Distinctive abnormalities of motor axonal strength–duration properties in multifocal motor neuropathy and in motor neurone disease


Department of Neurological Sciences, IRCCS Ospedale Maggiore di Milano, University of Milan, Italy

† Deceased July 17, 2002

Summary
The strength–duration function is a classic measure of neural excitability. When studied on peripheral motor axons it reflects the intrinsic nodal membrane properties, and its time-constant (\( t_{SD} \) or chronaxie) predominantly depends on non-voltage-gated, rest Na\(^+\) inward conductances. We assessed the strength–duration curve of ulnar motor axons in 22 nerves of healthy controls, in 18 nerves of patients with multifocal motor neuropathy with conduction blocks (MMN), and in 19 nerves of patients with motor neurone disease (MND). The compound muscle action potential (CMAP) was smaller in nerves of both groups of patients than in controls (\( P < 0.05 \)). The rheobasic current (\( rh_{50\%} \) [mean ± standard deviation (SD)]) was higher in patients with MMN than in controls (13.3 ± 16.3 mA; controls 4.7 ± 1.7 mA, \( P < 0.05 \)). The \( t_{SD} \) was differentially abnormal in the nerves of the two groups of patients: it was prolonged in the nerves of patients with MND for >40 years (227.2 ± 34.5 μs; controls 190.9 ± 51.0 μs, \( P < 0.05 \)), but it was shortened in the nerves of patients with MMN (146.5 ± 55.4 μs; controls 208.6 ± 51.2 μs, \( P < 0.05 \)) who had not been treated recently with high-dose intravenous immunoglobulin (IVIg). Nerves of patients with recently treated MMN (<6 weeks) who were under the therapeutic effect of IVIg had a normal \( t_{SD} \). Our results suggest that, probably due to an immuno-mediated rest Na\(^+\) channel dysfunction, Na\(^+\) conductances are reduced in MMN. This abnormality is a function of the time after the last IVIg treatment and involves also the axonal membrane outside the conduction block. Conversely, in MND, possibly owing to the ionic leakage of degenerating membrane, rest Na\(^+\) conductances are increased. Measuring the strength–duration curve of the ulnar motor axons might be useful in the differential diagnosis between de novo MMN and MND.

Keywords: motor axons; motor neurone disease; multifocal motor neuroneopathy with conduction block; rheobase; time constant

Abbreviations: CMAP = compound muscle action potential; IVIg = intravenous immunoglobulin G; MMN = multifocal motor neuroneopathy with conduction blocks; MND = motor neurone disease

Introduction
Multifocal motor neuropathy with conduction blocks (MMN) and motor neuron disease (MND) are two pathological conditions that may both phenotypically appear as a lower motor neurone syndrome (Kornberg and Pestronk, 1995; Rowland and Shneider, 2001). Yet the World Federation of Neurology (Brookes, 1994) criteria classify MMN among disorders that can ‘mimic’ the more frequent MND. The distinction between the two conditions is nonetheless clinically essential for the prognosis and proper treatment of the patient (Rowland and Shneider, 2001). Unlike MND, an untreatable disorder with an invariably fatal outcome, MMN is a rare immune-mediated disorder which responds to high-dose intravenous immunoglobulin (IVIg) and has a more benign course (Taylor et al., 2000; Nobile-Orazio, 2001; Nobile-Orazio et al., 2002).

Whereas MMN typically affects the myelin sheath (Nobile-Orazio, 2001), MND leads to axonal loss (Hughes, 1982). Myelin damage in MMN has traditionally been considered mostly ‘focal’ (i.e. spatially limited to the zone of the conduction block), also because routine

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neurophysiological studies reported almost normal motor conduction velocity outside the conduction block (Kuntzer and Magistris, 1995; Nobile-Orazio, 1996; Taylor, 2000). Similar subtle abnormalities of motor nerve conduction velocity can be found also in MND (Daube, 2000). Because the safety factor of impulse conduction along human motor axons compensates for a mild fibre dysfunction, routine motor conduction velocity studies might not disclose the full extent of MMN. A functionally unaffected nerve outside the conduction block seems unlikely, therefore the classic conduction block could simply be the area of severest conduction abnormalities (‘the tip of the iceberg’). Outside the conduction block, motor fibre dysfunction could be present all along the nerve. Although experimental studies in animals suggest Na+ channel involvement at the nodal membrane as a mechanism of dysfunction in immune-mediated neuropathies (Takigawa et al., 1995; Waxmann, 1995; Weber et al., 2000), the final pathogenetic mechanism in human MMN remains unknown (Nobile-Orazio, 2001).

A classic measure of neural excitability is the strength-duration curve, namely the variation in stimulus intensity needed to achieve the same evoked response at various stimulus durations. Although the description of the strength-duration curve technique dates back ~100 years [Lapique (1909), cited by Bourguignonn, 1938], only recently has its usefulness been reappraised in human nerves (Mogyoros et al., 1996). The strength–duration properties of an axon are the rheobase and the chronaxie. The rheobase is defined as the minimum current intensity needed to obtain excitation with a stimulus of infinite duration. The chronaxie (or time-constant, $t_{\text{SD}}$), defined as the stimulus duration needed to obtain excitation with a current intensity twice the rheobase, essentially reflects the capacitive membrane properties (Moruzzi, 1981). Both variables functionally reflect the nodal membrane and are influenced by changes in membrane potential, impedance, capacitance and area of axonal membrane devoid of myelin (Brismar, 1981; Bostock, 1983). Although several factors can theoretically affect the time-constant of the strength–duration curve (or chronaxie), its measurement provides an indirect estimate of the persistent non-voltage-dependent inward Na+ conductance of the axonal membrane at the node (Mogyoros et al., 1997b, 1998). Assessment of the strength–duration properties of motor axons would therefore represent an interesting new method to test specifically the experimental hypothesis of Na+ channel dysfunction (Takigawa et al., 1995; Waxmann, 1995; Weber et al., 2000) in patients with MMN.

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Affected sites = most involved sites (LLs = lower limbs; ULs = upper limbs; R = right; L = left); Last IVIg = interval from the last IVIg treatment in weeks. The Rankin disability scale: 0 = asymptomatic; 1 = non-disabling symptoms not interfering with lifestyle; 2 = minor disability symptoms interfering with lifestyle but not interfering with patients’ ability to look after themselves; 3 = moderate disability symptoms interfering with lifestyle or preventing a fully independent existence; 4 = moderately severe disability symptoms preventing independent existence, although patients do not need constant attention day and night; 5 = totally dependent, requiring constant attention day and night (Nobile-Orazio et al., 1993).
To find out whether MMN and MND differentially alter non-voltage-dependent rest Na⁺ conductances, and to clarify whether the strength–duration technique would be useful in routine clinical neurophysiology using standard EMG/ENG equipment to distinguish between the two conditions, we tested the strength–duration properties of motor axons in the ulnar nerves of patients with MMN and MND, and in healthy controls.

**Material and methods**

**Subjects**

We studied 22 nerves in 15 neurologically healthy volunteers (age range 31–77 years, mean 48.5 years) with no history of neurological diseases, 18 nerves in 11 patients with MMN (age range 27–67 years, mean 47 years), and 19 nerves in 13 patients with MND (age range 32–74 years, mean 54.1 years). Twelve and 15 nerves, respectively, were from healthy subjects and MND patients, all of whom were over 40 years of age. All the participants gave their informed written consent according to the Declaration of Helsinki, and the experimental procedures had the approval of the local ethical committee.

The diagnosis of MMN fulfilled the criteria proposed by the ENMC (European Neuromuscular Conference) workshop on multifocal motor neuropathy (Hughes, 2001). Table 1 summarizes the patients’ clinical features. In brief, the clinical diagnosis of MMN required: chronic or stepwise progressive, asymmetric limb weakness with a multineuropathic distribution, affecting the muscles of at least two distinct motor nerves and lasting at least 2 months; minimal or no sensory loss or sensory symptoms; and no definite clinical signs of upper motor neurone involvement.

High-dose IVIg treatment (Ig Vena, Sclavo, Siena, Italy, or Sandoglobulin, Sandoz, Basel, Switzerland) consisted of 0.4 g/kg/day for 5 consecutive days (Nobile-Orazio, 2001). Even though all the MMN patients had a good and consistent clinical improvement after IVIg treatment, all of them needed periodic IVIg cycles to maintain this improvement. For this reason and because IVIg therapy might have altered the neurophysiological properties of motor axons, we subdivided the MMN patients according to the time elapsed after the last IVIg therapy: patients who received the last IVIg cycle in the 5 weeks before the neurophysiological study (nine nerves) were assigned to a recently treated group, and those who received the last IVIg cycle >6 weeks previously (nine nerves) were assigned to a non-recently-treated group. The cut-off point was 6 weeks because, in our experience (see also Meucci et al., 1997), by this time the clinical improvement and the possible neurophysiological effects induced by IVIg have disappeared.

The diagnosis of MND was made according to the El Escorial criteria (Brookes, 1994). Most patients had a pure lower motor neurone syndrome and all underwent extensive clinical and neurophysiological assessment. Most patients underwent CSF analysis, immunological screening (anti-GM1, -asialoGM1, -GD1a, -GM2, -GD1b IgG and IgM antibodies), MRI scans (brain and spinal cord), and testing of motor-evoked and somatosensory-evoked potentials.

The disability in both groups of patients was assessed using the modified Rankin disability score (Nobile-Orazio et al., 1993) (Table 1). An extensive routine EMG and ENG study before the assessment of the strength–duration properties showed that all patients had a normal sensory action potential in the ulnar nerve of the wrist.

**EMG recording and nerve stimulation procedures**

The temperature of the wrist and the hand was maintained at >32°C.

The compound muscle action potential (CMAP) from the abductor digiti minimi muscle was recorded by a pair of non-polarizable round surface Ag/AgCl electrodes (diameter 9 mm; Meditec, San Polo di Torrile, Parma, Italy). One was placed over the motor point and the other over the first interphalangeal joint of the fifth finger. A ground electrode (20 mm diameter) was placed proximally to the recording electrode. The surface EMG signal was preamplified, amplified, filtered (5–3 kHz), A/D converted (sampling rate 100 kHz), stored and analysed using standard neurophysiological apparatus for clinical purposes (Nicolet VikingQuest; Nicolet Biomedical Inc., Madison, WI, USA).

The ipsilateral ulnar nerve was stimulated just proximally (~1 cm) to the wrist joint by a pair of non-polarizable round (diameter 9 mm) surface electrodes cast in a plastic support at a fixed inter-electrode distance (30 mm) (Nicolet Viking; Nicolet Biomedical Inc.). After the electrode position over the ulnar nerve was adjusted to obtain the largest submaximal CMAP at a fixed stimulation intensity, the plastic support was firmly fixed with a Velcro® strip to the subject’s wrist.

In preliminary experiments, nerve stimuli were generated with a Grass S88K stimulator (Grass Instrument Division Astro Med, Inc., West Warwick, RI, USA) connected to an isolation unit denoted SIU5 and to a constant current unit denoted CCU1. In subsequent experiments, because the study aimed to propose a method suitable for clinical application, electrical stimuli were generated and digitally controlled by an insulated constant-current stimulation unit incorporated in the EMG apparatus. The output current ranged from 0.1–100 mA. Stimuli were square pulses of variable duration (0.02–1 ms). The rise time of stimuli varied according to stimulus duration as follows (output impedance 10 kΩ, 10 mA)
[stimulus duration (ms)/rise time (μs)]: 0.02/13, 0.05/19, 0.1/19, 0.2/17, 0.3/16, 0.5/16, 0.7/16 and 1/16.

The strength–duration curve and other neurophysiological variables

The method used for assessing the strength–duration curve of human motor axons (Fig. 1) was developed from that originally described by Mogyoros et al. (1996) in normal subjects.

At fixed stimulus durations (1, 0.7, 0.5, 0.3, 0.2, 0.1, 0.05 and 0.02 ms), the intensity of ulnar nerve stimulation (0.2 Hz) was adjusted to elicit a CMAP in the abductor digiti minimi muscle, with an isoelectric-negative peak amplitude of 50% of the maximum CMAP. In agreement with Mogyoros and colleagues, in preliminary experiments (not systematically reported in this paper) we found no difference between $\tau_{SD}$ and various CMAP sizes in a given nerve (Mogyoros et al., 1996). Hence, to avoid unnecessary discomfort, for all nerves we used a CMAP size that was 50% of the maximum. Similarly, to shorten the procedure and reduce the number of stimuli, we used eight different stimulus durations to track the strength–duration curve. In preliminary experiments, again in agreement with Mogyoros and colleagues, and although a smaller number of measurements yielded larger variances, we found no difference between $\tau_{SD}$ estimated with various numbers of stimulus durations (32, 24, 16, eight, four and two) (Mogyoros et al., 1996). Hence, to avoid unnecessary discomfort, for all the nerves we used eight different stimulus durations. To minimize the effects of small fluctuations (<2%) in the CMAP size, especially in patients with MND (Daube, 2000), we averaged four to six responses at each intensity and for each stimulus duration. The strength–duration curve for each subject was then plotted (Prism 2.0,
Graph Pad), putting the current intensity (mA) on the y-axis and the stimulus duration (ms) on the x-axis. The $\tau_{SD}$ (chronaxie) of this curve was finally calculated after linear transformation of the function using the Weiss formula (Weiss, 1901). The runs test failed to show significant non-linearity in all the plots. According to Weiss’s charge–duration equation, the strength–duration function can be linearly transformed in the charge ($\mu$C)–duration (ms) function (Fig. 1). The x-intercept of this linear regression function is the $\tau_{SD}$, and the slope is the rheobasic current ($rh_{50\%}$) for a CMAP 50% of the maximum response. According to this formulation the $\tau_{SD}$ can be considered to be the chronaxie.

The maximum isoelectric-to-peak CMAP amplitude and the threshold current intensity for eliciting a maximum CMAP with a stimulus duration of 1 ms ($thr_{100\%}$) (mA) were also measured. Although $thr_{100\%}$ and $rh_{50\%}$ both reflect motor axonal excitability, $thr_{100\%}$ arises from an experimental measurement, and $rh_{50\%}$ is calculated after linearly transforming the strength–duration function to the charge-duration function according to the Weiss formula.

In most subjects the ulnar nerves were studied on both sides.

### Statistical analysis
Values are represented as means ± 1 standard deviation (SD). Data were analysed using the Mann–Whitney U-test because the variances differed among groups. The one-sample Wilcoxon signed rank test was used to test whether single values differed significantly from those of a group. A linear correlation analysis was used to test the possible correlation between two variables. A $P$ value <0.05 was considered to indicate statistical significance.

### Results

#### Control nerves
None of the strength–duration variables studied differed between the right and the left side. In control nerves, the $thr_{100\%}$ was 8.9 ± 2.9 mA, the $\tau_{SD}$ was 208.6 ± 51.2 ms, and the $rh_{50\%}$ was 4.7 ± 1.7 mA (Figs 1 and 3). Although the $\tau_{SD}$ was significantly shorter in the ulnar nerves of older subjects (<40 years of age, 229.8 ± 45.1 ms; ≥40 years, 190.9 ± 51.0 ms; $P = 0.041$), $\tau_{SD}$ values did not correlate with age ($r^2 = 0.038$, $P = 0.381$). $rh_{50\%}$ did not differ significantly between the nerves of subjects <40 and ≥40 years of age (4.4 ± 1.2 mA versus 5.1 ± 2.1 mA, $P = 0.552$).

#### Patients with MMN
In the ulnar nerves of patients with MMN, the CMAP amplitude was abnormally low (patients 7.0 ± 5.0 mV, controls 11.8 ± 2.4 mV; $P = 0.005$), and in all the patients at least one nerve had an abnormal CMAP amplitude. CMAP size was smaller in the nerves of the non-recently-treated subgroup than in controls (5.8 ± 4.1 mV and 11.8 ± 2.4 mV, respectively; $P = 0.001$). $thr_{100\%}$ was increased in patients with MMN (patients 24.2 ± 20.9 mA, controls 8.9 ± 2.9 mA; $P < 0.001$), and in nine of the 11 patients at least one nerve had an abnormal value. $thr_{100\%}$ was also increased in the group of non-recently-treated patients (31.2 ± 26.6 mA, $P < 0.001$).

No significant difference was found between $\tau_{SD}$ in patients as a group and controls (174.2 ± 56.7 μs and 208.6 ± 51.2 μs, respectively; $P = 0.1$), but in most patients (nine out of 11) at least one nerve had an individually abnormal value (Fig. 2).

$\tau_{SD}$ varied significantly in relation to the time after the last IVlg treatment (recently treated group 202.0 ± 45.1 μs, non-recently-treated group 146.5 ± 55.4 μs; $P = 0.040$) (Fig. 3), and was significantly longer in control nerves than in the

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**Fig. 2** Calculation of the time-constant of the strength–duration curve ($\tau_{SD}$) and of the rheobasic current ($rh_{50\%}$) for ulnar motor axons in two representative pathological nerves. The $\tau_{SD}$ and the $rh_{50\%}$ in a nerve of a patient with MMN, not recently treated with IVlg (right plot), and in a nerve of a patient with MND in the group ≥40 years (left plot). See also the legend to Fig. 1.
The $\tau_{SD}$ also did not differ significantly in patients as a group and controls (218.4 ± 35.4 $\mu$s and 208.6 ± 51.2 $\mu$s, respectively; $P = 0.326$), and in 11 out of 13 patients at least one nerve had an individually abnormal value (Fig. 2). $\tau_{SD}$ values differed significantly according to age (<40 years 185.8 ± 12.1 $\mu$s, ≥40 years 227.2 ± 34.5 $\mu$s; $P = 0.018$) (Fig. 3). They were also significantly longer in the nerves of patients ≥40 years than in age-matched controls (227.2 ± 34.5 $\mu$s and 190.9 ± 51 $\mu$s, respectively; $P = 0.012$).

$rh_{50\%}$ values did not differ significantly in nerves from patients and controls (5.2 ± 2.9 mA and 4.7 ± 1.7 mA, respectively; $P = 0.619$), but again, in many patients (eight out of 13), at least one nerve had an individually abnormal value. In patients ≥40 years the $rh_{50\%}$ was normal (5.5 ± 3.2 mA and 5.1 ± 2.1 mA in patients and controls, respectively; $P = 0.921$) (Fig. 3).

**Comparison between patients with MMN and MND**

CMAP sizes were similar in the nerves of the two groups (MMN, 7.0 ± 5.0 mV; MND, 6.1 ± 3.2 mV; $P = 0.883$). Conversely, $thr_{100\%}$ differed significantly (MMN, 24.2 ± 20.9 mA; MND, 11.1 ± 5.7 mA; $P = 0.003$). The strength–duration variable $\tau_{SD}$ also differed significantly between the two groups (MMN, 174.2 ± 56.7 $\mu$s; MND, 218.4 ± 35.4 $\mu$s; $P = 0.015$). The difference was even more pronounced for the non-recently IVIg-treated MMN subgroup (MMN, 146.5 ± 55.4 $\mu$s; MND, 218.4 ± 35.4 $\mu$s; $P = 0.001$). $rh_{50\%}$ also differed significantly between the two groups (MMN, 13.3 ± 16.3 mA; MND, 5.2 ± 2.9 mA; $P < 0.001$). Notably, in all the non-recently-treated MMN patients in whom two nerves were tested, at least one nerve had a significantly shorter $\tau_{SD}$ than that in the nerves of patients with MND.

**Discussion**

In this study we found distinctive abnormalities in the motor axonal strength–duration properties ($rh_{50\%}$ and $\tau_{SD}$) in nerves of patients with MMN and MND. Our findings indicate that MMN and MND differentially alter non-voltage-gated Na+ rest conductances. Measurement of the strength–duration curve variables can therefore be useful in distinguishing between the two conditions.

It is important to note that when interpreting our findings we explicitly set out to develop a simple method that would be easy to use with the commercially available EMG apparatus for routine clinical neurophysiology. Because these systems often deliver imprecisely rectangular stimuli and because we needed a simple, quick procedure for routine clinical practice, using averages, our protocol led to possible minor inherent sources of error in the estimation of absolute values. However, these inexactitudes have no influence on the general interpretation of our results because the three subject

![Figure 3](image-url)
groups were studied with the same apparatus and identical experimental techniques. Differences among groups are therefore accounted for only by intrinsic and specific pathophysiological abnormalities of MMN and MND.

**Strength–duration properties of motor axons in normal subjects**

From the technique originally described by Mogyoros and colleagues, we developed a protocol that is easily reproducible with standard apparatus for routine EMG/ENG, and where testing takes a reasonably short period of time (approximately 15–25 min per nerve) (Mogyoros et al., 1996). Hence, the method should be suitable for use in clinical practice. There are several indications that our protocol, although simpler than that of Mogyoros and colleagues, provides similar results in normal subjects (Mogyoros et al., 1996). In agreement with Mogyoros and colleagues, in preliminary experiments (not reported here) we found that the number of stimulus durations used did not affect the \( \tau_{SD} \) value significantly (Mogyoros et al., 1996). Our results also confirm that \( \tau_{SD} \) is significantly shorter in subjects \( >40 \) years of age than in younger subjects (Mogyoros et al., 1998). Besides age-related differences, we found an ulnar motor axon \( \tau_{SD} \) of \( \sim200 \) \( \mu \)s, and an \( rh_{50\%} \) of 5 mA. Both values differ from those reported for the normal median nerve by Mogyoros and colleagues (rheobase \( \sim2.5 \) mA, time constant \( 460 \pm 126 \) \( \mu \)s) (Mogyoros et al., 1996) and from the normal peroneal nerve (Kuwabara et al., 2000), but the \( \tau_{SD} \) value of our experiments almost matches that reported for the normal ulnar nerve using the method of latent addition (175 \( \pm \) 21 \( \mu \)s) (Bostock and Rothwell, 1997). We decided to study the ulnar nerve because it is less likely than the median nerve to induce bias from a possible entrapment at the wrist. Median nerve entrapment at the wrist is reported to increase the rheobase (Mogyoros et al., 1997a). The shorter \( \tau_{SD} \) in ulnar axons probably reflects differences in conduction velocities, some 2–3 ms higher for the ulnar than for the median nerve (Kimura, 1989; Liveson and Ma, 1992; Oh, 1993). Because the \( \tau_{SD} \) is inversely related to conduction velocity. Differences in rheobase are more difficult to explain. A possible explanation could arise from the different CMAP size used in the study of Mogyoros and colleagues (30–40% of the maximum; Mogyoros et al., 1998) and that used in the present study (50% of the maximum). In addition, differences in rheobase could depend also on technical factors such as the size and the impedance of stimulating electrodes, and the distance between them (Mogyoros et al., 1996) because all these variables can influence the rheobasic current. Notably, our experimental protocol yielded considerably smaller \( \tau_{SD} \) variances than did the original method (50 \( \mu \)s versus \( \sim125 \) \( \mu \)s, respectively) (Mogyoros et al., 1996).

**Strength–duration properties of motor axons in MMN**

In patients with MMN, non-recently-treated with IVIg, \( th_{100\%} \) and \( rh_{50\%} \) were increased, whereas \( \tau_{SD} \) was abnormally short. All the patients in whom two nerves were studied had abnormal values for these three variables in at least one ulnar nerve. To our knowledge this is the first systematic investigation dealing with motor axonal strength–duration properties in MMN.

Assuming that \( \tau_{SD} \) is mainly determined by non-voltage-gated persistent Na\(^+\) channels (Bostock and Rothwell, 1997; Mogyoros et al., 1997b, 1998), the enlarged nodal membrane due to demyelination should involve a large number of channels and should in turn lengthen the \( \tau_{SD} \); however, experimental studies have shown a prolonged \( \tau_{SD} \) in demyelination (Brismar, 1981; Bostock et al., 1983). An additional point is that according to single axon experiments, an increased rheobase should be coupled to an increased, but not a decreased, \( \tau_{SD} \) (Mogyoros et al., 2000). A shortened \( \tau_{SD} \) therefore suggests that demyelination may not be the whole story in MMN, and indicates a reduced Na\(^+\) inward conductance at the nodal membrane. Although several factors could account for decreased Na\(^+\) inward conductance, the most likely explanation is a specific antibody-mediated inactivation of the Na\(^+\) channels at the nodal membrane, as observed in animal models of immune-mediated neuropathy.
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(Takigawa et al., 1995; Waxmann, 1995; Weber et al., 2000). Whatever the mechanism, the evidence for reduced rest Na+ conductance fits with the original hypothesis that the pathogenetic process in MMN blocks Na+ channels (Kaji et al., 1994). Hence, our results indicate that in MMN at least two factors impair impulse conduction, even outside the conduction block: myelin dysfunction and axonal hyperpolarization. The impaired inward rest Na+ conductance hyperpolarizes the inner part of the axonal membrane, especially if the outward K+ current is relatively spared and the Na-K pump is active. The presence of axonal hyperpolarization explains the increased ulnar motor axon \( rh_{50\%} \) in our study and is also consistent with the increased threshold current found in patients with MMN (Yokota et al., 1996). An additional possible explanation for the increased \( rh_{50\%} \) and \( thr_{100\%} \) is the presence of demyelination. Available pathological data suggest that demyelination in MMN (Auer et al., 1989; Kaji et al., 1992; Kaji et al., 1993) exposes the paranodal and the internodal axonal membrane, finally leading to a decreased resistance and increased capacitance. To trigger the action potential, the inward depolarizing current should therefore be stronger for achieving an equivalent charge density over the abnormally enlarged nodal membrane. An intriguing question is why these membrane abnormalities leave the motor conduction velocity almost normal, even though the strength \( vs \) duration curve may already be abnormal. The reason for this is that despite the already abnormal local membrane properties (as tested by the strength–duration curve), the safety factor of the saltatory conduction could still ensure a nearly normal motor nerve conduction.

Most of our patients had defined conduction blocks in the forearm proximal to the wrist, and in some of them the ulnar nerve had no classic conduction block, therefore the strength–duration abnormality reported in this study must arise outside the conduction block. Hence, the pathogenetic process involves motor nerve fibres outside the conduction block as well as nerves with no conduction block. Pathological observations showing onion-bulb demyelination in nerve segments adjacent to the conduction block (Auer et al., 1989; Kaji et al., 1992) and also abnormalities in the sural nerve (Corse et al., 1996), as well as the clinical observation of tendon hyporeflexia or areflexia and muscle cramp or fasciculation in some 25% of patients, are all consistent with our observation and with the presence of widespread nerve fibre dysfunction in MMN.

Interestingly, the time after IVIg treatment influences strength–duration properties, and especially the \( \tau_{SD} \), therefore suggesting that IVIg treatment restores normal strength–duration properties, \( thr_{100\%} \), \( \tau_{SD} \) and \( rh_{50\%} \), possibly by improving the inward Na+ resting conductances at the axonal level. The short interval between IVIg treatment and the onset of clinical improvement (3–10 days) (Nobile-Orazio et al., 1993) cannot be accounted for by remyelination. At first glance, our finding of a consistently decreased \( \tau_{SD} \) within the group of non-recently-treated patients with MMN contrasts with the reported increased \( \tau_{SD} \) in patients with MMN (Cappelen-Smith et al., 2000). Besides the possible limitation arising from their small study sample (three patients), Cappelen-Smith and colleagues do not mention whether, how or when patients were treated (Cappelen-Smith et al., 2000). Also in line with the observation that treatment changes the threshold current in patients with MMN (Yokota et al., 1996), our data show that the time elapsing after treatment with IVIg is critical for detecting abnormal strength–duration properties. Finally, our findings indicate that IVIg treatment improves patients’ clinical dysfunction by acting also outside the conduction block, on the rest of the nerve. They could therefore explain the lack of correlation between the clinical improvement and the changes in conduction blocks (Cappellari et al., 1996). After IVIg treatment, the improved axonal function outside the conduction block (as demonstrated by changes in the strength–duration function) might be enough to induce a clinical improvement, even without changing conduction blocks.

Strength–duration properties of motor axons in MND

When compared with closely age-matched controls, patients aged \( \geq 40 \) years with MND had normal \( thr_{100\%} \) and \( rh_{50\%} \), but a prolonged \( \tau_{SD} \). Our findings are consistent with a previous observation by Mogyoros et al. (1998).

Although group statistics failed to show differences, most single patients had at least one nerve with an abnormally increased \( thr_{100\%} \) and \( rh_{50\%} \), thus showing a trend towards ‘hypoexcitability’ of surviving motor axons. A possible explanation is that owing to the ongoing degenerative process, the still excitable membrane diminishes progressively and is replaced by a damaged and inexcitable membrane. In addition, this late stage may be preceded by axonal inexcitability due to axonal depolarization, thereby making the membrane functionally unresponsive (depolarizing block) owing to the impairment of voltage-dependent K+ channels (Bostock et al., 1995). Our observation that several nerves were hypoexcitable contrasts with the motor axonal hyperexcitability reported by others (Mogyoros et al., 1998). Only after normalizing their data, however, did these investigators find a decreased rheobase in MND. Normalization aside, this discrepancy probably arose because the severity of disease differed in the two studies. Two additional factors could help to explain why in several nerves we found an increased \( thr_{100\%} \) and \( rh_{50\%} \): first, changes in the geometry of the nerve due to axonal loss and intrafascicular fibrosis (Hughes, 1982); and secondly, the early involvement of low-threshold motor axons by the degenerative process (Daube, 2000). Both factors can selectively increase the rheobase, but leave the \( \tau_{SD} \) unchanged (Mogyoros et al., 1998), thus explaining our findings.

In agreement with previous findings (Mogyoros et al., 1998), the prolonged \( \tau_{SD} \) indicates an abnormally increased
Clinical implications for the diagnostic approach to patients with lower motor neurone syndrome

In practice, the differential diagnosis between MMN and MND can be difficult or impossible, not only on clinical grounds (Chad et al., 1986; Parry and Clarke, 1988; Pestronk et al., 1988, 1990; Auer et al., 1989; Di Bella et al., 1991; Nobile-Orazio, 2001; Rowland and Shneider, 2001), but even after a detailed neurophysiological assessment using routine techniques (Kornberg and Pestronk, 1995; Kuntzer and Magistris, 1995). The first difficulty in differentiating between the two conditions arises when conduction blocks involve the most proximal segments of the nerve trunk or the spinal root. In these cases, routine EMG techniques are useless and a proximal conduction block must be sought using special magnetic or electrical stimulation techniques (Carpo et al., 1998). Conduction blocks can also be hard to detect reliably when marked muscle atrophy results in a small CMAP. Another problem concerns the widely varying quantitative criteria for defining conduction blocks on accessible nerve segments (see references in Kuntzer and Magistris, 1995; Nobile-Orazio, 2001). Finally, conduction blocks might also be present in MND (Sumner, 1991; Lange et al., 1993; Daube, 2000), and even needle EMG studies can be inconclusive.

In conclusion, if the distinction between de novo MMN and MND is difficult on clinical grounds, routine neurophysiological tests can be insensitive and aspecific, providing ambiguous answers. Hence, there is a pressing need for a diagnostic technique providing sensitive and specific answers for the differential diagnosis between MMN and MND. Our findings imply that a lower motor neurone syndrome might be diagnosed by assessing the strength–duration properties of ulnar motor axons, yet all the patients we studied with non-recently-treated MMN, whom one would reasonably expect to resemble de novo MMN patients, had at least one ulnar nerve with a significantly shorter $\tau_{SD}$ than that of patients with MND.

In the proper clinical setting, a patient with a lower motor neurone syndrome and a shortened $\tau_{SD}$ in the ulnar nerve motor axons could be diagnosed as having MMN. The protocol for strength–duration curve assessment described here can be done using routine ENG/EMG apparatus and basic statistical software, and testing takes no more than 35–45 min per patient. We therefore believe that this technique, in the proper clinical setting, might facilitate the diagnosis of lower motor neurone syndrome.

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