Abnormal nerve conduction velocity as a marker of immaturity in childhood muscle spinal atrophy

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Motor conduction velocity (CV) was tested in 117 infants and children with proximal spinal muscular atrophy (SMA), aged 1–53 months, and in 99 age-adjusted healthy controls. The children were classified into SMA forms 1 and 2 according to SMA International Consortium Criteria. In all children CV was tested in four nerves and the following parameters were taken into account: distal latency, conduction velocity, amplitude of muscle response. The electromyography of muscles revealed neurogenic changes.

In all cases of severe form 1 motor CV was markedly slowed, with significantly prolonged distal latency and reduced amplitude of M response. In surviving children CV, although increasing with age, was always below the values of normal age-adjusted children. The slowing was particularly pronounced in the femoral nerve. In SMA2 children the values of all tested parameters were closer to the values of age-adjusted healthy children, nevertheless they were always below the edge of normal values, also the rate of maturation was much slower than in normal children.

Sensory CV was normal in all tested groups.

The findings are suggestive of delayed nerve maturation in childhood SMA.

key words: conduction velocity, maturation, peripheral nerves, spinal atrophy

INTRODUCTION

The rate of conduction velocity in peripheral nerves changes with age [2, 8, 9, 15, 19]. Experience with full-term and preterm babies has shown that the rate of increase of conduction velocity (CV) depends mostly on the child’s age, much less on size and weight (e.g. small-for-date babies) [8, 24]. It may be assumed that the abnormally slow increase in CV with child’s age might be a sign of immaturity. Wagman and Lese [27] published findings on normal human motor conduction velocity in various nerves at different ages. Pinelli and Salla [19] were among the first to describe CV in young children, pointing out the difference between youngest and older children. Thomas and Lambert [26] have shown CV in newborn to be half of that in adults, to attain the full values at the age of 3–5 years. Cerra and Johnson [4] found slower values in preterm infants and stressed the difference between the upper and lower limb nerves. They suggested CV was a valuable objective indication of the maturation degree. Gamstorp [11] studied in detail three most often tested nerves in normal children from birth to adolescence. Several other papers presented CV correlation with maturation [5, 12, 16, 28], i.a. with EEG maturation [7].

Such developmental CV changes of normal children give the opportunity to use CV measurements in children with type 1 SMA (spinal muscular atrophy).
Slight CV abnormalities in type 1 SMA are not surprising and have been reported in literature [1, 10, 14, 15, 17–19, 21] and in our studies [13, 23], however, this has not been studied in a systematic way.

The purpose of this study was to examine CV in infants and young children diagnosed as type 1 and 2 SMA, to analyse the character of the abnormalities, if any, and to correlate those findings with clinical features.

MATERIAL AND METHODS

The studies were carried out on 117 SMA children followed-up at the Children’s Memorial Health Institute during the period 1979–1989. Apart from clinical examinations, the diagnosis was further confirmed by electromyography (EMG) in all the children and by muscle biopsy in most. At that time, molecular genetics had not yet been introduced into the SMA diagnosis. The classification criteria, based on SMA International Consortium instructions, were used, such as: the children being alert and floppy, with severely affected motor system, lower limbs being affected more than the upper ones. Their diaphragm and sensory system were spared; neuro-vegetative symptoms were pronounced. Respiratory failure in infants and youngest children developed during the follow-up period. The exclusion criteria strictly applied were: mental retardation, metabolic abnormalities, sensory deficit, congenital joint contractures, involvement of diaphragm or extraocular muscles. The katamnesis confirmed a typical course of SMA in all examined children.

The children were divided into the following 3 groups, depending on the severity of the disease:

Group A: 26 most severely affected infants diagnosed during their first 5 months of life, with mean age of onset already in 3rd week (from birth to two months). The infants died between 2.5–11 months of life (mean age at death: 6.4 months). These infants met the clinical criteria of severe SMA, type 1, according to the International SMA Consortium, or type 1.3–1.9 according to Dubowitz (Table 1).

Group B: 23 infants and children also severely affected, unable to sit unaided, diagnosed at 6th–38th months of life, with mean age of onset at 7.5 weeks. Mean age of death: 16.5 months. One child died at the age of 8.5 years. These infants and children met the clinical criteria of severe SMA, type 1, according to the International SMA Consortium or type 1.3–1.9 according to Dubowitz (Table 1).

Group C: 68 children less severely affected, sitting without support but not walking, diagnosed at 7th–53rd months of life, with mean age of onset at 5.5 months.

Two children of this group died, one at the age of 34 months and the other at 9.5 years. The age range at the follow-up period in that group was 11 months–16 years (mean 4.5 years), pointing to the protracted course of the disease. These infants and children met the clinical criteria of intermediate type 2 SMA, according to the International SMA Consortium, or type 2.1–2.9 according to Dubowitz (Table 1).

The three control groups of 99 age-adjusted children without any disease affecting the neuromuscular system were examined with the same method as the patients.

An informed consent from parents was obtained on admission.

In all the subjects the EMG of two muscles and electroneurography (ENG) in 4 motor nerves and 2 sensory nerves were performed, using DISA EMG with standard equipment. In all tested muscles EMG was neurogenic (not shown). Basically we used the technique described by Thomas and Lambert [26] of recording after stimulation. Motor nerves were stimulated with a surface electrode (type 13L36 or 13L35) using supra-maximal rectangular stimuli of 0.3 ms duration and 1 Hz frequency. The median nerve was stimulated at elbow and wrist, the peroneal nerve at the caput fibulae and ankle, the musculocutaneous nerve at Erb’s point, and the femoral nerve below the inguinal ligament. The compound muscle response was recorded from the following muscles: abductor pollicis brevis, extensor digitorum brevis, biceps brachii, rectus femoris. Conduction in the afferent part of the median nerve was tested using the ring surface electrodes (type 13L69) and so-called forceps surface electrodes in the youngest children. The skin of the 2nd and 3rd finger was stimulated with a supra-maximal stimulus of 0.2 ms duration and 2 Hz frequency. The sensory nerve potential was recorded at the wrist and elbow level using a surface electrode (type 13L36 or 13L35). Conduction in the sural nerve was tested by antidromical method, using the same surface electrodes, the skin over the gastrocnemius muscle was stimulated and the sensory nerve potential was recorded at the ankle. The temperature of the child’s limb was maintained within 30–33°C. We did not find significant differences between right and left side, which is in agreement with other authors.

The number of conduction tests in motor and sensory nerves in the patients of A, B and C groups and their respective age-adjusted control groups is presented in Table 1.

The following electrophysiological parameters were evaluated in each ENG test in motor nerves:
— conduction velocity (CV) in m/s in the median nerve in the elbow — wrist segment, and in peroneal nerve in the caput fibulae — ankle segment;
— distal latency (L) in the median nerve and peroneal nerve, and Conduction Time calculated in musculocutaneous and femoral nerves;
— amplitude (Amp) in mV and shape of evoked muscle response in the sural and afferent part of the median nerve;
— conduction velocity (CV) in the sural nerve in the calf — ankle segment and in the median nerve in the fingers — wrist and wrist — elbow segments.

For the statistical methods used in the evaluation of the material, see “Appendix”.

**RESULTS**

Mean values and standard deviation of conduction velocity (CV), latency (L), and amplitude (Amp) in motor nerves of the patient groups and their respective controls are presented in Table 2 and Figures 1–3.

Musculocutaneous and femoral nerves: conduction time in two short nerves was prolonged in the patient groups as compared with the controls, with significant differences (p < 0.001). Prolongation of conduction time was most pronounced in the A group in both nerves and more distinct in the lower limbs. In the femoral nerve the prolongation of conduction time was considerable even in group C (similar to that in group B) (Fig. 1).

Median and peroneal nerves: conduction velocity in long nerves was slower in the A and B groups as compared with the controls, with significant differences (p < 0.001). Normal CV in both nerves was found only in the C group (Fig. 1).

A comparison between the CV mean values in the SMA groups revealed significant differences (p < 0.001). Distal latency in both nerves was prolonged, as compared with the controls, only in the A group (significant differences, p < 0.001), while normal L values were found in B and C groups.

Significantly lower amplitude of evoked M responses in all nerves was observed in all SMA groups, being particularly pronounced in the femoral nerve (Table 2, Fig. 2).

The most significant electrophysiological parameters (CV, L or Amp) in the tested motor nerves, permitting differentiation between the SMA groups, were CV and L in the median nerve, L and Amp in the peroneal nerve, and L in the musculocutaneous and femoral nerves (Table 2).

The detailed analysis of the shape of M response is beyond the scope of this paper. It is however worth mentioning that the M response evoked by stimulation of immature nerve is less smooth, consisting of few asynchronous components.

Conduction velocity in group A was slowed in all the infants except two. The function of CV mean value with age was below the lower normal limit in the A group infants and began in the first month of life with the values observed in preterm infants (19.5 m/s), to reach 24 m/s at the age of four months (Fig. 3).

No further increase of CV was found during the following months. The mean CV value in the patients aged 4–10 months was 24 m/s, remaining within the lower normal limit for full-term newborns (mean value 27.6; range 21.2–34.1 m/s).

Conduction velocity in group B was slow or within the lower normal limit in all the children. The function

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**Table 1. Clinical material — three groups of SMA children and age-adjusted control**

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Number of children</th>
<th>Age (months)</th>
<th>Number of tested nerves</th>
<th>Sensory nerves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe type 1</td>
<td>1.1–1.2</td>
<td>A</td>
<td>26</td>
<td>1–5.5</td>
</tr>
<tr>
<td></td>
<td>1.3–1.9</td>
<td>B</td>
<td>23</td>
<td>6–38</td>
</tr>
<tr>
<td>Intermediate type 2</td>
<td>2.0–2.9</td>
<td>C</td>
<td>68</td>
<td>7–53</td>
</tr>
<tr>
<td>Total no.</td>
<td></td>
<td></td>
<td>117</td>
<td>1–53</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td>18</td>
<td>1–5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>6–24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42</td>
<td>12–48</td>
</tr>
</tbody>
</table>

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Table 2. The values of conduction velocity, latency and amplitude of evoked muscle response in three groups of SMA children as compared with age—adjusted control.

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Musculocutaneous n.</th>
<th>Median n.</th>
<th>Femoral n.</th>
<th>Peroneal n.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±1SD</td>
<td>±1SD</td>
<td>±1SD</td>
<td>±1SD</td>
</tr>
<tr>
<td>Severe A</td>
<td>0.55</td>
<td>±0.08</td>
<td>3.0</td>
<td>±1.1</td>
</tr>
<tr>
<td>type 1 B</td>
<td>0.40</td>
<td>±0.07</td>
<td>6.0</td>
<td>±2.2</td>
</tr>
<tr>
<td>Intermediate C</td>
<td>0.29</td>
<td>±0.04</td>
<td>7.8</td>
<td>±3.0</td>
</tr>
<tr>
<td>Control 1–5.5 month</td>
<td>0.32</td>
<td>±0.03</td>
<td>10.5</td>
<td>±3.4</td>
</tr>
<tr>
<td>Intermedia 2 type 1</td>
<td>0.26</td>
<td>±0.02</td>
<td>14.3</td>
<td>±4.4</td>
</tr>
<tr>
<td>6–24 month</td>
<td>0.25</td>
<td>±0.02</td>
<td>13.9</td>
<td>±3.7</td>
</tr>
</tbody>
</table>

![Graphs showing latency and conduction velocity](image_url)

Figure 1. The latency in proximal nerves (L), conduction velocity (CD) and latency (L) in long nerves in three groups of SMA children as compared with age-adjusted control.
Figure 2. Amplitude of evoked muscle response in three groups of SMA children as compared with age-adjusted control.

Figure 3. Conduction velocity of median nerve during first months of life in two groups of SMA1 children as compared with preterm children.
of CV mean value with age was below the lower normal limit in the B group infants. It began in the sixth month of life from 27 m/s, typical of normal newborns, to reach maximum value of 40 m/s in the 24th month, typical of seven-month-old normal infants. No further increase of CV was found during the following months, as opposed to normal children, in whom CV increase in median nerve is observed up to 44 months of life.

Therefore, the premature arrest of CV function development in group A infants was observed earlier (at 4 months) than in group B (at 24 months). In both groups maximum CV values were low, similar to the level of newborns CV values (group A) or 7-month-old infants (group B).

Low CV values in infants at the age of 1–12 months of the A and B groups were similar to those of pre-term babies studied by Cruz Martinez [5] (Fig. 3).

Conduction velocity in group C was normal in most (80%) children, with slow or border-line values in the other 20%. The function of CV mean value with age in group C was within the normal range up to 18 months of life, reaching maximum value of 50.5 m/s at approximately 24 months of age, earlier than in healthy children (57 m/s at 44 months). Dissociation between the mean CV values in group C and normal children was observed during the subsequent two years. The mean CV value in group C was at the level of normal 2-year-old children and at approximately 44 months decreased to the lower normal limit (51 m/s), to remain at that level during the subsequent years.

Therefore, the premature arrest of CV function development in group C infants was observed at the same time as in group B (at 24 months). Both groups had different maximum CV values, with lower or premature values in group B, and normal or borderline values in group C.

Latency in group A was prolonged or at the upper borderline in most (70%) youngest infants studied in the first four months of life. In the other 30% L was within the normal limits. The function of L mean value with age was different from the normal function, starting with 25% prolonged values in the first month of life and reaching in the 10th month of life the values observed in five-month-old normal infants (0.83 ms/cm). Latency and the function of L mean value with age in group B and C were within normal limits.

Sensory CV in both tested nerves was within normal values (not shown).

**DISCUSSION**

In all three examined groups some electrophysiological abnormalities were found in CV of long nerves, with the degree of the abnormalities being different in each group. Nevertheless, each of the groups examined differed from the controls in one or more electrophysiological parameters. The most pronounced changes of the parameters tested were found in group A, which also showed significant differences in latency as compared not only with group C but also B. The amplitude changes are rather common in all three groups.

The proximal short nerves are also affected, more in legs, with the changes being especially pronounced in the electrophysiological parameters of the femoral nerve.

Generally, the severe groups A and B are affected in respect of CV, latency and amplitude, which is in agreement with the results of other authors [14, 15, 17, 18]. Most chronic cases from our group C have CV or conduction time similar to the controls but the amplitude of M response is significantly lower than in the controls.

In all the groups the CV increase did not follow the age of the children in a normal way; there was always some delay expressed, first of all, in group A and also in group B.

Evolution of CV during development corresponds to maturation of peripheral nerves, i.e. to myelination and increase of the number of nerve fibres, their diameter and internode distance [6, 12, 20]. In normal conditions the maturation reaches the level of adult maturity at the age of 3–5 years [12, 22].

The degree of myelination of peripheral nerves increases with age during gestation and the first years of life.

The relationship between CV increase during development and age was experimentally studied in chicken and kitten [3, 25] and, of course, in normal, preterm and small-for-dates children [2, 8, 24].

In all the groups of the SMA children examined by us, especially those in groups A and B, lower values of CV and amplitude of M response as well as prolonged latency were found. In these two groups the values as well as maturation curves are similar to those observed in preterm children.

It seems that the abnormalities of CV found in the groups of SMA type 1 children fulfil the criteria of delay in CV development of immature children. In our material the delay of CV was much more expressed in the lower than in the upper limbs, as observed by many authors in preterm children [16].

It is hard to say if the delayed CV is ever compensat-ed in our group A, since a considerable majority of the children die before the age of 1 year. In group B very few children reach normal values quite rapidly, while the majority never reach normal values. In agreement
with the data of Thomas and Lambert [26], we also observed that in spite of reaching normal CV and normal excitability by children, the M response was still of lower amplitude and shorter duration than in adults. It is also possible that in the course of disease (some subset of SMA1 may survive longer), the selective loss of large fibres occurs. Also, the low temperature, which may be present in paretic limbs, may contribute to low value of CV measured.

Group C behaves in a different manner. The majority of cases have normal CV but low M response, which may suggest that it is due to the loss of some number of axons in the course of the disease rather than development disturbances. It is interesting however that in group C the rate of CV increase is compensated till the age between one and two years, being stabilised later in SMA children at this level, while in the controls it is still increasing up to 3–5 years. In consequence, the dissociation between normal CV values and those in SMA group C children is progressing, to become most pronounced at the age of 3–4 years.

In Thomas and Lambert’s paper [26] the CV in premature babies (21–40 days before full term) was 20.7± 0.74. The CV increase was very rapid and even in those premature children CV at the age of 3 years reaches the lowest values of the adult range, to reach normal adult values at the age of 5 years.

We might speculate that in premature normal babies the maturation is delayed but runs in a normal way whereas in SMA the delay in maturation is connected with disturbances of innervation and myelination. The low physiological parameters of peripheral nerves correlate with morphological changes. Drac in SMA type 1 children observed in ulnar and sural nerves much fewer myelinated fibres, nerve fibres with smaller diameter and/or shorter internodes, as compared with age-adjusted controls. She suggested the delay in maturation [6].

CONCLUSIONS

We suggest that the slow CV in SMA infants is due to the delay in maturation, which is also expressed in the arrest of further CV increase occurring earlier than in the controls. It seems that this is one more piece of evidence of immaturity occurring in childhood SMA, which corresponds to other signs of immaturity which we have been collecting for a long time.

APPENDIX

(prepared by Anna Karwańska)

1. Mean values with standard deviation of Conduction velocity, latency, and amplitude of evoked potential in the A, B, and C groups of patients and in three control groups were calculated. Comparisons were made between the results of the patient groups and the respective control groups, and between the results of A and B, and B and C groups of patients, using t Student test.

2. The most significant electrophysiological parameters (CV, L or Amp) in the tested motor nerves, permitting the differentiation between the A, B, C and control groups, were selected using the stepwise logistic analysis. Analysis was made for each motor nerve based on the changes in CV and Amp values in the patients as compared with the respective age-adjusted normal subjects.

3. The relationship between the CV and age for the patients in A, B, and C groups for the median n is presented as the exponential function:

\[ CV = (CV_{\text{max}} - CV_o) (1 - \exp(-k \times \text{age}) + CV_o) \]

where: CV is the value of conduction velocity in m/s calculated as the function of age; CV_{\text{max}} is the maximum value of conduction velocity; CV_o is the value of conduction velocity at birth (at 0 age); k is a coefficient (constant rate of maturity) determining the rate of reaching the CV_{\text{max}} value.

The relationship between L and age for the patients in A, B, and C groups for the median n is presented as the exponential function:

\[ L = (L_o - L_{\text{min}}) (\exp(-k \times \text{age}) + L_{\text{min}}) \]

where: L is the value of latency in ms/cm calculated as the age function; L_o is the value of latency at birth (at 0 age); L_{\text{min}} is the minimum value of latency; k is a coefficient (constant rate of maturity) determining the rate of reaching the L_{\text{min}} value.

The calculation of the function of the mean CV and L value with age, separate for each group, is based on 140 ENG of patients and control examinations (Table 2). The parameters of the exponential function were estimated by the generalised least square method (NLIN procedure in the SAS system). The results of the CV and L tests as the age function in the median n in the patients of the A, B and C groups of children were compared with the exponential function calculated for the controls.

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