Nerve excitability properties in Charcot–Marie–Tooth disease type 1A

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Summary
Charcot–Marie–Tooth disease type 1A (CMT1A) is commonly considered a prototype of a hereditary demyelinating polyneuropathy. Apart from the myelin involvement, there has been little information on axonal membrane properties in this condition. Taking advantage of the uniform nature of the disease process, we undertook the in vivo assessment of multiple axonal excitability properties at the median nerve in nine CMT1A patients with PMP22 (peripheral myelin protein 22) gene duplication and 53 controls. The thresholds of CMT1A patients were much higher than normal, and threshold electrotonus (TE) exhibited a consistent pattern of abnormalities: early steep changes (fanning out) of both hyperpolarizing and depolarizing responses were followed by increased inward rectification to hyperpolarizing currents and unusually fast accommodation to depolarizing currents. Strength–duration time constants and the shapes of recovery cycles were normal, although refractoriness and superexcitability were reduced relative to controls. The high thresholds and early fanning out of electrotonus indicated altered cable properties, such that a greater proportion than normal of applied currents reached internodal rather than nodal axolemma. The rapid accommodation to depolarizing currents suggested activation of fast K+ channels, which are normally sequestered from the nodal membrane. The excitability abnormalities are therefore consistent with a demyelinating pathology and exposure or spread of K+ channels from under the myelin. It remains to be seen whether the TE abnormalities in CMT1A, which resemble previous recordings from normal immature rats, can be distinguished from those in acquired demyelinating neuropathies.

Keywords: Charcot–Marie–Tooth disease type 1A; paranode; membrane properties; threshold tracking; potassium channel

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; CMAP = compound muscle action potential; CMT1A = Charcot–Marie–Tooth disease type 1A; CV = conduction velocity; DL = distal motor latency; PMP22 = peripheral myelin protein 22; SNAP = sensory nerve action potential; TE = threshold electrotonus

Introduction
Charcot–Marie–Tooth disease type 1A (CMT1A) is the most common form of hereditary motor and sensory neuropathy and its hallmark is diffuse demyelination (Dyck et al., 1993; Birouk et al., 1997). However, secondary axonal degeneration is common and its degree determines the patient’s functional disability (Hattori et al., 2003; Krajewski et al., 2000; Hanemann and Gabreels-Festen, 2002). To date, the pathophysiology of the secondary axonal degeneration in CMT1 is unknown, although abnormal axon–Schwann cell interaction has been considered to play a major role (Sahenk and Mendell, 1999a; Kamholz et al., 2000; Maier et al., 2002). Intact Schwann cells are important in maintaining axonal integrity and development (Peles and Salzer, 2000; Martini, 2001; Scherer and Arroyo, 2002), so it would be reasonable to assume that in CMT1A abnormalities exist in axonal membrane properties, as well as in myelin.

Measurements of axonal excitability properties by threshold tracking have recently shed light on a variety of conditions affecting peripheral nerves (Bostock et al., 1998; Burke et al., 2001). The excitability properties are particularly sensitive to membrane potential, but also depend on nodal and internodal ion channels, as well as the passive
membrane properties, such a nodal width, and the extent to which the internodal axonal compartment is electrically isolated from the nodal compartment (Bostock et al., 1998). Although many of these parameters are expected to be altered in demyelinating disease, several clinical studies have failed to reveal a clear-cut pattern of excitability changes related to demyelination. Thus a study of chronic inflammatory demyelinating polyneuropathy (CIDP) found raised thresholds but a shorter strength–duration time constant and no consistent changes in threshold electrotonus (Cappelen-Smith et al., 2001). Studies of multifocal motor neuropathy have found evidence of membrane hyperpolarization distal to sites of conduction block (Kiernan et al., 2002b), reduced Na\(^+\) conductance (Priori et al., 2002) and normal membrane properties proximal to sites of block (Cappelen-Smith et al., 2002), but at the sites of conduction block, where demyelination has been reported (Kaji et al., 1993), thresholds are very high and specific excitability changes relatable to demyelination have not been reported. A study of axonal and demyelinating forms of Guillain–Barré syndrome (Kuwabara et al., 2002a) also failed to find any changes in nerve excitability properties at the wrist that could be directly related to the demyelination, probably because the major pathology occurred more distally in these patients. It has previously been argued that the reason why threshold electrotonus studies have failed to reveal consistent abnormalities in demyelinating neuropathies is because axons and nodes are affected non-uniformly, and fibres demyelinated at the point of stimulation will preferentially be excited at adjacent normal nodes, or other, more normal fibres will be excited in their place (Bostock et al., 1998). This argument should be less applicable to CMT1A, in which it is possible to limit cases to a well-defined genetic defect [duplication of the PMP22 (peripheral myelin protein 22) gene] and axons are affected relatively uniformly.

This study was therefore undertaken to test the hypothesis that CMT1A patients, unlike those with previously studied acquired demyelinating diseases, would exhibit a consistent pattern of abnormal excitability measures. A further aim was to test for secondary changes in axonal membrane properties, such as changes in membrane potential, which could not be related directly to altered myelination but which might be related to the secondary axonal degeneration. In the event, a consistent pattern of abnormal nerve excitability properties was found, which was consistent with demyelination, but there was little evidence of degeneration, or excitability changes that might be related to degeneration, in the sample of patients studied.

**Patients and methods**

**Patients**

Recordings were made from nine patients with genetically proven CMT1A (aged 11–75 years; mean 48.1 years; seven males and two females) from three university hospitals in Japan. All patients showed typical but variable clinical features of CMT type 1, such as diffuse areflexia/hyporeflexia, length-dependent sensory loss, distal atrophy and foot deformities. A fluorescence in situ hybridization-based assay identified the 1.5 Mb duplication on chromosome 17p11.2–12 containing the PMP22 gene in all the subjects. No patient had a past history of diabetes, connective tissue disease, malignancy, electrolyte abnormality or use of neurotoxic drugs or steroids. All the patients had a clear family history of similar symptoms and signs of autosomal dominant inheritance. All the patients (and a parent for a minor) gave informed consent to participation in the study. This study was performed in accordance with the principles embodied in the Declaration of Helsinki and the protocol was approved by institutional review boards of all participating hospitals.

**Conventional nerve conduction studies**

Nerve conduction studies were performed with percutaneous stimulating and recording electrodes. The distal motor latency (DL), motor nerve conduction velocity (CV) and compound muscle action potentials (CMAP) were elicited with distal and proximal stimulation from the median (in the wrist with 7 cm stimulating–recording distance, and in the elbow), ulnar (in the wrist with 7 cm stimulating–recording distance, and in the forearm) and tibial (in the ankle with 8 cm stimulating–recording distance, and in the knee) nerves. Sensory nerve action potentials (SNAPs) were recorded antidromically from the median, ulnar and sural nerves using surface recording electrodes and stimulating–recording distances of 13, 11 and 14 cm respectively.

**Nerve excitability measures**

Studies were performed using a recently described protocol (Kiernan et al., 2000) designed to measure multiple nerve excitability parameters rapidly.

CMAPs were recorded from thenar muscles using surface electrodes over the abductor pollicis brevis on the dominant hand side, with the active electrode at the motor point and the reference on the proximal phalanx. The EMG signal was amplified (gain 1000, bandwidth 1.6 Hz to 2 kHz) and digitized by a computer (486PC) with an A/D board (DT2812; Data Translation, Marlboro, MA, USA) using a sampling rate of 10 kHz. Stimulus waveforms generated by the computer were converted to current with a purpose-built isolated linear bipolar constant-current stimulator (maximum output ±100 mA). The stimulus currents were applied via non-polarizable electrodes (Unique Medical, Tokyo, Japan), with the active electrode over the median nerve at the wrist and the reference electrode 10 cm proximal over muscle. Stimulation and recording were controlled by QTRAC software (©Institute of Neurology, London, with multiple excitability protocol TRONDXM).

Test current pulses of 0.2 or 1 ms were applied at 0.8 s intervals, and were combined with suprathreshold condition-
Table 1 Results of the nerve conduction studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>DL (ms)</th>
<th>CMAP amplitude (mV)</th>
<th>Motor CV (m/s)</th>
<th>SNAP amplitude (µV)</th>
<th>Sensory CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>8.5 (6.9–10.2)</td>
<td>4.7 (1.8–8.9)</td>
<td>22.3 (16–39)</td>
<td>2.1 (0–6.8)</td>
<td>22.4 (18–28; n* = 5)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>7.4 (5.9–9.1)</td>
<td>3.1 (0.9–4.2)</td>
<td>22.2 (15–38)</td>
<td>0.5 (0–3.0)</td>
<td>23 (20–26; n = 2)</td>
</tr>
<tr>
<td>Tibial</td>
<td>10.3 (6.5–12.1)</td>
<td>1.2 (0–3.2)</td>
<td>18.7 (13–35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sural</td>
<td></td>
<td>1.47 (0–12)</td>
<td></td>
<td></td>
<td>23 (16–29; n = 2)</td>
</tr>
</tbody>
</table>

Data are mean (range). There were nine patients (seven men, two women), with mean age 48.1 years (range 11±75 years). n* is the number of patients in whom CV was obtainable (i.e. presence of SNAP). DL = distal latency; CMAP = compound muscle action potential; CV = conduction velocity; SNAP = sensory nerve action potential.

ing stimuli or subthreshold polarizing currents as required. The polarizing, conditioning and test current pulses were all delivered through the same electrodes. The amplitude of the CMAP was measured from baseline to negative peak. For all tracking studies, the target CMAP was set to 40% of maximum. Skin temperature was recorded using an adhesive probe over the nerve, adjacent to the stimulation electrode, to monitor temperature close to the site where axonal excitability was tested. The sequence of recordings followed that previously described (Kiernan et al., 2000). Stimulus–response curves were recorded separately for test stimuli of durations 0.2 and 1 ms. The stimuli were increased in 6% steps, with two responses averaged for each step, until three averages were considered maximal. The ratio between the 0.2 and 1 ms stimuli required to evoke the same response was used to estimate the strength–duration time constant of axons of different threshold. A target response was then set at 40% of the maximum and the 1.0 ms test stimuli adjusted automatically by the computer to maintain this peak CMAP amplitude. Proportional tracking was used, whereby the change in stimulus amplitude from one trial to the next was made proportional to the ‘error’, or the difference between the last response and the target response (Bostock et al., 1998). The slope of the stimulus–response curve was used to set the constant of proportionality and to optimize the tracking efficiency. Prolonged subthreshold currents were used to alter the potential difference across the internodal as well as the nodal axonal membrane. The changes in threshold associated with these electrotonic changes in membrane potential normally have a similar time course and are known as threshold electrotonus (TE) (Bostock et al., 1998). Threshold tracking was used to record the changes in threshold induced by 100 ms polarizing currents, set to 40% (depolarizing) and −40% (hyperpolarizing) of the control threshold current. Three stimulus combinations were tested in turn: (i) test stimulus alone (to measure the control threshold current); (ii) test stimulus + depolarizing conditioning current; and (iii) test stimulus + hyperpolarizing conditioning current. Threshold was tested at 26 time points (maximum separation 10 ms) before, during and after the 100 ms conditioning currents. Each stimulus combination was repeated until three valid threshold estimates were recorded, as judged by the response being within 15% of the target response or alternate responses being either side of the target. We checked for the lack of CMAP response in all the raw traces after applying only conditioning stimulation.

The current–threshold relationship was tested with 1 ms pulses at the end of 200 ms polarizing currents, which were altered in 10% steps from +50% (depolarizing) to −100% (hyperpolarizing) of the control threshold. As with the conventional TE protocol, stimuli with conditioning currents were alternated with test stimuli alone, and each stimulus combination was repeated until three valid threshold estimates had been obtained.

The final part of the protocol recorded the recovery of excitability following a supramaximal conditioning stimulus. These changes were recorded at 18 conditioning (1/n) test intervals, decreasing from 200 to 2 ms in approximately geometrical progression. Three stimulus combinations were tested in turn: (i) unconditioned test stimulus (of 1 ms duration) tracking the control threshold; (ii) supramaximal conditioning stimulus (1 ms duration) alone; and (iii) conditioning + test stimuli. The response to (ii) was subtracted on-line from the response to (iii) before the test CMAP was measured, so that the conditioning maximal CMAP did not contaminate the measured response when the conditioning–test interval was short. Each stimulus combination was repeated until four valid threshold estimates had been obtained.

Control data

For threshold tracking studies, control data were obtained from 53 healthy individuals with mean age 43.1 years (range 23–84 years) at Chiba University Hospital. Given the fact that additional control data from an 8-year-old girl (not included for analysis at the parent’s request) has shown a similar trend of the nerve excitability properties to the adult controls, data from an 11-year-old CMT1A patient was included for the study. All subjects (and a parent for a minor) gave informed consent.

Data analysis

Values for the excitability measures obtained in the present study were compared with normative data. The Mann–Whitney U test or repeated measures ANOVA (analysis of variance) was used for comparison using SPSS 11.0J (Tokyo, Japan). TED (5 ms), TED (10–20 ms) and TED (90–100 ms) were the mean threshold reductions at or between the specific
latencies after the onset of depolarizing current, and \( \text{TEm} \) (10–20 ms), \( \text{TEm} \) (20–40 ms) and \( \text{TEm} \) (90–100 ms) were the corresponding threshold changes after the onset of hyperpolarizing current. \( \text{TEd} \) (16 ms) ± \( \text{TEd} \) (5 ms) was the difference in the threshold reductions at the respective latencies.

## Results

### Clinical features and nerve conduction study

Clinical profiles of the patients are shown in Table 1. Electrophysiological features showed diffuse demyelinating sensorimotor polyneuropathy with uniform conduction slowing, typical of CMT1, in all the subjects (Birouk *et al*., 1997). Note that the median CMAP amplitudes were normal in 66% of the patients. As expected, there was an inverse relationship between age and median CMAP amplitude (\( r = -0.61, y = -0.0637x + 7.9344 \)), but otherwise no age effect was observed in the analyses described below.

It has been shown that serum potassium level significantly affects axonal excitability (Kiernan *et al*., 2002a; Kuwabara *et al*., 2002b); the level was obtained in six of the nine subjects and all values were within normal limits (mean 4.1 mEq/l, range 3.7–5.3 mEq/l, normal, 3.5–5.5 mEq/l). As there was no significant change in the parameters assessed below between those from all the CMT patients and from patients with normal serum potassium levels, the remaining statistical analyses compared all the CMT patients with the controls.

### Multiple excitability measures using threshold tracking

#### Stimulus–response curves

In the stimulus–response curves, the threshold currents in the nine CMT1A patients were significantly higher than those in the 53 healthy controls (Fig. 1). The stimulation current required to produce a minimal (10%) CMAP in the CMT1A patients was more than three times as high as that required to produce a maximal CMAP in healthy controls (Fig. 1). To produce a CMAP 40% of maximum, the mean absolute current for the 0.2 ms test stimulus was 48.7 ± 18.8 mA in the CMT1A patients and 9.5 ± 0.6 mA in the controls (\( P < 0.001 \)). The mean absolute current for the 1.0 ms test stimulus was 21.5 ± 8.2 mA in the patients and 5.3 ± 0.5 mA in the controls (\( P < 0.001 \)). Despite the significantly greater stimulation current in the patients, the test was well tolerated by the patients, possibly because of impaired sensation.

#### Strength–duration properties

Although the strength–duration time constant was slightly increased in the CMT group, there was no significant difference between the two groups (Fig. 2). The strength–duration time constant was fairly stable in both controls and CMT1A patients throughout the different CMAP amplitude levels. However, in CMT1A patients, an inverse relationship between the maximum CMAP amplitude and the strength–duration time constant at the 50% maximum CMAP level (\( r = -0.51 \)) was found.

#### Recovery cycle

The patterns of the recovery cycles were similar in controls and CMT patients, the relative refractory period lasting <3 ms, supernormality being maximal at the 5-ms conditioning–test interval and late subnormality maximal at ~40 ms (Fig. 3). The extent of the changes in threshold during the refractory period was significantly greater in the control group at the 2-
ms conditioning–test interval ($P < 0.0007$), but not significantly different at the 2.5-ms interval ($P = 0.10$). For supernormality, the control group demonstrated a greater threshold change than the CMT group ($P < 0.02$), but there was no difference in late subnormality ($P = 0.88$) (Fig. 3). These findings of normal durations of the periods and reduced threshold changes in the patient group compared with those in controls are similar to the data in chronic inflammatory demyelinating polyneuropathy (Cappelen-Smith et al., 2001).

**Threshold electrotonus and current–voltage relationships**

The most striking abnormalities in excitability parameters were revealed by the recordings of TE (Fig. 4). Table 2 documents comparisons of various excitability measures. Significant changes were observed in the responses to hyperpolarizing current. These were most pronounced in the early part of the responses [TEh (10–20 ms) and TEh (20–40 ms)] (Table 2) but still present at 90–100 ms. A closer look at the early part of the response to depolarizing current [TEd (10–20 ms)] also disclosed steeper than normal changes. Because families of these electrotonus response curves can resemble the ribs of a Japanese fan, coming from a point near the origin of the plot (Fig. 6B), these changes can be described as a ‘fanning-out’ of the responses (Kaji, 1997). The more pronounced curvature in the CMT hyperpolarizing electrotonus suggests more accommodation due to activation of inward rectification by the hyperpolarization-activated current $I_{H}$ (see Discussion).

The depolarizing electrotonus was more complicated, the CMT patients exhibiting first more, then less, and then more threshold reduction than the controls. At 5 ms, the depolarizing current induced a significantly greater threshold reduction than in controls (fanning-out). This was, however, quickly followed by an accommodative fall in threshold, between 5 and 16 ms. At longer delays, the CMT patients again showed a significantly greater threshold reduction than controls.

The current–threshold relationship (Fig. 5) also showed evidence of contrasting changes in passive and voltage-dependent membrane properties. With small currents, the slope of the current–threshold relationship was reduced, which, like the early fanning out of the TE, indicates that a greater fraction of the applied current was reaching the internodal axon (see Discussion). With larger currents, however, the slope was increased, in both the depolarizing and hyperpolarizing directions, until the absolute threshold changes returned towards and crossed the control curves respectively, indicating increased outward and inward rectification. Neither the TE nor the current–threshold relationship revealed correlation between CMAP amplitude and the extent of the nerve excitability abnormalities.

**Discussion**

The present study has shown that, in CMT1A, recognized as a polyneuropathy with uniform demyelination, there are consistent changes in nerve excitability properties, especially in resting thresholds and in TE. These changes were unlikely to be related to axonal degeneration, as CMAP amplitudes were fairly well preserved in the tested nerves, and there was no correlation between CMAP amplitude and the extent of the electrotonus abnormalities. Here we will consider the likely biophysical basis of the excitability changes observed.
creased, i.e. that $R_\text{il}$ is reduced in relation to $R_n$. If $R_n$ were increased, the current threshold would fall, so we conclude that there is a reduction in $R_\text{il}$, which could be caused either by thin or ‘leaky’ myelin, or by a loosening of the axon–Schwann cell paranodal seal; both of these changes are consistent with the pathology of CMT1A. The reduction in $R_\text{il}$ reduces $I_\text{il}/I$, so that the applied current has to be increased to reach the same threshold depolarization of the node. The reduction in $R_\text{il}$ also increases $I_\text{il}/I$ and the initial rate of polarization of the internodal axolemma. In a previous paper we introduced the idea of the ‘fan’ origin of TE (Bostock 1995; Kaji 1997; Yang et al., 2000): the point (found by projecting back the tangents to the initial portion of slow electrotonus to the resting threshold) from which the slow electrotonus appears to originate (O in Fig. 6B). The time interval ($t_\text{f}$) from the fan origin to the time of current application was shown to be $C_\text{i} (R_\text{il} (R_\text{il} + R_\text{an})/R_\text{n}$ for the simplified circuit of Fig. 6A. A reduction in $R_\text{il}$ reduces $t_\text{f}$ and causes a more acute fanning-out of electrotonus.

**Increased inward rectification in CMT1A**

On the hyperpolarizing side, the early increased fanning out of TE in CMT1A is not maintained (Yang et al., 2001). Inward rectification, most likely due to the slowly activating hyperpolarization-activated current $I_{\text{H}}$, sets in, so that by 100 ms the CMT1A and control curves are approaching each other, and by 200 ms (the time used for the current–threshold measurements in Fig. 5) the curves cross over for hyperpolarizing currents in excess of 40% of threshold. Greater activation of $I_{\text{H}}$ during hyperpolarization TE in CMT1A patients is also indicated by the excitability overshoot after the end of the hyperpolarizing current at 150 ms, since $I_{\text{H}}$ deactivates slowly. Although the TE and current–threshold data thus both indicate increased activation of $I_{\text{H}}$ in CMT1A patients relative to normal controls, it is not clear whether this implies any alteration in axonal channel function (e.g. channel density). Because threshold currents are abnormally high in CMT1A, the polarizing currents used in the TE and current–threshold recordings are also abnormally high, so that the degree of hyperpolarization of the internodal axon must be much greater. It is therefore quite possible that the increased activation of $I_{\text{H}}$ in CMT1A patients simply reflects
this increased membrane hyperpolarization rather than any abnormality in ion channels.

**Rapid outward rectification in CMT1A**

On the depolarizing side, the early increased fanning out of TE in CMT1A is much shorter-lived and quickly gives way to rapid accommodation. This rapid accommodation is similar to that previously seen in young rats, which was shown to be due to activation of fast K+ channel channels that were blocked by 4-aminopyridine (Yang et al., 2000). Whereas in normal, mature myelinated axons the fast K+ channel channels Kv1.1 and Kv1.2 are concentrated in the juxtaparanodal region of the internode (Vabnick et al., 1999; Girault and Peles, 2002), where they only affect slow components of electrotonus, in CMT1A they are activated rapidly by applied currents, either because they have spread to the nodal region, or because disruption of the axon–Schwann cell paranodal seal allows more current to reach the juxtaparanodal zone. Prior observations in the experimental demyelination demonstrated similar participation of the internodal K+ channel channels to action potentials, in accordance with the present findings (Bostock et al., 1981; Brismar, 1981; Chiu and Ritchie, 1981). An alternative viewpoint, suggested by the resemblance of TE in CMT1A patients to that in immature rats (Yang et al., 2000), is that overproduction of the myelin protein PMP22 in the disease may inhibit normal nodal maturation. This interpretation is in accordance with studies demonstrating that axonal cytoskeleton in CMT1A is similar to those in immature axons (Sahenk et al., 1999b), and that PMP22 overexpression in mice causes dysmyelination (Robaglia-Schlupp et al., 2002).

**Is membrane potential altered in CMT1A?**

One of the aims of this study was to test for changes in axonal membrane properties which might be related to secondary axonal degeneration, such as membrane depolarization. Our recordings provide no evidence that membrane potential is appreciably abnormal in CMT1A. It might be argued that the raised thresholds and fanning out of TE are characteristics of membrane hyperpolarization. However, the early fanning out in CMT1A patients is very different from the fanning out seen in hyperpolarization, whether caused by DC currents, release of ischaemia, hypokalaemia or occurring in multifocal motor neuropathy (Kiernan and Bostock, 2000; Kiernan et al., 2002b; Kuwabara et al., 2002b), in which the deviation from normal increases during 100 ms hyperpolarization. In all of these examples of membrane hyperpolarization, superexcitability was increased relative to normal and relative to the late subexcitability. In CMT1A, however, the recovery cycle is relatively normal (Fig. 3), although refractoriness and superexcitability are significantly reduced. These changes in the recovery cycle are difficult to interpret in the presence of the substantial changes in passive membrane properties, but
are no more consistent with depolarization (which invariably increases refractoriness) than with hyperpolarization.

**Comparison with other chronic demyelinating neuropathies**

The results of the axonal excitability measures in the present study are different from those previously described in acquired demyelinating neuropathies, namely CIDP, multifocal motor neuropathy and Guillain–Barré syndrome, as described in the Introduction. Interestingly, a more recent study has found that a subset of CIDP patients, corresponding to those with a diffuse pattern of demyelination, exhibit features rather similar to those in CMT1A, namely increased thresholds, early fanning-out of TE, with increased activity of inward rectification on hyperpolarization (Sung et al., 2004).

There may be a contribution from endoneurial inflammation to the findings in these demyelinating neuropathies (Redford et al., 1997), but it is unlikely that this plays a major role in CMT1A. It remains to be determined whether there are any consistent differences between the abnormal excitability properties in CMT1A and CIDP that could relate to the different aetiologies of demyelination.

**Decreased nerve conduction velocity in CMT1A**

Many factors may contribute to the decreased nerve conduction velocities typically seen in CMT1A, including axon diameter, myelin thickness and internodal distance. Recently, a few molecules, such as contactin, have been shown to play an important role in segregating nodes and juxtanodaparanes and in anchoring Schwann cells to paranodes (Boyle et al., 2001). The disruption of the paranodal junction alone in contactin mutant mice may account for the impaired conduction velocity (Boyle et al., 2001). The disruption of the paranode is expected to reduce \( R_\text{d} \) (Fig. 6A), with consequent effects on excitability parameters, as found in CMT1A, as well as on conduction velocities (Boyle et al., 2001; Kaji, 2003). An alternative explanation for the reduction in velocity is decreased Na\(^+\) channel function (e.g. decreased density) (Kazarinova-Noyes et al., 2001). However, our results did not support abnormal Na\(^+\) channel function, as strength–duration time constant, a sensitive parameter, was not significantly different from that of age-matched controls.

In summary, our data indicate that CMT1A patients exhibit a consistent pattern of abnormal nerve excitability properties. This pattern indicates increased access of applied currents to the internodal compartment of the axon and increased activation of fast K\(^+\) channels. This is the first time that abnormal excitability properties have been found in a neuropathy that are logically attributable to altered myelination, and which may therefore aid the interpretation of excitability abnormalities in other conditions. However, the resemblance of the TE recordings to those in immature rats raises the possibility that the changes are related more specifically to nodal dysmaturity, and may differ in some respects from those in other demyelinating neuropathies.

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