F response and somatosensory and brainstem auditory evoked potential studies in HMSN type I and II

V Scaioli, D Pareyson, G Avanzini, A Sghirlanzoni

Abstract
To evaluate conduction along the proximal and distal segments of motor and sensory long limb nerves, as well as along the very short acoustic nerve, F response and somatosensory and brainstem auditory evoked potential were studied in a series of patients with hereditary motor and sensory neuropathy (HMSN) types I and II. A diffuse and comparable slowing of conduction in proximal and distal nerve segments, as well as along the acoustic nerve, seems to favour a primary myelin defect in HMSN I. F response and motor conduction velocity showed a similar derangement in both proximal and distal motor segments. Latencies of somatosensory evoked potentials were symmetrically prolonged and correlated with motor nerve impairment. Central conduction times were normal. Studies of brainstem auditory evoked potentials showed a high incidence of acoustic nerve involvement, the most evident abnormality being a statistically significant increase in the latency of the I wave. Our data seem to support the presence of primary myelinopathic damage in HMSN I.

Materials and methods
Patients
Sixty five patients seen at the "C Besta" Neurological Institute of Milan and diagnosed as having Charcot-Marie-Tooth disease entered the study. All were evaluated according to a clinical, genetic, and electrophysiological protocol. Briefly, the necessary criteria for a diagnosis of HMSN were the presence of symmetric sensorimotor peripheral neuropathy with a chronic course, associated with skeletal deformities (pes cavus); positive family history; and exclusion of other hereditary or acquired chronic polyneuropathies (on clinical and laboratory grounds).

Further subdivision into HMSN type I and type II was based on nerve conduction studies. According to the criteria of Dyck and Harding and Thomas, 44 patients whose ulnar nerve motor conduction velocity was < 43 m/s (range 37–31 m/s) were diagnosed as being affected by HMSN type I, the 21 patients whose ulnar nerve MCV was > 40 m/s (range 43–66.6 m/s) were classified as HMSN type II. The MCV cut off values were chosen to avoid cases of uncertain classification in the so called intermediate group.

Forty one of the 44 HMSN I patients belonged to 24 families with autosomal dominant inheritance, while 18 of the HMSN II patients belonged to 10 families showing autosomal dominant transmission. One HMSN I and 3 HMSN II cases were sporadic. Autosomal recessive inheritance was likely in 2 HMSN I patients.

The mean age of the patients with HMSN I (20 male and 24 female) was 32 years (range 4–72 years); mean duration of the disease was 21 years and mean age at onset was 11 years. Patients affected by HMSN type II (16 male and 5 female) had a mean age of 34 years (range 8–64 years), a mean duration of disease of 17 years and a mean age of onset of 17 years.
Electrodiagnostic procedures: ulnar nerve MCV and F response

The MCV of the ulnar nerve was studied by recording the compound muscle action potential from the abductor digiti minimi muscle by means of surface electrodes. Needle electrodes were used in the case of severe denervation.

The F response of the ulnar nerve was obtained by means of supramaximal nerve stimulation at the wrist, and recorded using surface electrodes (or needle electrodes in the case of severe denervation) placed on the abductor digiti minimi muscle. The initial latency of at least ten F and M responses was evaluated. Maximal F response motor conduction velocity (FCV) was measured as: max FCV = 2D/(Fmin – M – 1) where D = distance from wrist to the 7th cervical spinous process, Fmin = the minimal latency of the 10 F responses, M = the latency of the direct response.

Somatosensory evoked potentials

Somatosensory evoked potentials (SEPs) were obtained by stimulating the median nerve at the wrist. The stimuli were square shaped electrical pulses of a duration of 0.2 ms delivered at 3 Hz through surface electrodes; the intensity, checked by a current probe, was adjusted until only a small thumb twitch was produced (8–25 mA).

Responses were recorded by means of needle electrodes placed at Erb’s point for the N9 brachial plexus component, at the 6th vertebral spinous process (Cv6) for the N13 (cervical spinal cord) component, and at C3’ or C4’ for the N20 cortical component. Cephalic (Fz) and non-cephalic reference electrodes (linked ear and shoulder contralateral to the stimulated arm) were used, and ground electrodes were placed on the forearm of the stimulated side. At least two sets of 1500 artifact free, averaged responses were obtained from each stimulated side by means of a 5–3000 Hz (–12 dB/oct) bandpass filter. Absolute latencies from stimulus onset to the negative peak were measured at Erb’s point (N9), at Cv6 (N13), and at the contralateral somatosensory cortex (N20). Interpeak conduction times (N9–N13, N13–N20, and N9–N20) were also measured. Individual scores were regarded as abnormal if absolute or interpeak latencies exceeded the mean control value (45 subjects) by 2.5 SD.

Brainstem auditory evoked potentials

Brainstem auditory evoked potentials (BAEPs) were obtained by means of clicks generated by pulses of 0.1 ms and rarefaction polarity. Stimuli were delivered at a rate of 10 per second and at an intensity of 60 dB above the hearing threshold for each ear determined at the time of testing. The unstimulated ear was masked with white noise (–20 dB). EEG activity was recorded by means of surface electrodes: the active electrode was placed at Cz and the reference electrodes were placed on the ipsilateral and contralateral mastoid process. At least two trials of 2000 single responses each were averaged by means of 50–3000 Hz

Results

F response motor conduction velocity

An ulnar nerve F response was obtained in 36 patients, 23 with HMSN I and 13 with HMSN II. Both max FCV and MCV had a bimodal distribution and were greatly slowed in HMSN I patients, but normal or only slightly slowed in HMSN II subjects (table 1). In the HMSN I group, mean MCV did not significantly differ from mean max FCV (table 1), and there was a high correlation (r = 0.84) when the MCV and FCV of the same patients were compared.

Somatosensory evoked potentials

SEPs were obtained in 34 patients, 25 with HMSN I and 9 with HMSN II. The absolute latencies of all SEP components ranged from slightly increased to greatly increased in HMSN I patients, whereas they were normal or only slightly higher in HMSN II patients (table 2; fig). The amplitude of the N20 component was often decreased in both HMSN I and II groups; only in one HMSN I patient could no response be obtained.

The N13 cervical spinal cord component was recorded in 16 HMSN I and in all HMSN II patients; the N13–N20 central conduction time was within normal values in all patients (table 2).

Attempts were made to measure nerve conduction in the most proximal segment of the peripheral sensory pathway through the N9–N13 interpeak time. However, the N9 component was measurable only in eight patients with HMSN I: bilaterally in five, unilaterally in three. In these eight patients, the N9–N13 interpeak time was bilaterally normal (<4.3 ms) in two patients and increased (from 5 to 15 ms) in six patients.

The N13 and N20 components showed no significant asymmetry in latency: indeed, there was a high correlation between the N13 and Table 1 Nerve conduction studies

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean (SD) motor conduction velocity (m/s)</th>
<th>Mean (SD) F-wave conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMSN I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 23)</td>
<td>21.2 (5.2)</td>
<td>22.6 (6.4)</td>
</tr>
<tr>
<td>HMSN II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 13)</td>
<td>54.9 (6.8)</td>
<td>54.9 (5.3)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 27)</td>
<td>56.4 (3.1)</td>
<td>60.1 (2.8)</td>
</tr>
</tbody>
</table>
Table 2 Mean (SD) somatosensory evoked potentials

<table>
<thead>
<tr>
<th>Controls (n = 45)</th>
<th>HMSN I (n = 24)</th>
<th>p Value</th>
<th>HMSN II (n = 9)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9* Right</td>
<td>9-6 (0-8)</td>
<td>1-5 (3-6)</td>
<td>*</td>
<td>10-7 (0-5)</td>
</tr>
<tr>
<td>Left</td>
<td>9-4 (0-8)</td>
<td>1-7 (5-7)</td>
<td>*</td>
<td>10-9 (1-1)</td>
</tr>
<tr>
<td>N13 Right</td>
<td>12-9 (1-0)</td>
<td>21-7 (7-4)</td>
<td>*</td>
<td>14-4 (1-3)</td>
</tr>
<tr>
<td>Left</td>
<td>12-8 (1-0)</td>
<td>24-9 (6-9)</td>
<td>*</td>
<td>14-4 (1-2)</td>
</tr>
<tr>
<td>N20 Right</td>
<td>18-8 (1-2)</td>
<td>33-3 (7-7)</td>
<td>*</td>
<td>20-4 (1-1)</td>
</tr>
<tr>
<td>Left</td>
<td>18-8 (1-2)</td>
<td>33-4 (7-7)</td>
<td>*</td>
<td>20-3 (1-1)</td>
</tr>
<tr>
<td>N13-20 Right</td>
<td>5-9 (0-5)</td>
<td>5-6 (0-7)</td>
<td>NS</td>
<td>5-9 (0-9)</td>
</tr>
<tr>
<td>Left</td>
<td>6-0 (0-6)</td>
<td>5-7 (0-6)</td>
<td>NS</td>
<td>5-9 (0-5)</td>
</tr>
</tbody>
</table>

* p < 0.005; NS = not significant.

In one HMSN I patient no response could be obtained.

† N13 was obtained in 16 patients and N9 in 8 patients with HMSN I.

Table 3 Mean (SD) brainstem auditory evoked potentials

<table>
<thead>
<tr>
<th>Wave</th>
<th>Controls (n = 58)</th>
<th>HMSN I (n = 29)</th>
<th>p Value</th>
<th>HMSN II (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1-6 (0-1)</td>
<td>1-7 (0-2)</td>
<td>*</td>
<td>1-5 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td>1-6 (0-1)</td>
<td>1-7 (0-2)</td>
<td>*</td>
<td>1-5 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Wave III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>3-7 (0-1)</td>
<td>3-9 (0-3)</td>
<td>*</td>
<td>3-7 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td>3-7 (0-1)</td>
<td>3-9 (0-3)</td>
<td>*</td>
<td>3-7 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Wave V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5-5 (0-2)</td>
<td>5-7 (0-4)</td>
<td>*</td>
<td>5-6 (0-2)</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td>5-5 (0-2)</td>
<td>5-7 (0-4)</td>
<td>*</td>
<td>5-6 (0-2)</td>
<td>NS</td>
</tr>
<tr>
<td>Interpeak latency I-III</td>
<td>2-1 (0-1)</td>
<td>2-1 (0-2)</td>
<td>NS</td>
<td>2-2 (0-1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Left</td>
<td>2-1 (0-1)</td>
<td>2-2 (0-2)</td>
<td>NS</td>
<td>2-2 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Interpeak latency III-V</td>
<td>1-8 (0-1)</td>
<td>1-9 (0-2)</td>
<td>NS</td>
<td>1-8 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Right</td>
<td>1-8 (0-1)</td>
<td>1-9 (0-3)</td>
<td>NS</td>
<td>1-8 (0-1)</td>
<td>NS</td>
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<tr>
<td>Left</td>
<td>1-8 (0-1)</td>
<td>1-9 (0-3)</td>
<td>NS</td>
<td>1-8 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Interpeak latency I-V</td>
<td>3-0 (0-2)</td>
<td>4-0 (0-3)</td>
<td>NS</td>
<td>4-0 (0-1)</td>
<td>NS</td>
</tr>
<tr>
<td>Right</td>
<td>4-0 (0-2)</td>
<td>4-0 (0-3)</td>
<td>NS</td>
<td>4-0 (0-2)</td>
<td>NS</td>
</tr>
<tr>
<td>Left</td>
<td>4-0 (0-2)</td>
<td>4-0 (0-3)</td>
<td>NS</td>
<td>4-0 (0-2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* p < 0.0005; NS = not significant.

Figure: Latency distribution of the N13 and N20 components of somatosensory evoked potentials in normal subjects and subjects with HMSN I and II.

Discussion

The comparable values of FCV and distal MCV in HMSN I patients, both as a group and as individuals, support the hypothesis of a

N20 latencies of the two sides in HMSN I patients (r = 1 and r = 0.97, respectively).

In HMSN I patients, the latencies of N13 and N20 SEP components were compared with the latency of the F response and with MCV. Correlations between motor and sensory latencies and velocities were good, suggesting the reasonably homogeneous involvement of both motor and sensory nerves (ulnar nerve MCV v N20 latency, r = 0.77; ulnar nerve FCV v N20 latency, r = 0.93; ulnar nerve F wave latency v N20 latency, r = 0.95). In HMSN II patients, the absolute latencies of the N9, N13, and N20 components were slightly increased in three patients, whereas the N9–N13 and N13–N20 interpeak times were always normal, suggesting that the decrease in conduction took place distally to the N9 component.

Brainstem auditory evoked potentials

BAEP studies were performed in 31 HMSN I and 11 HMSN II patients. The results of three patients (two with HMSN I and one with HMSN II) were not eligible for data analysis because of abnormalities of audiometric tests, which were consistent with presbycusis in two and pronounced hearing loss due to previous middle ear infection in the third. Table 3 shows BAEP results of the remaining 39 patients. The HMSN I group showed a significant increase in I, III, and V absolute latency. The HMSN II group showed no significant increase in absolute latencies. BAEPs were normal in 7 of 29 (24%) HMSN I patients.

Wave I latency or I–III interpeak latency, or both exceeded the mean control value by more than 2.5 SD in 10 patients (35%). In detail, wave I latency was higher in five patients (bilaterally in three and unilaterally in two); I–III interpeak latency was increased in four patients (bilaterally in one and unilaterally in three); and in one patient both wave I and I–III interpeak latencies were bilaterally increased. Only one patient had a bilateral increase in all of the interpeak times (I–III, III–V, I–V). In the remaining 12 HMSN I patients (42%), the increase in absolute latencies or interpeak times ranged from 2 to 2.5 SD above the mean control group value. In detail, wave I was increased by 2–2.5 SD in nine patients (bilaterally in three); the latency of wave III was unilaterally increased in two patients; I–III interpeak time was bilaterally increased in one patient; and two patients had borderline values for the III–V interpeak time, as well.

Absolute wave latencies and interwave times were within 2.5 SD for all of the 10 HMSN II patients. BAEPs were normal in 7 HMSN II patients. Borderline values were obtained in three cases: in detail, a unilateral increase in I–III interpeak time was found in two cases and a unilateral increase in wave III was observed in the third patient.
homogeneous involvement of motor fibres. Increased F latency has previously been reported by Kimura in a group of HMSN patients.5 However, Panayiotopoulos et al also found a significant delay in lower limb F latency in some patients with Charcot-Marie-Tooth disease.9 A selective evaluation of type I versus type II was not attempted by these authors, nor was the correlation statistically assessed.

As far as SEPs are concerned, we found a clearcut increase in N20 latency (mean latency 14-5 ms above control value) in all but one HMSN I patient, in whom this component was not detectable at all. Similar results have been reported by Jones et al.11 This prolongation in latency was entirely due to peripheral conduction slowing, since no abnormality in central conduction time (N13–N20 interpeak latency) was detected.

The involvement of the peripheral sensory pathway was highly symmetrical. The severity of conduction slowing along the sensory pathway seemed to be roughly correlated with motor nerve involvement. The absence of a distoproximal gradient in conduction slowing along motor nerves, the symmetry of SEP latency delay, and the motor-sensory correlations are in favour of diffuse and comparable myelinopathic damage in HMSN I.

Distal (N9 latency) and proximal (N9–N13 interpeak latency) conduction along the median nerves could be compared in only eight out of 25 patients with HMSN I. The results were conflicting because of the large scatter of conduction in proximal sensory segments, a variability that may be due to nerve potentials originating from the activation of the motor branch of the mixed nerves and impairing the correct recording of N9–N13 interpeak latencies.12 Additional difficulties in recording the N9 component were probably due to the considerable desynchronisation and reduced amplitude of sensory action potential.

Conduction changes in the short acoustic nerve were also studied. Cranial nerve involvement in HMSN has been previously reported.13 14 Kimura has shown neurophysiological abnormalities in the trigeminal and facial nerves by studying blink reflexes and the direct M response of the VII nerve.15 Other authors have reported similar findings.16 17

BAEP abnormalities indicating acoustic nerve involvement in HMSN patients have also been reported.18 24 However, only a few studies of patient groups systematically deal with the frequency, extent, and pattern of VIII cranial nerve involvement. Given that this is the shortest body nerve (about 20 mm),25 the acoustic nerve may be particularly informative for pathogenetic investigations. It would be expected to be involved late, if at all, in primary axonal damage with secondary demyelination, whereas it would be expected to be demyelinated early in a primary and diffuse myelinopathy.

Wave I is believed to originate from the distal intracanalicular tract of the acoustic nerve, and waves II and III from the proximal intracranial acoustic nerve and from the cochlear nuclei, respectively.20 26 28 Therefore an increase in the latency of wave I and in the I–III interpeak time (in the absence of transmission defects) indicates slowing in conduction along the acoustic nerve.20 29 30

Our BAEP studies showed a high incidence of acoustic nerve involvement in HMSN I patients: 22 out of 29 (76%) HMSN I patients showed some change in early BAEP components (latency exceeding mean control values by more than 2 SD) and in 10 of them (34-5%) the early waves were greatly delayed (by more than 2-5 SD). The most evident abnormality was the significantly increased latency of wave I (table 3). These findings are in keeping with a slowing in conduction along the acoustic nerve.

Similar evidence of abnormal acoustic nerve conduction has been presented by Raglan et al, who compared audiological and electrophysiological data in 12 HMSN I subjects.21 On the basis of BAEP findings in nine patients, Triantafyllou et al have suggested that the involvement of the VIII nerve in HMSN I is more common than clinically expected and is probably related to a demyelinating process.22

We found an increase in III–V interpeak time (suggestive of brainstem acoustic pathway dysfunction) in only one HMSN I patient, who showed no other sign of central nervous system involvement. A mild and unilateral increase in the latency of wave I or III was found in three HMSN II patients.

The normal BAEP findings in 7 (24%) HMSN I patients deserve some comment. The acoustic nerve lacks the large myelinated fibres that are particularly affected in HMSN I. Their estimated conduction velocity is about 20 m/s26 28 and might not be further slowed by the disease. In addition, the proximal segment of the acoustic nerve, close to the brainstem, is ensheathed by central oligodendroglial myelin,23 which is not affected by the pathological processes of HMSN I. This tract varies in length in individual patients.24 The variability of the ratio of Schwann cells to central myelin may explain the variability of our findings in HMSN I: it is possible that no increase in latency can be detected when the Schwannian tract is too short, but when it is longer an expected increased latency of either wave I or the I–III interpeak time (or both) can be observed.

In conclusion, we found a homogeneous slowing in conduction along the peripheral motor pathways in HMSN I, with both FVC and MCV similarly decreased. Comparison between studies of conduction velocity and somatosensory evoked potential indicates that the motor and sensory peripheral pathways are proportionally involved; no significant asymmetry was found, which suggests an illness homogeneously affecting all of the peripheral sensory and motor nerves. This evidence is further supported by the high incidence of peripheral conduction abnormalities found in the acoustic nerve. Our neurophysiological data, considered as a whole and compared with those of HMSN II patients, seem to support the hypothesis of myelinopathic primary dam-
age in HMSN I.

This conclusion contrasts with the hypothesis of Dyck et al., of an axonal primary deficit in HMSN I. On the basis of morphological findings and axonal flow studies, they maintain that demyelination occurs secondarily to axonal atrophy. Their evidence partly comes from the finding of a higher frequency and greater degree of distal morphological abnormalities, which is suggestive of axonal atrophy affecting the extremities of the nerve cell first and more severely; they also found that demyelination was clustered on certain teased nerve fibres, as for a primary axonal disease, and not at random, as expected in primary Schwann cell dysfunction.

Neuropathological studies provide only indirect evidence of morphopathogenetic events—in this study, random demyelination or clustering of demyelination on individual fibres cannot be distinguished—but such studies do allow an extensive and reproducible evaluation of many nerve segments and districts in many patients at different disease stages. In our opinion, they seem to reflect the presence of a diffuse and homogeneously distributed demyelinating process, suggestive more of primary than secondary demyelination (depending on axonal atrophy or degeneration). Although our data cannot be taken as definite proof, they do suggest the need to reconsider the pathogenesis of HMSN I in an attempt to reconcile apparently conflicting results.

We thank Eng F Pansica for his skilled technical assistance. This paper was presented in part at the 41st annual meeting of the American Academy of Neurology, Chicago, in April 1989.


10 Panayiotopoulos CP, Scarpalezos S, Nastas PE. Sensory (1a) and F-wave conduction velocity in the proximal segment of the tibial nerve. Muscle and Nerve 1978;1:181–9.


