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Chapter 4

Motor nerve conduction velocity in very preterm infants

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Sufficient reference values of motor nerve conduction velocity (MNCV) in very preterm infants are not yet available. In the placebo infants within an L-thyroxine supplementation trial, born at less than 30 weeks' gestation, ulnar and posterior tibial MNCV measurements were performed shortly after birth. Repeated measurements were done at two weeks, at term and at six months corrected age. Cross-sectional MNCV values obtained in 50 infants and longitudinal MNCV values obtained in 15 infants, were analyzed in relation to postmenstrual age (PMA). Mean ulnar MNCV increased from 13 to 44 m/s and mean tibial MNCV from 11 to 37 m/s. MNCV was clearly related to PMA. Longitudinal MNCV values were consistent with cross-sectional MNCV values. Possible confounding factors did not have any significant effect on MNCV. In the ulnar nerve, extrauterine maturation during the first two weeks of life was delayed compared with intrauterine maturation.

**Key words:** Electroneurography, neural conduction, motor nerve conduction velocity, preterm infant
Introduction

In recent years, much progress has been made in neonatal care. Improvement of monitoring equipment and mechanical ventilation, the introduction of surfactant treatment and centralization of resources, and the availability of specialized medical and nursing staff have led to a higher survival rate and better treatment results. Although the limit of viability has decreased, clinical electroneurographic data derived from preterm infants are scarce. Reference values for motor nerve conduction velocity (MNCV) in infants born at less than 30 weeks' gestation are not yet available. Recently, we carried out a randomized, double-blind, placebo-controlled L-thyroxine supplementation trial in 200 infants (irrespective of their thyroid hormone levels) born at less than 30 weeks' gestation to determine whether neurodevelopmental outcome at the age of two years had improved. The present paper describes cross-sectional and longitudinal reference values of the ulnar and posterior tibial MNCV in the placebo group. Possible confounding factors and the comparison of intrauterine and extrauterine maturation were also studied.

Patients and Methods

Between January 1991 and July 1993, 200 very preterm infants were enrolled. 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, MNCV data obtained in the placebo group were analyzed.

Measurement of motor nerve conduction velocity

MNCV was measured in the ulnar and posterior tibial nerves as described by Moosa and Dubowitz by means of a Neuropack Four Mini MEB-5304K (Nihon Kohden, Tokyo, Japan). The ulnar nerve was stimulated at the wrist and elbow, and the compound muscle action potential (CMAP) of the hypothenar muscles was recorded by surface electrodes. The posterior tibial nerve was stimulated posterior to the medial malleolus.
and in the popliteal fossa, and the CMAP of the flexor hallucis brevis muscle was recorded. Supramaximal stimuli (0.1 ms square wave) were ensured by increasing the intensity of the stimulus (up to 25-50 mA) until no further increase in amplitude of the CMAP occurred. For reproducibility, CMAPs were subsequently recorded following two distal and two proximal stimuli. Latencies were calculated from the stimulus artefact to the first well-defined negative peak of the CMAP. The distance between proximal and distal stimulation sites (i.e. the intercathode distance) was divided by the difference in peak latencies of the CMAPs elicited by stimulation at these sites to calculate the conduction velocity in meters per second. The intercathode distance was measured with a sliding metal caliper while the limb was held in the same position as during stimulation. During the investigations, skin temperature was guaranteed to be above 36° C either by an incubator in which the infant was nursed or by means of a radiant heater.

All CMAPs were stored on disk and later reassessed and classified for quality according to predefined criteria taking into consideration both configuration and reproducibility. If both configuration and reproducibility were good, the quality of the CMAP was considered good. If the configuration was good, but reproducibility moderate, i.e. two proximal or distal CMAPs showed a difference in peak latency between 1 and 10% of the largest latency, the quality was considered moderate. If the peak latency difference was more than 10% of the largest latency or no peak could be recognized, the quality was considered poor. In cases of moderate quality, the mean value of the two CMAPs was

**Fig. 1a.** Hypothenar CMAPs in a very preterm infant (28.3 wk, 1145 g) and peak latency measurements with ulnar MNCV values at the first two measurements in time (W=Wrist, E=Elbow)

**Fig. 1b.** Flexor hallucis brevis CMAPs in a very preterm infant (27.4 wk, 925 g) and peak latency measurements with posterior tibial MNCV values at the first two measurements in time (A=Ankle, P=Popliteal fossa)
used for the analysis. CMAPs classified as poor were excluded from the analysis. In each infant MNCVs were measured shortly after birth (0-3 days), at two weeks after birth (14-17 days), at term age (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. Figs. 1a and 1b provide examples of good quality CMAPs from the hypothenar and flexor hallucis brevis muscles, and latency measurements with ulnar and posterior tibial MNCV values.

**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 MNCV values were analyzed using linear regression analysis providing regression formulas for MNCV corrected for PMA with 95% prediction interval at mean PMA (BMDP-7.1® 6D). By using linear regression analysis (BMDP-7.1® 1R), the MNCV measurement shortly after birth and at two weeks after birth were compared. They were assumed to represent intrauterine and two weeks of extrauterine maturation. Analysis of variance (BMDP-7.1® 5V) was used to study the effect of possible confounding factors on ulnar and posterior tibial MNCV after correction for PMA. The factors included sex, weight class for gestational age, maternal ethnic origin, antenatal use of steroids and quality of CMAPs. We also used analysis of variance to study longitudinal MNCV values which provided reference formulas for MNCV corrected for PMA. A *p* value of less than 0.05 was considered statistically significant.

**Results**

**Patient population**
One hundred very preterm infants were enrolled in the placebo group. At the first measurement 83 infants were studied (26-30 weeks PMA). At the second measurement 68 infants were studied (28-32 weeks PMA), and at the third and fourth measurements 58 infants (37-43 weeks PMA) and 51 infants (63-69 weeks PMA), respectively, were studied. The reasons for the reduction in numbers were death, poor clinical condition and such other reasons as parental discomfort with the time-consuming aspects of measuring MNCV in addition to other investigations the same day. The clinical characteristics at the first MNCV measurement are summarized in Table 1.
Table 1. Baseline characteristics at first MNCV measurement 0-3 days postpartum

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gestational age (wk)</td>
<td>27.9 ± 1.3</td>
</tr>
<tr>
<td>birth weight (g)</td>
<td>1086 ± 239</td>
</tr>
<tr>
<td>male/female</td>
<td>38/45</td>
</tr>
<tr>
<td>SGA</td>
<td>11</td>
</tr>
<tr>
<td>maternal ethnic origin: caucasian</td>
<td>65</td>
</tr>
<tr>
<td>antenatal steroids</td>
<td>56</td>
</tr>
</tbody>
</table>

Values either number or mean ± SD; SGA = small for gestational age, i.e. birth weight below the 10th percentile for gestational age in a Dutch reference population.

MNCV data

Only CMAPs of good or moderate quality were analyzed. Causes for poor quality included an unstable clinical condition and local factors seen especially during the neonatal period, such as edema. Data reduction amounted to 45% (n=37) at 0-3 days after birth, 25% (n=17) at two weeks after birth, 10% (n=6) at term age and 6% (n=3) at six months corrected age. After this reduction, the baseline characteristics of corresponding patients remained similar to those at first MNCV measurement (Table 1).

Cross-sectional MNCV values

Mean ulnar and posterior tibial MNCV values (± SD) at time of measurement are given in Table 2. At all four measurements in time MNCV was significantly related to PMA using linear regression analysis (Table 3).

MNCV values in relation to intrauterine and extrauterine maturation

In order to compare intrauterine and extrauterine maturation, ulnar and posterior tibial MNCV values were available for two subgroups of 28 and 32 infants each, in which we were able to measure MNCV with good or moderate quality at both the

Table 2. Postmenstrual age (PMA)(mean ± SD), ulnar and posterior tibial MNCV (mean ± SD) and number of patients (n) at four points in time

<table>
<thead>
<tr>
<th>time of measurement</th>
<th>PMA wk</th>
<th>ulnar MNCV m/s</th>
<th>tibial MNCV m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3 days after birth</td>
<td>28.3 ± 1.3</td>
<td>13.3 ± 2.6 (n=46)</td>
<td>11.4 ± 1.7 (n=44)</td>
</tr>
<tr>
<td>14 - 17 days after birth</td>
<td>30.4 ± 1.3</td>
<td>14.4 ± 2.4 (n=51)</td>
<td>13.0 ± 1.9 (n=50)</td>
</tr>
<tr>
<td>term age</td>
<td>40.6 ± 1.0</td>
<td>27.7 ± 3.9 (n=52)</td>
<td>23.0 ± 2.5 (n=56)</td>
</tr>
<tr>
<td>6 months corrected age</td>
<td>66.3 ± 1.0</td>
<td>44.4 ± 5.0 (n=48)</td>
<td>37.5 ± 2.3 (n=50)</td>
</tr>
</tbody>
</table>
Table 3. Regression formulas for MNCVs in ulnar and posterior tibial nerve at four points in time with 95% predicted interval at mean PMA

<table>
<thead>
<tr>
<th>time of measurement</th>
<th>nerve</th>
<th>MNCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3 days after birth</td>
<td>ulnar nerve</td>
<td>-23.64 + (1.31 x PMA) ± 4.2</td>
</tr>
<tr>
<td></td>
<td>tibial nerve</td>
<td>-13.25 + (0.87 x PMA) ± 2.6</td>
</tr>
<tr>
<td>14 - 17 days after birth</td>
<td>ulnar nerve</td>
<td>-19.78 + (1.12 x PMA) ± 4.0</td>
</tr>
<tr>
<td></td>
<td>tibial nerve</td>
<td>-17.43 + (1.00 x PMA) ± 3.0</td>
</tr>
<tr>
<td>term age</td>
<td>ulnar nerve</td>
<td>3.27 + (0.60 x PMA) ± 8.0</td>
</tr>
<tr>
<td></td>
<td>tibial nerve</td>
<td>10.97 + (0.30 x PMA) ± 5.0</td>
</tr>
<tr>
<td>6 months corrected age</td>
<td>ulnar nerve</td>
<td>32.90 + (0.17 x PMA) ± 10.3</td>
</tr>
<tr>
<td></td>
<td>tibial nerve</td>
<td>-17.64 + (0.83 x PMA) ± 4.5</td>
</tr>
</tbody>
</table>

Fig. 2. Comparison of MNCV in the ulnar nerve (a) and posterior tibial nerve (b) 0-3 days after birth (○) and 14-17 days after birth (●), assumed to represent intrauterine (○) and extrauterine maturation (●). Regression lines are indicated by dotted lines (intrauterine maturation) and solid lines (extrauterine maturation).
first and second points in time, i.e. shortly after birth (0-3 days) and two weeks after birth, representing intrauterine maturation and two weeks of extrauterine maturation, respectively (Figs. 2a and 2b). During the first two weeks of extrauterine life, the mean ulnar MNCV increased from 13.5 m/s at a mean age of 28.4 wk PMA to 14.7 m/s at a mean age of 30.4 wk PMA (Fig. 2a). Mean ulnar MNCV at two weeks of age was delayed in comparison with the expected value based on MNCV measurements shortly after birth (16.2 m/s; means difference, corrected for PMA: -1.6 m/s; 95 % CI: -2.8 to -0.3). During the first two weeks, the mean posterior tibial MNCV increased from 11.5 m/s at 28.4 wk PMA to 13.4 m/s at 30.4 wk PMA (Fig. 2b). For the posterior tibial nerve at two weeks of age, no difference was found between mean MNCV and the expected value based on MNCV measurement shortly after birth. This finding suggests no difference between intrauterine and extrauterine maturation in that nerve.

**MNCV values in relation to possible confounding factors**

After correction for PMA, analysis of covariance produced no significant effects on ulnar or posterior tibial MNCV values shortly after birth and at two weeks of age due to possible confounding factors including sex, weight class for gestational age, maternal ethnic origin, antenatal use of steroids or quality of CMAPs.

**Longitudinal MNCV values**

Longitudinal ulnar and posterior tibial MNCV values were available in two smaller subgroups of 13 and 16 infants each, in which we were able to measure MNCV with good or moderate quality at all four points in time (Figs. 3a and 3b). We were able to define reference formulas on the basis of these values. For the ulnar nerve, MNCV was -38.16 + (2.20 x PMA) - (0.014 x PMA²) m/s and for the posterior tibial nerve it was -32.53 + (1.89 x PMA) - (0.013 x PMA²) m/s. The two subgroups had baseline characteristics similar to the other infants and those shown in Table 1. Moreover, longitudinal MNCV values (Figs. 3a and 3b) were consistent with cross-sectional values (Table 2).

**Discussion**

In the 1960s, measuring MNCV in newborn infants focused on differentiating between term and preterm infants. MNCV seemed to depend on postmenstrual age rather than on gestational age at birth or postnatal age. It was thought that MNCV could
serve as an easy, objective and reliable index of neurologic maturity of the newborn infant\textsuperscript{8} and it was used to assess gestational age.\textsuperscript{10,13,15} More recently, MNCV measurements have been used in studies seeking to understand maturational processes in the peripheral nervous system\textsuperscript{7} and for studying possible interventions.\textsuperscript{18}

Until now, MNCV studies were performed in small groups of very preterm infants.\textsuperscript{4,6,13} Cruz Martinez et al. were the first to report on median and posterior tibial MNCV in a group of six preterm infants; four were born at less than 30 weeks’ gestation.\textsuperscript{6} To our knowledge, our study is the first to present ulnar and posterior tibial MNCVs related to PMA in a large group of very preterm infants.

Measuring MNCV in very preterm infants has its limitations due to unstable clinical conditions and adverse circumstances. Furthermore, local factors such as edema can
lead to low-amplitude CMAPs despite high stimulus intensities. As far as the reproducibility of CMAPs is concerned, spontaneous movements of the extremities or difficulty in finding the optimal location to stimulate the nerve may limit the ability to obtain CMAPs of maximal amplitude. Small distances of less than 40 mm between the distal and proximal sites of stimulation may also contribute to less accurate estimations of MNCVs, which may worsen the reproducibility of the MNCV results. Finally, we measured the latency to the first well-defined negative peak (according to the method of Moosa and Dubowitz\textsuperscript{14}) rather than to CMAP onset because of difficulties with measuring onset latency. This method improves MNCV reproducibility but may have an impact on pathological cases. For example, in neuropathies with temporal dispersion and a markedly prolonged rise time of the proximal CMAP, MNCV may be artificially slower than when measured using onset latency. Previous studies showed no difference between MNCV values in relation to intrauterine and extrauterine maturation, although Dubowitz\textsuperscript{8} reported a conduction velocity that increased at a faster rate after birth than in utero. By contrast, in our larger group, we found a significant delay in extrauterine maturation of the ulnar nerve compared with intrauterine maturation. This delay is of uncertain cause but may relate to adverse clinical conditions, such as hyaline membrane disease and undernutrition, especially during the first weeks of extrauterine life, compared to the more physiological conditions characterizing intrauterine life. Moreover, a delay in maturation is known to be associated with hypothyroxinemia, which is common in preterm infants during the first weeks of life.\textsuperscript{7,18} We did not find a delay in extrauterine maturation of the posterior tibial nerve. MNCV increases in proportion with the diameter of the axon and thickness of the myelin sheath. The maturation of the posterior tibial nerve is less advanced compared to the ulnar nerve because of its greater length and may therefore have been delayed to a lesser degree after two weeks of extrauterine life. Earlier studies addressed birth weight, twins and intrauterine growth retardation as possible confounding factors.\textsuperscript{2,10,15,17} Only Bhatia and Prakash\textsuperscript{2} found significantly lower MNCV in a small group of full term intrauterine growth-retarded infants. Our study did not reveal a significant effect of any possible confounding factors on MNCV. The fact that the longitudinal MNCV values analyzed in a small subgroup of infants were consistent with cross-sectional values analyzed in a larger group, suggests that these values can be used as reliable reference values. In summary, our study presents cross-sectional and longitudinal reference values of the ulnar and posterior tibial MNCV in very preterm infants in relation to PMA.
Possible confounding factors did not have any significant effect on MNCV. In the ulnar nerve, extrauterine maturation during the first two weeks of life was delayed compared with intrauterine maturation. No such delay was found in the posterior tibial nerve. The MNCV values presented here can be a useful reference for the assessment of maturational processes in the peripheral nervous system as well as for suspected neuropathies.

Acknowledgments

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