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

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Chapter 2

Motor nerve conduction velocity in the newborn and young child. A literature review

Introduction

The anatomy and development of the peripheral nerve and the methodology and applications of myelinated nerve conduction velocity (MNCV) of the ulnar nerve are described. Special attention is paid to the newborn and young child as well as to other aspects relevant to this thesis.

Anatomy and development

Peripheral nerves contain unmyelinated and myelinated fibers. The myelinated fibers are served by Schwann cells that contribute to CNS myelination. Myelination is a highly controlled process that involves a single Schwann cell wrapping itself around the axon for the entire length of an internode. Conduction velocity increases in proportion to the diameter of the nerve fiber and the degree of myelination. The nodes of Ranvier are remodeled, with increasing internodal distances reaching a peak at 5 years. Ulcer MNCV increases significantly during infancy, especially during the first 6 months of life and usually reaches adult MNCV values by 4 years of age. Adult values of the posterior tibial MNCVs are reached by about 2 years of age. Moreover, during childhood the amplitude of compound muscle action potentials (CMAP) after peripheral nerve stimulation triples in size for the upper extremity and doubles for the lower extremity. Neonatal hypothyroidism can delay myelogenesis in the developing rat brain. Acceleration of myelination by thyroxin was noted in vitro. Neonatal hyperthyroidism in the rat may first accelerate myelin synthesis but subsequently may increase oligodendroglial cell death by apoptosis. This results in permanent myelin deficit.

Methodology

Surface cathode and anode electrodes with an interelectrode distance of 1.5 to 2.0 cm are used for nerve stimulation. The ulnar nerve is stimulated at the wrist and elbow sulci (Fig. 1a) and the CMAP is recorded from the hypothenar muscles. The posterior tibial nerve is stimulated posterior to the medial malleolus and in the popliteal fossa (Fig. 1b) while the CMAP is recorded from the flexor hallucis brevis muscle. A ground electrode is usually placed between the stimulating and recording electrodes. Supramaximal 0.1 ms square wave stimuli are insured by increasing the stimulus intensity (up to 25-50 mA) until no further increase
Chapter 1

Introduction

The anatomy and development of the peripheral nerve and the methodology and clinical applications regarding motor nerve conduction velocity (MNCV) of the ulnar and posterior tibial nerves are described. Special attention is paid to the newborn and young child as well as to other aspects relevant to this thesis.

Anatomy and development

Peripheral nerves consist of bundles of nerve fibers and their associated supporting tissues and vascular supply. In most fibers, axon caliber, myelin sheath thickness and internodal length are interrelated. Myelination begins at about the 15th week of gestation and continues throughout the first 3 to 5 years after birth. Myelination is a highly controlled process that involves a single Schwann cell wrapping itself around the axon for the entire length of an internode. Conduction velocity increases in proportion to the diameter of the nerve fiber and the degree of myelination. The nodes of Ranvier are remodeled, with increasing internodal distances reaching a peak at 5 years. Ulnar MNCV increases significantly during infancy, especially during the first 6 months of life and usually reaches adult MNCV values by 4 years of age. Adult values of the posterior tibial MNCVs are reached by about 2 years of age. Moreover, during childhood the amplitude of compound muscle action potentials (CMAPs) after peripheral nerve stimulation, triples in size for the upper extremity and doubles for the lower extremity.

Neonatal hypothyroidism can delay myelogenesis in the developing rat brain. Acceleration of myelination by thyroxine was noted in vitro. Neonatal hyperthyroidism in the rat may first accelerate myelin synthesis but subsequently may increase oligodendroglial cell death by apoptosis. This results in permanent myelin deficit.

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Fig. 1a. Schematic representation of ulnar nerve and two stimulation sites (E=elbow, W=wrist; ● active electrode, ○ reference electrode, ○ ground electrode)

Fig. 1b. Schematic representation of posterior tibial nerve and two stimulation sites (A=ankle, P=poplitea; ● active electrode, ○ reference electrode, ○ ground electrode)
amplitude of the CMAP occurs. CMAPs following supramaximal stimulation of peripheral nerves represent the temporal and spatial summation of all muscle fiber action potentials in the region under the recording surface electrodes. The area or amplitude of the CMAP is correlated with the number of functioning muscle fibers. For reproducibility CMAPs are recorded after multiple distal and proximal stimuli. When MNCV is calculated using latencies from the onset of the stimulus artefact to the onset of the CMAP, MNCV reflects the conduction capacity of the fastest fibers that show the maximum MNCV. In preterm infants, latencies are calculated from the onset of the stimulus to the first well-defined negative peak of the CMAP because of difficulties with measuring onset latencies. To calculate MNCV in meters per second, the intercathode distance is divided by the difference in latencies of the distal and proximal CMAPs (Fig. 2). Skin temperature should be guaranteed to be above 36°C.

Clinical applications
The measurements of the ulnar and posterior tibial MNCVs reflect the functional integrity and maturational state of the nerves. The literature describing the following clinical applications are reviewed: reference values for term and preterm infants, assessment of maturity / gestational age, intrauterine growth retardation and hypothyroidism / hypothyroxinemia.

Reference values for term and preterm infants
Several authors have contributed towards establishing reference values of ulnar and posterior tibial MNCVs in the newborn and young child (Table 1a en 1b). Studies from the early sixties onwards are reviewed here. The first reference values published

Fig. 2. Hypothenar CMAPs in a very preterm infant (28.4 wk, 965 g) and peak latency measurements at two weeks of age (W=wrist, E=elbow; distance between proximal and distal stimulation sites: 32 mm, difference in latencies of distal and proximal CMAP: 2.36 ms, calculated ulnar MNCV: 13.6 m/s)
Table 1a. Reference values of ulnar nerve MNCVs in the newborn and young child

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>age</th>
<th>n</th>
<th>MNCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas and Lambert, 1960</td>
<td>34-37</td>
<td>1-46 d</td>
<td>6</td>
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<td></td>
<td>37-42</td>
<td>&lt; 3 d</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0-14 y</td>
<td>98</td>
</tr>
<tr>
<td>Cai and Zhang, 1997</td>
<td>37-42</td>
<td>1-3 d</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>37-42</td>
<td>0-3 m</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>37-42</td>
<td>4-6 m</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>37-42</td>
<td>7-12 m</td>
<td>20</td>
</tr>
</tbody>
</table>

d=days, GA= gestational age, m= months, m/s= meters/second, wk= weeks, y= years;
adult values: 58.7 ± 5.1 m/s

Table 1b. Reference values of posterior tibial nerve MNCVs in the newborn and young child

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>age</th>
<th>n</th>
<th>MNCV (m/s)</th>
</tr>
</thead>
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<tr>
<td>Thomas and Lambert, 1960</td>
<td>37-42</td>
<td>&lt; 3 d</td>
<td>10</td>
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<tr>
<td>Cruz Martinez et al, 1977</td>
<td>34-37</td>
<td>&lt; 3 d</td>
<td>30</td>
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<td></td>
<td>37-42</td>
<td>&lt; 3 d</td>
<td>72</td>
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<tr>
<td>Cruz Martinez et al, 1978</td>
<td>-</td>
<td>7-28 d</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1-3 m</td>
<td>11</td>
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<tr>
<td></td>
<td>-</td>
<td>3-6 m</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>6-12 m</td>
<td>11</td>
</tr>
<tr>
<td>Cruz Martinez et al, 1983</td>
<td>23-32</td>
<td>&lt; 3 d</td>
<td>6</td>
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<td>Cai and Zhang, 1997</td>
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<td>1-3 d</td>
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<td></td>
<td>37-42</td>
<td>7-12 m</td>
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</tr>
</tbody>
</table>

d=days, GA= gestational age, m= months, m/s= meters/second, wk= weeks;
adult values: 48.5 ± 3.6 m/s

are by Thomas and Lambert. They measured ulnar MNCV in a group of six preterm infants with a gestational age of 34 to 37 weeks, 42 term infants and 98 children with ages up to 14 years. They reported that MNCV values obtained in newborns are about one-half of those seen in normal young adults. Cruz Martinez et al. were the
first to present a MNCV study performed in very preterm infants. They studied posterior tibial MNCVs in six infants with a gestational age from 23 to 32 weeks and a birth weight from 600 to 2050 g and reported that MNCV values for these very preterm infants are about one third of the values for fullterm infants.

Large studies of posterior tibial MNCVs in newborn infants and children were conducted by Cruz Martinez et al.7,16 The posterior tibial MNCV reaches a mean adult value at about two years of age. The most recent large study is that by Cai and Zhang.17 They studied ulnar and posterior tibial MNCVs in Chinese patients, hospitalized at the age of one day (gestational age ≥ 37 wk) to 30 years. These patients did not suffer from any developmental, neurologic, endocrine or metabolic disease. Again, MNCV values in newborns are roughly half of those present in adults and about two thirds of adult values at the age of six months. Adult values are reached by about 3 years of age. Upon which can be concluded that reference values of ulnar and posterior tibial MNCVs for very preterm infants are scarce.

Assessment of maturity / gestational age
Dubowitz et al.18 reported a study in which they measure the calculation of MNCV in the newborn infant as an index of neurological maturity. They suggest that newborns with a gestational age of 32 - 38 weeks have a consistently slower MNCV at 40 weeks PMA in comparison to MNCV in term infants. Moosa and Dubowitz11 confirm their own findings in a later longitudinal study. From 44 weeks PMA onwards, however, a significant difference between MNCV of preterm infants compared to term infants is no longer found. Furthermore, Moosa and Dubowitz19 use the MNCV value in newborn infants as an assessment score of gestational age in comparison to a neurologic maturity score. They were able to predict gestational age with a 95 % confidence interval of 2.7 weeks when combining ulnar and posterior tibial MNCV, as opposed to 2.1 weeks when based on the neurologic maturity score.

Intrauterine growth retardation
Having first established that MNCV is dependent on gestational age, the relation to birth weight and intrauterine growth retardation was studied. Schulte et al.20 presented a study of 25 small for gestational age (SGA) term infants and 20 appropriate for gestational age (AGA) term infants, as well as 38 preterm infants, 14 twins and 1 triplet. No significant correlation is found between weight and MNCV. Koenigsberger et al.21 reported on a small study concerning multiple births. In 8 twins, 1 triplet and
1 quadruplet, a similar MNCV is found in infants of different birth weights. Goeschen et al.\textsuperscript{22} studied 20 pairs of twins and confirm no difference between twins, even if weight differences are $> 300$ g or $> 15\%$. Prakash et al.\textsuperscript{23} studied 26 term and 8 preterm twins. When birth weight difference is $> 20\%$ (n=4) or when infants with and without intrauterine growth retardation are compared (n=13 and 16, respectively), they find no relationship between MNCV and growth retardation. In conclusion, MNCV seems to be unrelated to birth weight and intrauterine growth retardation.

**Hypothyroidism / hypothyroxinemia**

Moosa and Dubowitz\textsuperscript{24} were the first to describe ulnar and posterior tibial MNCVs in cretins. They studied a group of nine cretins with ages ranging from one month to nine years, six of whom were studied prior to any thyroxine supplementation treatment. In four of the untreated children they found a slow conduction velocity alongside a delay in bone age. After treatment, MNCVs improve and reach normal values. De Vries et al.\textsuperscript{25} reported on MNCV in a group of 33 very low birth weight infants (gestational age $\leq 31$ weeks and birth weight $\leq 1500$ g). They collected data on thyroid hormones and TSH on days 3, 7 and 21 and performed both an ulnar and a posterior tibial nerve MNCV on day 21 and at 40 weeks PMA. A prolonged hypothyroxinemia (thyroxine $< 60$ nmol/l on day 7 and 21) correlates with a decreased MNCV at 40 weeks PMA. These findings lead to the conclusion that MNCV can be utilized for studying the effect of hypothyroidism and hypothyroxinemia on the peripheral nervous system.

**Conclusions**

In the last decade, the use of ulnar and posterior tibial MNCV in the newborn and young child has received little attention. Insufficient reference values in very preterm infants are available. In those studies regarding clinical applications, the association between hypothyroidism / hypothyroxinemia and MNCV is challenging. The measuring of MNCV may be used to study the effect of thyroid function on the developing peripheral nervous system.
References


