerve SEPs (good / moderate quality SEPs) and poor quality SEPs (without a \( N_1 \) peak latency value) were related to neurologic development at two years of age, assessed according to the method of Hempel. The results of these Hempel assessments were classified as normal, abnormal, or suspect. Abnormal was defined as severe abnormality in tone, posture and movement leading to functional impairment or delay in motor development. Suspect was defined as a moderate functional impairment or developmental delay. Adverse outcome is defined as a suspect or abnormal neurologic development.

Statistical analysis
Categorical data were analyzed using the Chi-square test for two and multiway tables. Continuous data were analyzed using the Student’s \( t \)-test. Cross-sectional cortical \( N_1 \) peak latency values were analyzed using linear regression analysis (BMDP-7.1® 6D). Linear regression analysis (BMDP-7.1® 1R) was also used to study the effect of possible confounding factors on cortical \( N_1 \) peak latency at two weeks and at term age after correction for PMA. These factors included sex, weight class for gestational age, ethnic origin of the mother, antenatal use of steroids, asphyxia (Apgar score < 7 at 5 minutes after birth), hyperbilirubinemia, cranial ultrasound findings (on day 14 and on day 42 [final diagnosis]), behavioral state, quality of SEPs and body length (at day 14). Also, in order to compare cross-sectional and longitudinal cortical \( N_1 \) peak latency values and those of infants with and without ultrasound abnormalities, linear regression analysis was used (BMDP-7.1® 1R).

We used analysis of variance (BMDP-7.1® 5V) to study longitudinal cortical \( N_1 \) peak latency values, which provided a reference formula for cortical \( N_1 \) peak latency corrected...
for PMA. Linear regression analysis (BMDP-7.1® 1R) was used to analyze cross-sectional and longitudinal cortical N<sub>1</sub> peak latency values in relation to neurologic development at two years of age. A p value of less than 0.05 was considered statistically significant.

**Results**

**Patient population**
The placebo group consisted of one hundred very preterm infants. At the first measurement at two weeks 59 infants were studied. At the second and third measurements, performed at term and six months corrected age, 65 and 54 infants were studied, respectively. The reasons for the reduction in numbers at first measurement, were death and poor clinical condition. At the second and third measurements, other reasons were found such as parental discomfort with the time-consuming aspects of measuring cortical N<sub>1</sub> peak latency in addition to other investigations on the same day. The clinical characteristics at the first SEP measurement at two weeks of age are summarized in Table 1. All infants, in whom SEPs were recorded, were treated with caffeine at two weeks. Later on this medication was discontinued at about 34 weeks PMA. Throughout the study, in none of the infants SEP recordings were performed during anticonvulsive treatment.

**SEP data**
Only SEPs classified as good or moderate quality were analyzed. Causes for poor SEP quality included an unstable clinical condition especially during the neonatal period. At two weeks of age, we were able to record SEPs of good or moderate quality in 24 of the 59 infants, while SEPs of poor quality were recorded in the remaining 35 infants. The latter were more preterm, had a lower birth weight and had more ultrasound abnormalities (Table 1). At term age, poor quality SEPs were recorded in seven of the 65 infants. At 6 months corrected age this number was four of the 54 infants.

**Cross-sectional cortical N<sub>1</sub> peak latency values**
Cross-sectional cortical N<sub>1</sub> peak latency values are shown in Figure 2. Mean N<sub>1</sub> peak latency values (± SD) at the three time points are given in Table 2a. At term age, cortical N<sub>1</sub> peak latency was significantly related to PMA using linear regression analysis (r=-0.38; p=0.003). Reference formulas of cortical N<sub>1</sub> peak latency could be defined as shown in Table 2b. At two weeks and at six months corrected age, no
Table 1. Baseline characteristics at first SEP measurement 14-17 days after birth

<table>
<thead>
<tr>
<th></th>
<th>good/moderate quality</th>
<th>poor quality</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=24</td>
<td>n=35</td>
<td>n=59</td>
<td></td>
</tr>
<tr>
<td>sex (♀)</td>
<td>9</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>gestational age (weeks)</td>
<td>28.9 ± 0.7s</td>
<td>27.9 ± 1.3</td>
<td>28.3 ± 1.1</td>
</tr>
<tr>
<td>birthweight (g)</td>
<td>1208 ± 208s</td>
<td>1068 ± 260</td>
<td>1125 ± 248</td>
</tr>
<tr>
<td>SGA*</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>maternal ethnic origin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>caucasian</td>
<td>19</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>antenatal steroids†</td>
<td>8</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>asphyxia†</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>serum peak concentration of bilirubin 250 mmol/l</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>cerebral hemorrhage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>5</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>grade 3 or 4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>cerebral ischaemia: flaring</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ventriculomegaly:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ventricular index &gt; P97</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>ventricular index &gt; P97 + 4 mm</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>normal cranial ultrasound</td>
<td>17</td>
<td>19</td>
<td>36</td>
</tr>
</tbody>
</table>

Values either number or mean ± SD; *SGA = small for gestational age, i.e. birth weight below 10th percentile for gestational age in a Dutch reference population; †two doses of 12 mg betamethasone; ‡Apgar score < 7 at 5’; § p < 0.05 good/moderate quality SEPs compared with poor quality SEPs

significant relation was found between cortical N1 peak latency and PMA (p = 0.11 and p = 0.84, respectively).

Cross-sectional cortical N1 peak latency values in relation to possible confounding factors

Linear regression produced no significant effects on cortical N1 peak latency values at two weeks of age due to confounding factors including sex, weight class for gestational age, maternal ethnic origin, antenatal steroids, asphyxia, hyperbilirubinemia, behavioral state, quality of SEPs or body length. However, in seven infants with cranial ultrasound abnormalities, mean cortical N1 peak latency was decreased (59.0 ± 7.3 ms) compared to that in 17 infants with normal ultrasound findings (69.3 ± 6.9 ms). In addition, adjusted for covariates, the difference between the mean cortical N1 peak latency values in infants with and without cranial ultrasound abnormalities was -13.3 ms; 95% confidence interval was -3.1 to -23.5 ms. Cranial
ultrasound abnormalities consisted of grade 1 or grade 2 cerebral hemorrhages (n=5) and ventriculomegaly (n=2; Table 1). At term age, after correction for PMA, linear regression revealed no significant effects on cortical N\textsubscript{1} peak latency values due to any possible confounding factors including cranial ultrasound findings.

**Longitudinal cortical N\textsubscript{1} peak latency values**

Longitudinal cortical N\textsubscript{1} peak latency values were available in a subgroup of 15 infants, in whom we were able to measure cortical N\textsubscript{1} peak latency with good or moderate quality at all three points in time (Fig. 3). Nine of the 15 infants did not have any
Table 2a. Cortical N₁ peak latency in median nerve SEP at three time points

<table>
<thead>
<tr>
<th>time of measurement</th>
<th>PMA (wk)</th>
<th>N₁ peak latency Normal US (ms)</th>
<th>N₁ peak latency Abnormal US (ms)</th>
<th>N₁ peak latency All patients (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks after birth</td>
<td>31.1 ± 0.8</td>
<td>69.3 ± 6.9 (n=17)</td>
<td>59.0 ± 7.3 (n=7)</td>
<td>66.3 ± 8.4 (n=24)</td>
</tr>
<tr>
<td>term age</td>
<td>40.7 ± 1.3</td>
<td>38.1 ± 10.7 (n=30)</td>
<td>39.6 ± 8.7 (n=28)</td>
<td>38.8 ± 9.7 (n=58)</td>
</tr>
<tr>
<td>six months (corrected) age</td>
<td>66.1 ± 1.2</td>
<td>19.8 ± 1.2 (n=23)</td>
<td>20.3 ± 1.1 (n=27)</td>
<td>20.1 ± 1.1 (n=50)</td>
</tr>
</tbody>
</table>

Values are mean ± SD

Table 2b. Reference formulas for cortical N₁ peak latency in median nerve SEP at three time points

<table>
<thead>
<tr>
<th>time of measurement</th>
<th>Reference formula</th>
<th>p value Normal US</th>
<th>Reference formula</th>
<th>p value All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks after birth</td>
<td>109.2 - 1.29 PMA</td>
<td>0.57</td>
<td>178.8 - 3.61 PMA</td>
<td>0.11</td>
</tr>
<tr>
<td>term age</td>
<td>180.5 - 3.48 PMA</td>
<td>0.008</td>
<td>156.7 - 2.90 PMA</td>
<td>0.003</td>
</tr>
<tr>
<td>six months (corrected) age</td>
<td>21.3 - 0.023 PMA</td>
<td>0.91</td>
<td>21.9 - 0.028 PMA</td>
<td>0.84</td>
</tr>
</tbody>
</table>

PMA in weeks.

cranial ultrasound abnormalities. The other six infants had a subependymal hemorrhage at most. Longitudinal cortical N₁ peak latency values were consistent with cross-sectional cortical N₁ peak latency values. A reference formula was defined on the basis of these values (Fig. 3).

Follow up with respect to neurologic development at two years

Neurologic development according to Hempel could be assessed in all but one infant in the subgroups of 24 and 58 infants in whom we had been able to measure cortical N₁ peak latency (good / moderate quality SEPs) at two weeks and term age, respectively. In all infants in the group of 50 infants measured at six months corrected age (good / moderate quality), neurologic development could be assessed. Linear regression analysis did not reveal any significant correlation between cortical N₁ peak latency values (good / moderate quality SEPs) at any time point and adverse outcome (suspect / abnormal neurologic development) at two years of age. Also in the surviving infants, in whom a cortical N₁ peak latency measurement with poor quality was recorded, neurologic development was assessed (n=32, 6 and 4 infants at two weeks at term and at six months, respectively). Recording poor quality SEPs (without a N₁ peak
latency value) at two weeks of age was significantly related to adverse outcome. Poor quality SEPs carried a relative risk of 4.31 (95% CI: 1.07 - 17.45) for adverse outcome in comparison with good / moderate quality SEPs (Table 3). If adverse outcome also included mortality after SEPs recording at two weeks (n=3), the relative risk for adverse outcome increased to 4.93 (95% CI: 1.24 - 19.56). The recordings of poor quality SEPs at term and six months corrected age were not related to adverse outcome at two years of age (RR: 0.63 [95% CI: 0.10 - 3.99] and 0.78 [95% CI: 0.14 - 4.47], respectively).

<table>
<thead>
<tr>
<th>quality of SEPs</th>
<th>normal</th>
<th>suspect</th>
<th>abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>good/moderate</td>
<td>21</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>poor</td>
<td>20</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Relative risk for adverse outcome at two years of age in infants with poor quality SEPs at two weeks of age: 4.31 (95% CI: 1.07 - 17.45).
Discussion

This study presents cross-sectional and longitudinal reference values of cortical N1 peak latency in very preterm infants born at less than 30 weeks’ gestation. Mean cortical N1 peak latency decreased from a mean value of 66 ms at two weeks to 38 ms at term and 20 ms at six months corrected age. With the increment of PMA the decrease of cortical N1 peak latency diminished. Longitudinal cortical N1 peak latency values in a subgroup of 15 infants were consistent with cross-sectional cortical N1 peak latency values in a larger group of about 50 infants, suggesting that these values and the derived reference formula can be used as reliable reference values.

Until now, only two other reports regarding reference values of latencies in median nerve SEPs in preterm infants included infants born at less than 30 weeks’ gestation. Klimach and Cooke described median nerve SEP findings in 102 neurologically normal preterm infants with a median gestational age of 32.0 weeks (range 26.7 - 40.4 weeks) in stable clinical condition without ventilator or oxygen requirement. At the first SEP recording, their median postmenstrual age is 33.9 weeks (range 27.7 - 41.4 weeks). The success rate of an acceptable SEP recording is 90.2%. In fact, only 3 infants born at less than 30 weeks’ gestation contribute to the data presented. Taylor et al. report on maturational patterns of median nerve SEPs in a group of 22 preterm infants selected on the basis of normal cranial ultrasounds during admission, no signs of asphyxia and normal neurological examination at a mean corrected age of 14.8 months. The mean gestational age of these infants is 28.4 weeks (range 27 - 32 weeks). Their mean postmenstrual age when first tested is 29.6 weeks. The success rate is 100%. Repeated SEPs were done in 20 infants. Sixteen infants were tested twice and four infants were tested three times. With a total of 46 SEPs, of which 22 completed at a postmenstrual age of less than 30 weeks, latency values are presented, showing a rapid maturational change in the SEPs over the early preterm period.

In contrast to these two studies, we studied a large group of infants born at less than 30 weeks’ gestation who had not been selected on the basis of clinical condition, ultrasound findings and follow-up. Such a group of high-risk preterm infants represents an important part of a level III intensive care unit population. Presumably as a result of this, at the age of two weeks the success rate of a recordable SEP, classified as good or moderate was 41%. In the present study, in fact, a recordable SEP was only found at a postmenstrual age of more than 30 weeks except in one infant (at 29 weeks PMA [Figs. 1a and 2a]. Thus, the low success rate at two weeks of age may also be explained by insufficient maturation in addition to technical problems and brain
damage. At term and six months corrected age, success rate was much higher with 89% and 93%, respectively.

The mean cortical N1 peak latencies found at two weeks and at term age (66.3 ± 8.4 ms and 38.8 ± 9.7 ms, respectively) were in agreement with those reported by Klimach and Cooke, and Taylor et al. However, compared to values reported by others in infants born at full-term (for term age: 24.6 - 31.0 ms and for six months of age: about 17.5 ms), in the presented study cortical N1 peak latencies found at term and six months corrected age were longer (38.8 ± 9.7 ms and 20.1 ± 1.1 ms, respectively). This could suggest that extrauterine maturation of the somatosensory pathway in high-risk preterm infants is delayed compared to maturation in full-term infants, probably due to a delay in central myelination in preterm infants at term age compared with full-term infants. Former suggestions that maturation of the sensory pathway is unaffected by the extrauterine environment is possibly true in a selected group of low risk preterm infants.

In studies regarding cortical N1 peak latency in the preterm infant, several possible confounding factors should be taken into account. In this study cortical N1 peak latency values were not affected significantly by any possible confounding factor except cranial ultrasound abnormalities at two weeks of age. In contrast to what we expected, we found a decreased cortical N1 peak latency at 2 weeks of age in a small subgroup of seven infants with cranial ultrasound abnormalities. This difference was even greater after adjustment for covariates (-13.3 ms). However, the clinical relevance of this finding may be rather small in view of the large confidence interval (95% CI: -3.1 to -23.5 ms). Our finding could be explained by the assumption that the first negative peak which was measured was not, in fact, the cortical N1 peak but a peak derived from subcortical structures, such as the thalamus rather than the somatosensory cortex itself due to injury to the thalamocortical projections. Confounding by other factors such as body length could be excluded.

De Vries et al. described an increase in cortical N1 peak latency in nine infants with rapidly progressive ventricular dilatation. Others report conflicting information about the effect of intracerebral hemorrhage and periventricular leukomalacia on cortical N1 peak latency. At term age, we found no difference in mean cortical N1 peak latency in infants with and without cranial ultrasound abnormalities. This suggests that maturational state (PMA) may be of predominant importance at that time.

Observed cortical N1 peak latency values were not related to neurologic development, assessed according to Hempel at the age of two years. However, our analysis of
comparing the poor quality with good/moderate quality SEPs at two weeks of age in relation to neurologic development at two years (Table 3), supported the hypothesis that poor quality SEPs predict adverse outcome. A correlation with outcome is in agreement with Ekert et al. who found that cortical N₁ peak latency in median nerve SEPs in the first weeks of life is associated with later cerebral palsy. At term and at six months corrected age, we could not demonstrate a relation between poor quality SEPs and adverse outcome.

We may conclude that this study presents cross-sectional and longitudinal values of cortical N₁ peak latency that can be used as reference values in very preterm infants, born at less than 30 weeks’ gestation. However, measuring N₁ peak latency in median nerve SEPs at two weeks of age can be impeded in such a group of high-risk preterm infants by unstable clinical condition, insufficient maturation and brain damage. All these factors could be interrelated. They could also be an epiphenomenon of a common factor as prematurity.

Acknowledgments

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