Sensory pathophysiology in chronic acquired demyelinating neuropathy

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Summary

Pathophysiological changes in sensory fibres in chronic acquired demyelinating neuropathy (CADP) are poorly understood, and it is not known to what extent sensory loss may be due to axonal loss or to conduction block. Motor and sensory nerve conduction were studied in 18 patients with CADP to delineate abnormalities in the compound sensory action potential (CSAP) recorded proximally along the limb. To distinguish small CSAPs from noise, near-nerve needle electrodes and electronic averaging were used. In all, 58 motor and 78 sensory nerves in the upper and lower limbs were studied, and in 29 nerves, motor and sensory conduction was compared over the same proximal and distal segments of the upper limbs. The proximal/distal amplitude ratio (P/D ratio) of the compound muscle action potential (CMAP) was reduced in 76% of the nerves compared with only 21% of the CSAPs. The amplitudes of CMAPs evoked and of CSAPs recorded distally were reduced to the same extent. The prolongation of the distal motor latency (DML) was linearly related to the reduction in amplitude of the CMAP whereas reduction of the distal sensory conduction velocity (SCVd) mainly occurred if the amplitude of the CSAP was reduced more than 70%. The proximal motor nerve conduction velocity (MCVp) was reduced by 40–50%, twice as much as the reduction in distal MCV (MCVd) (calculated from the reciprocal DML), and related to the reduction in the P/D ratio of the CMAP. The proximal SCV (SCVp) decreased ~20%, similar to the reduction in SCVd, and out of proportion to the marked reduction of the MCVp. The results suggest different pathophysiological changes in sensory and motor fibres in CADP. Thus, nerve fibre loss could account for most of the abnormal parameters in sensory conduction, whereas demyelination was the dominating cause of motor nerve dysfunction.

Keywords: muscle and sensory action potentials; nerve conduction velocity; conduction block; demyelination; axonal loss

Abbreviations: CADP = chronic acquired demyelinating neuropathy; CIDP = chronic inflammatory demyelinating neuropathy; CMAP = compound muscle action potential; CSAP = compound sensory action potential; DML = distal motor latency; Ig = immunoglobulin; MCV = motor conduction velocity; MCVd = distal motor conduction velocity, calculated from the reciprocal; MCVp = proximal motor conduction velocity; P/D ratio = ratio of the amplitude of the response evoked at proximal stimulation to that evoked at distal stimulation; SCV = sensory conduction velocity; SCVd = distal sensory conduction velocity; SCVp = proximal sensory conduction velocity

Introduction

Sensory symptoms and signs in patients with CADP may vary, being severe with sensory ataxia in some but absent in others. Similarly, the recorded CSAP may be normal, markedly reduced in amplitude or absent (Thomas et al., 1969; Dyck et al., 1975; Prineas and McCleod, 1976; Lewis et al., 1982; McCombe et al., 1987). However, the pathophysiological changes in sensory nerve fibres in these patients are not well understood. The motor deficit may be associated with loss of fibres or conduction block. Similar changes could occur in sensory fibres but sensory conduction along proximal parts of the limb has rarely been studied (Meché et al., 1989). It is therefore not known whether the sensory loss could, in part, be due to sensory conduction block. By contrast, in multifocal motor neuropathy, it is well established that sensory conduction is spared even across sites of conduction block (Parry and Clarke, 1988; Krarup et al., 1990; Kaji et al., 1993; Chaudry et al., 1994). For a better understanding of the sensory pathophysiology, we compared sensory and motor conduction over proximal nerve segments in patients with CADP. Recording of the CSAP...
through needle electrodes placed close to the nerve, combined with electronic averaging, enables recording of potentials with amplitudes of \( \leq 0.1 \mu V \) (Buchthal and Rosenfalck, 1971; Behse and Buchthal, 1978; Krarup-Hansen et al., 1993). This degree of resolution is necessary to record the CSAP from nerves with marked loss of sensory fibres and to evaluate the degree of temporal dispersion.

The main findings suggested that the degree of motor and sensory fibre loss was similar, but that sensory conduction block rarely occurred and that the SCV was less reduced than the MCV. These findings were similar to those reported for the mixed nerve action potential (Luciano et al., 1995) and suggest that pathophysiological changes in sensory fibres may differ from those in motor fibres. Preliminary reports have been published (Krarup and Trojaborg, 1993, 1994).

**Material and methods**

We studied 18 patients (six women, 12 men) aged 16–80 years with progressive or relapsing CADP (Table 1), fulfilling the 'research criteria for diagnosis of chronic inflammatory demyelinating polynuropathy' of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (Cornblath et al., 1991a). All the patients had weakness, in 10 generalized, in four asymmetrical and in four, arms were weaker than legs. Four of 18 patients had normal sensation on clinical testing, whereas 14 had mild to severe generalized sensory loss. Tendon jerks were weak or absent in 15 and normal or slightly diminished in three patients.

The spinal fluid protein was increased without an increased cell count in nine patients and in one patient spinal protein was at the upper normal limit (Table 1). In one who was HIV-positive and another who had a positive borrelia titre in the CSF, there was mild leukocytosis. Four of five patients tested had raised antibody titres to GM1 (Simone et al., 1993). Five patients had normal spinal fluid: one had raised anti-GM1 antibody titre, another an immunoglobulin (Ig)M-k and a third an IgG-k M-component in serum. One patient refused a spinal tap.

Thirteen patients had idiopathic chronic inflammatory demyelinating neuropathy (CIDP) without concurrent disorders (Cornblath et al., 1991a), and five patients had concurrent disorders. The concurrent abnormalities included gammopathy in two and a positive HIV-titre in one (but not manifest AIDS), and both these abnormalities have been described in CADP indistinguishable from idiopathic CIDP (Kelly, 1985; Cornblath et al., 1987; Bromberg et al., 1992; Bleasel et al., 1993). One patient with raised spinal protein had additional mild non-insulin dependent diabetes mellitus for a period of 1 year. One patient with Lyme neuroborreliosis was included because the physiological changes fulfilled the criteria for CADP. Demyelinating neuropathy in neuroborreliosis has been described previously (Sterman et al., 1982). The clinical manifestations of borreliosis are usually characterized by painful radiculitis and mononeuropathy multiplex, predominantly cranial, with features of vasculitis and axonal degeneration (Hansen and Lebech, 1992; Hansen, 1994). None of these clinical characteristics were present in our patient. The physiological abnormalities did not differ in the patients with idiopathic CIDP and in those with concurrent disorders.

The duration of the disease varied widely from few months to 10 years (Table 1) without obvious influence on the clinical or physiological features. Immunosuppressive treatment was given at the time of study to five patients (Table 1) who had clear clinical and physiological manifestations of the disorder. Following the study, treatment was given to a further five patients. Follow-up electrophysiological studies were carried out in two patients after intravenous IgG treatment and showed only mild reduction in motor conduction block. The patient with neuroborreliosis was treated with high dose intravenous penicillin which improved his distal dysaesthesiae and weakness and was associated with a reduction in CSF protein, cells and intrathecal synthesis of IgG. Only mild changes in the electrophysiological abnormalities could be demonstrated.

**Electrophysiological studies**

**EMG**

Quantitative analysis of motor unit action potentials was carried out as previously described (Dahl and Buchthal, 1978; Trojaborg 1981, 1990; Buchthal and Kaminiecka, 1982) in distal and proximal muscles of upper and lower limbs in 17 patients.

**Nerve conduction studies**

Motor and sensory nerve conduction were determined in the nerves listed in Table 2, using near-nerve needle electrodes for stimulation and recording as previously described (Buchthal and Rosenfalck, 1966; Trojaborg and Sindrup, 1969; Behse and Buchthal, 1971; Trojaborg, 1976). An automatically controlled infrared heating lamp kept the temperature along the limb at 35–37°C.

The needle electrode was placed close to the nerve and adjusted to a threshold of the muscle response of 0.5 mA which ensured a needle position of <1 mm from the nerve (Buchthal and Rosenfalck, 1966). The orthodromic CSAPs evoked by supramaximal stimulation were recorded unipolarly through the electrodes placed close to the nerve. To identify small CSAPs electronic averaging was necessary (sample intervals of 20–40 \( \mu s \)). To ensure reproducibility of the averaged potentials, they were recorded in two groups of each 250–500 responses, which remained the same regarding shape and amplitude when they were summed. Needle movements caused by muscle contraction were avoided by recording the maximal CSAP before the supramaximally evoked CMAP. The CMAP was usually recorded with a surface electrode. In some instances, a low threshold of the motor response could not be obtained, probably due to...
## Table 1 Clinical findings in 18 patients with CADP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Muscle force</th>
<th>Sensory findings</th>
<th>Tendon reflexes*</th>
<th>CSF protein&lt;sup&gt;†&lt;/sup&gt; cells</th>
<th>Other findings</th>
<th>Duration of symptoms</th>
<th>Development</th>
<th>Treatment at study</th>
<th>Treatment after study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td>Generalized weakness</td>
<td>Vibration sense decreased in toes</td>
<td>UE: n/n</td>
<td>LE: n/n</td>
<td>Normal/0</td>
<td>—</td>
<td>2 months</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>16</td>
<td>Generalized weakness</td>
<td>Normal</td>
<td>UE: 0/weak</td>
<td>LE: 0/0</td>
<td>142/0</td>
<td>—</td>
<td>6 months</td>
<td>Relapsing</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>55</td>
<td>Generalized weakness</td>
<td>Severe generalized hypeaesthesia</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>270/0</td>
<td>—</td>
<td>2 months</td>
<td>Progressive</td>
<td>Plasma-pheresis</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>18</td>
<td>Generalized weakness</td>
<td>Normal (paraesthesia)</td>
<td>UE: weak/weak</td>
<td>LE: 0/0</td>
<td>86/0</td>
<td>—</td>
<td>1 year</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>80</td>
<td>Legs weaker than arms</td>
<td>Hypaesthesia</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>160/0</td>
<td>—</td>
<td>3 months</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>46</td>
<td>Asymmetrical weakness</td>
<td>Vibration and position sense decreased</td>
<td>UE: 0/brisk</td>
<td>LE: 0/0</td>
<td>74/23 leukocytes</td>
<td>HIV positive</td>
<td>5 months</td>
<td>Stepwise progressive</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>46</td>
<td>Legs weaker than arms</td>
<td>Asymetrically decreased vibration sense</td>
<td>UE: weak/weak</td>
<td>LE: 0/0</td>
<td>110/0</td>
<td>—</td>
<td>3 years</td>
<td>Relapsing</td>
<td>Prednisone, azathioprine</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>25</td>
<td>Generalized weakness</td>
<td>Hypaesthesia</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>98/0</td>
<td>—</td>
<td>2 years</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>57</td>
<td>Asymmetrical weakness</td>
<td>Vibration sense absent</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>92/0</td>
<td>GM1 antibodies</td>
<td>3 years</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>48</td>
<td>Arms weaker than legs</td>
<td>Vibration sense absent</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>normal/0</td>
<td>M-component (IgM kappa)</td>
<td>4 years</td>
<td>Stepwise progressive</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>45</td>
<td>Asymmetrical weakness</td>
<td>Normal</td>
<td>UE: 0/weak</td>
<td>LE: n/n</td>
<td>Not done</td>
<td>—</td>
<td>6 years</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>60</td>
<td>Asymmetrical weakness</td>
<td>Vibration and position sense decreased</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>131/0</td>
<td>Diab. mell.</td>
<td>1 year</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>52</td>
<td>Arms weaker than legs</td>
<td>Hypalgesia</td>
<td>UE: n/n</td>
<td>LE: n/n</td>
<td>normal/0</td>
<td>GM1 antibodies</td>
<td>10 years</td>
<td>Progressive</td>
<td>Prednisone, azathioprine</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>71</td>
<td>Legs weaker than arms</td>
<td>Vibration and position sense decreased</td>
<td>UE: 0/0</td>
<td>LE: n/n</td>
<td>238/0</td>
<td>—</td>
<td>2 months</td>
<td>Progressive</td>
<td>Intravenous IgG</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>72</td>
<td>Arms weaker than legs</td>
<td>Hypaesthesia, hypalgesia</td>
<td>UE: 0/0</td>
<td>LE: weak/weak</td>
<td>166/37 leukocytes</td>
<td>Lyme borrelia</td>
<td>3 months</td>
<td>Progressive</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>75</td>
<td>Generalized arms and legs</td>
<td>Hypaesthesia and hypalgesia</td>
<td>UE: 0/0</td>
<td>LE: 0/0</td>
<td>normal/0</td>
<td>—</td>
<td>4 months</td>
<td>Progressive</td>
<td>Prednisone</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>38</td>
<td>Arms weak, legs normal</td>
<td>Normal</td>
<td>UE: weak/weak</td>
<td>LE: n/n</td>
<td>upper normal limit (58/0)</td>
<td>GM1 antibodies</td>
<td>2 months</td>
<td>Progressive then stationary</td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>68</td>
<td>Mild weakness in arms and legs</td>
<td>Hypaesthesia distal arms and legs</td>
<td>UE: n/n</td>
<td>LE: 0/0</td>
<td>normal/0</td>
<td>M-component (IgG kappa)</td>
<td>1 year</td>
<td>Progressive</td>
<td>None</td>
</tr>
</tbody>
</table>

*UE = upper extremity, LE = lower extremity; reflexes, left/right, nl = normal, 0 = absent. †mg/100 ml, upper normal limit 60 mg/ml.
Table 2 Nerve conduction studies in 18 patients with CADP

| Nerves studied | Motor nerves | | Sensory nerves | |
|----------------|--------------|-----------------|-----------------|
|                | Motor nerves | | Sensory nerves | |
|                | n | Site of recording | n | Site of recording | |
| Median         | 18 | APB | 17 | DI | |
| Ulnar          | 20 | ADQ | 17 | DIII | |
| Axillary       | 1 | Deltoid | — |  | |
| Musculocutaneous | 2 | BB | 2 | Elbow | |
| Radial         | 1 | EDC | 1 | Wrist | |
| Peroneal       | 13 | EDB | 10 | Ankle | |
| Tibial         | 1 | AH | 1 | Toe I | |
| Sciatic        | 1 | GA | — |  | |
| Sciatic        | 1 | AT | — |  | |
| Sural          | 58 |  | 16 | LM | |
| Total          | 58 |  | 16 | LM | |

APB = abductor pollicis brevis; ADQ = abductor digiti quinti; BB = brachial biceps; EDC = extensor digitorum communis; EDB = extensor digitorum brevis; AH = abductor hallucis; GA = gastrocnemius; AT = anterior tibial; LM = lateral malleolus; D = digit. One reduced excitability of the nerve rather than to poor placement of the electrode, as the evoked CSAP had short rise times of the individual components indicating that it was recorded close to the source. The following variables were determined: (i) DML; (ii) the amplitude and duration of the negative phase of the CMAP; (iii) the peak-to-peak amplitude of the CSAP; (iv) the latency to the first positive peak of the CSAP; and (v) the duration of the CSAP measured at its first negative phase. These latencies of both the motor and sensory responses reflect the conduction velocity of the fastest conducting fibres (maximal CV). In an attempt to compare the MCV_d with the SCV_d, the percentage deviation from normal of the reciprocal DML was calculated. The MCV_p was calculated from the differences in latencies between sites of stimulation, and the SCV_p from the conduction times between recording sites.

The change in amplitude of the CMAP and CSAP as a function of conduction distance was calculated as the reduction of the proximal response amplitude relative to the distal response amplitude (P/D ratio).

Criteria for the diagnosis of demyelinating neuropathy

This diagnosis was considered if motor conduction block or focal dispersion of conduction of motor fibres could be demonstrated outside entrapment sites in at least one nerve. For initial diagnosis a P/D ratio of 0.7-0.5 or less was considered suggestive of conduction block (Albers and Kelly, 1989; Cornblath et al., 1991b). However, at further analysis, the P/D ratio was evaluated as a function of the conduction distance. In patients without conduction block or focal dispersion of the CMAP, demyelinating neuropathy was diagnosed if the DML was increased by >30% above the upper control limit or the MCV was reduced by >25% below the lower control limit matched for age (Albers and Kelly, 1989). Abnormalities in sensory conduction were not used for the diagnosis of the type of neuropathy.

Normal controls

Motor and sensory conduction studies were carried out in 18 normal median and ulnar nerves to delineate the normal P/D ratios of the CMAPs and the CSAPs as a function of the conduction distance.

Amplitudes, DML, MCV and SCV were compared with age-matched controls (Rosenfalck and Rosenfalck, 1975; Horowitz and Krarup, 1992) and the deviation from the mean was expressed as a percentage.

Statistical analysis

The comparisons of distributions of abnormalities between motor and sensory conduction abnormalities were carried out by the \( \chi^2 \) test. Non-parametric comparisons between values were performed using Mann–Whitney \( U \) test or, when dealing with paired values, by the Wilcoxon test. A significance level of 0.05 was used.

Results

Quantitative EMG showed evidence of chronic partial denervation. The reduced interference pattern or discreet activity during maximal effort in weak muscles indicated loss of motor units due to axonal loss or proximal conduction block.

Conduction studies in normal subjects

Figure 1 illustrates CMAPs recorded from the abductor digiti quinti and CSAPs recorded from the ulnar nerve of a normal subject. The most conspicuous difference between motor and
sensory action potentials was the different effect of conduction distance on the amplitude. The Erb/wrist amplitude ratio of the CMAP was 0.8, corresponding to a 20% amplitude reduction of the proximally evoked response compared with the distal (Fig. 1A and D), whereas the sensory P/D ratio was 0.05, i.e. the CSAP recorded at Erb’s point was 95% smaller than that recorded at wrist (Fig. 1B and D). The average slope of the decline of the CSAP was 16–17 times higher than that of the CMAP in 18 normal median and ulnar nerves (Fig. 2A; \( P < 0.001 \); comparison of slopes, Zar, 1984). The lower 95% confidence limit (Fig. 2A) of, for example, the axilla/wrist amplitude ratio at a distance of \(-45 \) cm, was 33% for the CMAP and 96% for the CSAP. The SCV \( p \) along the arm was 8% higher than the MCV \( p \) \( (P < 0.01; \) Figs 1E and 2B). The faster sensory than motor conduction confirms previous findings in humans (Krarup et al., 1990) and baboons.
and corresponds to a larger diameter of the largest myelinated sensory than motor fibres (McLeod and Wray, 1967). The duration of the negative phase of the CMAP increased ~10% and the CSAP ~300% between wrist and axilla (Fig. 1F); in the pooled data the slope of the CSAP was 11 times higher than that of the CMAP ($P < 0.001$; Fig. 2C). At long conduction distances, the CSAP became polyphasic (Fig. 1B), indicating a greater effect of temporal dispersion on the CSAP than on the CMAP (Figs 1G and 2D). The decline in amplitude of the CSAP was not only due to changes in shape as a similar amplitude decline of the mixed nerve action potential occurred with less change in its shape (Fig. 1C). The areas of the CSAP and the CMAP both declined linearly with the amplitude, more so for the CSAP than for the CMAP (Fig. 2E).

**Proximal/distal ratios in patients**

Motor conduction block with P/D ratios of 0.55–0.01 occurred in at least one nerve in 16 of the 18 patients, whereas two patients showed only markedly reduced MCV suggesting a demyelinating neuropathy. Overall, an abnormally low P/D ratio occurred in 32 out of 55 (58%) CMAPs but only in nine out of 49 (18%) CSAPs ($P < 0.0001$).

The CMAPs and the CSAPs from the same distal and proximal sites were compared in 29 nerves from the upper
Sensory conduction in CADP

Table 3 Comparison of motor and sensory conduction along 29 upper extremity nerve segments from 18 patients with chronic acquired demyelinating neuropathy (CADP)

<table>
<thead>
<tr>
<th>Amplitude (mV)</th>
<th>Amplitude (% from control mean)</th>
<th>Distal latency (ms)</th>
<th>Dist. Lat. (% from control mean)</th>
<th>MCV (m/s)</th>
<th>MCV (% from control mean)</th>
<th>P/D ratio patients</th>
<th>P/D ratio mean control</th>
<th>P/D ratio 95% limit control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 3.9</td>
<td>-54</td>
<td>4.2</td>
<td>+39</td>
<td>36</td>
<td>-43</td>
<td>0.42</td>
<td>0.90</td>
<td>0.71</td>
</tr>
<tr>
<td>SEM 0.5</td>
<td>5</td>
<td>0.3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0.06</td>
<td>0.01</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**MCV** = motor conduction velocity; **P/D** = proximal/distal amplitude ratio at the site of maximal reduction. The corresponding ratio in controls was determined at a similar conduction distance. **SEM** = standard error of the mean.

<table>
<thead>
<tr>
<th>Amplitude (µV)</th>
<th>Amplitude (% from control mean)</th>
<th>Distal SCV (m/s)</th>
<th>Dist. SCV (% from control mean)</th>
<th>SCV (m/s)</th>
<th>SCV (% from control mean)</th>
<th>P/D ratio patients</th>
<th>P/D ratio mean control</th>
<th>P/D ratio 95% limit control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 8.6</td>
<td>-56</td>
<td>43</td>
<td>-23</td>
<td>50</td>
<td>-21</td>
<td>0.19</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>SEM 2.2</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**SCV** = sensory conduction velocity; **P/D** = the ratio for the compound sensory action potential was determined at the site of maximal reduction in P/D ratio for the compound muscle action potential. **SEM** = standard error of the mean.

Extremities (Table 3). A reduced P/D ratio was found in 22 CMAPs (76%) compared with in only six of the CSAPs (21%, *P* = 0.0001). In three nerves, the CSAP block was complete at a proximal site (Fig. 3), and in one nerve a sensory response was absent both distally and proximally.

The abnormal decline of the P/D ratio (Fig. 4A) of the CMAPs occurred focally in 19 of the 22 nerves (Fig. 5), and a gradual decline occurred in three nerves (Fig. 3). The sites of focal decline were at the Erb–axilla segment in seven nerves, the axilla–elbow segment in 10, and the elbow–wrist segment in two. The abnormal decline of the P/D ratio (Fig. 4B) of the CSAPs occurred focally in three out of the six nerves (Fig. 3), and there were no instances where an abnormal decline in the CSAP ratio occurred at sites where the CMAP ratio was normal.

The mean P/D ratio of the CMAP was 0.25 ±0.05 (±SEM) in the 22 nerves with abnormal proximal studies. When compared with the lower normal 95% confidence limits (Table 3, Fig. 4A and B), the decline of the CMAP was 44±4% below the lower limit. Across the same segments, the P/D ratio of the CSAP was 0.15±0.03 which was 4±3% above the lower normal limit. In patients with CADP as well as in controls, the P/D ratio was lower for the CSAP than for the CMAP. However, when compared with the normal limit, the decline in CMAP was significantly greater than the decline in CSAP (*P* < 0.001). The CSAP P/D ratios did not differ according to whether abnormal ratios occurred in the CMAP.

**Amplitudes of motor and sensory responses in patients**

Thirty-three of the 58 (57%) CMAPs evoked distally had reduced amplitudes compared with 50 of the 78 (64%) CSAPs recorded distally (*P* = 0.5). The mean amplitude of the CMAP was 64±4% reduced and that of the CSAP was 58±6% reduced (*P* = 0.6).

The CMAP amplitude was reduced in 13 out of 32 (41%) nerves with abnormally low P/D ratio and in 17 out of 23 (74%) without abnormal ratio (*P* = 0.06). Although this distribution did not differ significantly, the mean amplitude of CMAPs with a reduced P/D ratio was higher (4.2±0.5 mV) than that in cases with a normal P/D ratio (2.2±0.5 mV, *P* < 0.005). Abnormalities in amplitudes of the CSAPs were not related to CMAP or CSAP P/D ratios (*P* > 0.1).

Abnormal median and ulnar CSAPs and normal sural CSAPs are considered characteristic features of some patients with CADP (Bromberg and Albers, 1993). The pattern of CSAP abnormalities was ascertained from 51 CSAPs recorded from the arms and from 27 sural, peroneal and tibial nerves recorded from the legs. The CSAP was normal in five out of the 16 sural nerve. Two of these had reduced median or ulnar CSAP amplitudes and three had normal amplitudes. The amplitudes were equally often reduced in the arms (65%) and in the legs (63%) (*P* = 0.9), and the mean amplitude was 59±8% reduced in the arm nerves and 57±8% in the leg nerves (*P* = 0.4). In comparison, the CMAP amplitudes were reduced in 21 out of 43 (49%) arm muscles compared with 12 out of 15 (80%) in the legs (*P* < 0.1). Although this distribution did not differ significantly, the mean CMAP amplitude was less reduced in arm muscles (57±5%) compared with leg muscles (83±5%, *P* < 0.002).

**Conduction velocities in patients**

The DML was prolonged in 40 out of 58 CMAPs (69%) and the SCVd was reduced in 16 out of 32 CSAPs (50%, *P* = 0.1). The reduction of the mean reciprocal DML (MCVd)
and the SCV did not differ significantly (32±8% versus 23±3%, P = 0.1). The low amplitude CSAPs were often markedly polyphasic shape (Fig. 6) with long-latency components indicating that groups of fibres had more reduced conduction velocities than apparent from the maximal SCV.

The MCVd and SCVd decreased with increasing reduction of the distal CMAP and CSAP amplitudes (Fig. 7). When the same distal segments were compared, the MCVd decreased linearly with the CMAP amplitude (Fig. 7A) whereas the SCVd decreased logarithmically with a marked decline when the CSAP was >60-70% reduced (Fig. 7B). The differences between abnormalities in CMAPs and CSAPs are illustrated in Fig. 3 showing marked reduction in CSAP amplitudes, whereas the SCVs were only slightly reduced or normal. The motor latencies increased markedly at proximal stimulation sites (Fig. 4C) and the proximal sensory latencies increased much less (Fig. 4D). Accordingly, the MCVp was reduced in 50 out of the 53 nerves (94%) compared with the SCVP which was reduced in only 31 out of 68 (46%) nerves (P = 0.0001). The mean MCVp was reduced by 41±3% and the SCVP by only 16±2% (P = 0.0001). These findings suggested that MCVd and the SCVd did not differ significantly, whereas the MCVp was markedly lower than the SCVP. Comparisons of the MCV and the SCV along corresponding segments in 28 nerves (Table 3), showed that the MCVp was decreased by 26±3%, the MCVp by 43±3%, the SCVP by 23±3% and the SCVP by 21±3% (P < 0.001, ANOVA, repeated measures). The MCVd was significantly less reduced than the MCVp (P < 0.001) whereas the SCVP and the SCVP were reduced to the same extent (P > 0.5).

The difference in MCV and SCV could be related to a more abnormal P/D ratio of the CMAP than of the CSAP. The MCV and the SCV decreased logarithmically as a function of the P/D ratio (Fig. 8). The mean reduction in MCVp was 51±3% in the 30 studies with abnormal P/D ratios compared with 30±3% in the 23 studies with normal ratios (P < 0.0005).

**Discussion**

We studied abnormalities in conduction along motor and sensory fibres in CADP and found that in ~75% of the motor studies the P/D ratios were reduced compared with only ~20% in the sensory studies. The patients included in the present study fulfilled the proposed clinical and electrophysiological criteria (Cornblath et al., 1991a) which include patients with concurrent disorders such as HIV-infection and monoclonal gammopathies. Other studies have also included patients with concurrent disorders (Barchohn et al., 1989; Steck, 1992). Several of our patients had raised antibody titres to GM1 gangliosides, often found in patients with neuropathy and lower motor neuron involvement (Sadiq et al., 1990).

The differences between abnormalities in the CMAP and the CSAP raises the question as to whether the difference in P/D ratio reflects sparing of sensory fibres in CADP, difficulties in demonstrating conduction block of the CSAP, or differences in pathophysiological mechanisms.

Weakness was present in all 18 patients, whereas 14 had sensory signs, suggesting that sensory abnormalities might be less pronounced, consistent with other studies (Prineas and McCleod, 1976; McCombe et al., 1987). However, pronounced abnormalities of the CSAP occurred even in the absence of sensory symptoms (Fig. 6) and as often and to the same degree as those of the CMAPs. These findings indicate that the differences between motor and sensory findings could not be explained in terms of sparing of sensory as compared with motor fibres. The amount of fibre loss or distal conduction block were similar in motor and sensory fibres.

The decline of the amplitude of the normal CSAP with increasing conduction distance was more pronounced than that of the CMAP, in agreement with other studies (Kimura...
Fig. 4 Percentage changes in motor (CMAP) and sensory (CSAP) amplitudes (A and B) and latencies (C and D) versus conduction distances in median and ulnar nerves. Amplitude = 100% and distance = 0 mm at wrist. Continuous curves = mean, dashed curves = lower 95% confidence limits of amplitudes (A and B) and upper 95% confidence limits of latencies (C and D) in controls.

Fig. 5 Motor and sensory action potentials from Patient 7 with CADP and motor but not sensory conduction block. Upper three traces: CMAPs after stimulation at wrist, forearm, and elbow with motor conduction block between forearm and elbow. Distal latency indicated above the upper trace, conduction velocities between traces. Lower traces: CSAPs recorded at wrist and elbow after stimulation at digit I (left) and digit III (right). Conduction velocities are indicated above traces. n = number of averaged responses.
et al., 1986; Krarup et al., 1990; Liguori et al., 1992). In controls, the CMAP evoked at the elbow was 85% of that evoked at the wrist, whereas the CSAP recorded at the elbow was only 25% of that recorded at the wrist. This greater effect of temporal dispersion (Fig. 2D) may be related to the 10 times longer duration of the motor unit potential than of the single nerve fibre action potential and the greater range of conduction velocities of sensory than of motor fibres (Kimura et al., 1986; Kincaid et al., 1988). Thus detection of partial sensory conduction block is complicated as drop-out of single fibre action potentials probably would have little influence on the amplitude or area of the CSAP. This difficulty may be even more pronounced when the CSAP has a dispersed shape. In the situation where the reduced CSAP is well synchronized (Fig. 5B), conduction block of remaining fibres can probably be detected. However, the distal CSAP was often polyphasic (Fig. 6) which could make detection of block of some fibres difficult or impossible.

**Pathophysiologival changes in motor and sensory fibres**

Previous studies have suggested that conduction block in motor fibres may be localized distally or distributed along proximal segments in the Guillain–Barré syndrome (Meché and Meulstee, 1988; Meché et al., 1988), and distal abnormalities have been confirmed morphologically (Hall et al., 1992). In agreement with other studies (Meché et al., 1989), we found that the amplitude of the CMAP evoked at distal sites was more reduced in nerves without than in those with proximal conduction block. Moreover, CMAP amplitudes were more markedly reduced in the small foot muscles than in hand muscles, and that the P/D ratio was more often normal in the legs than in the arms, where conduction block frequently occurred. In contrast, the amplitude of the distally recorded CSAP was not related to the P/D ratio and there were no consistent differences in the upper and lower limbs.

That pathophysiological changes in motor and sensory fibres may be different was supported by the recorded conduction velocity changes along proximal nerve segments. The MCV was twice as much reduced proximally along the limb as distally, and the slowing was related to the degree of reduction of the P/D ratio. This is compatible with the presence of demyelination, causing slowing and conduction block along motor fibres (Feasby et al., 1985; Bromberg, 1991). By contrast, the SCV was only moderately reduced and to the same extent along distal and proximal segments. In accordance with our study, Luciano et al. (1995) found that the mixed nerve conduction velocity from wrist to elbow in two patients with CADP was 60–63 m/s compared with a MCV of 9–28 m/s.

The slowing of sensory conduction occurred mainly when the CSAP amplitude was markedly decreased, suggesting that loss of large fibres could account for the reduced SCV. This relationship between amplitude and conduction velocity is similar to the slowing in axonal neuropathies with loss of...
mainly large fibres (Donofrio and Albers, 1990; Krarup-Hansen et al., 1993; Trojaborg et al., 1994). The CSAPs were often markedly polyphasic with late components indicating that some fibres conducted more slowly than was apparent from the maximal conduction velocity (Shefner et al., 1991). Morphological studies of sensory nerves in CADP have shown axonal loss as well as demyelination (Dyck et al., 1975; Primeas and McLeod, 1976; Barbieri et al., 1991; Bleasel et al., 1993). In teased fibre preparations, Dyck et al. (1975) found that ~20% of fibres showed signs of demyelination and 25% evidence of degeneration. Barohn et al. (1989) found that almost half of nerve biopsy specimens from 56 CIDP patients showed predominantly demyelination, 21% showed axonopathy, 13% mixed demyelination and axonal changes, and 18% were normal. The discrepancy between the maximal SCV, the reduced minimum SCV, and the demyelination on histological examination may suggest that the pathological changes are heterogeneously distributed within the nerve. The prolonged rise time of the mixed nerve action potential and a slightly reduced conduction velocity (Luciano et al., 1995), is also in agreement with the notion of heterogenous demyelination among nerve fibres. Consistent with this mechanism, the sural nerve biopsy of one of our patients (Case 18) showed signs of demyelination, whereas the number of large myelinated fibres was normal, the diameters of the largest caliber fibres were normal (12.5 μm), and the sural nerve CSAP amplitude and SCV were normal. The difference between motor and sensory involvement is in contrast to hereditary hypertrophic neuropathies with marked slowing of the maximal SCV and MCV in parallel with demyelination (Behse and Buchthal, 1977; Buchthal and Behse, 1977).

Hence, even though detection of conduction block of sensory fibres is difficult, the less pronounced proximal slowing in sensory than in motor fibres supports the assumption that motor and sensory nerve fibres were affected differently by the pathological process in CADP. Differences in the safety factor of conduction in sensory and motor fibres could account for conduction block occurring mainly in motor fibres. A similar mechanism was suggested in multifocal motor neuropathy (Krarup et al., 1990). Recent studies in human motor and sensory nerve fibres have shown differences in the effect of ischaemia suggesting that ion channels may differ (Bostock et al., 1994). The immune mechanism in CADP is not clarified. It has been suggested that multifocal motor neuropathy with conduction block is a variant of CIDP. In multifocal motor neuropathy, antibodies against GM1 gangliosides are often present and accumulate at the node of Ranvier (Santoro et al., 1990; Thomas et al., 1991). Partial sparing of sensory fibres has been related to a higher concentration of GM1 in motor than in sensory fibres. It has been suggested that sodium channels could be the
target of the immune attack resulting in conduction block (Takigawa et al., 1995). Recently it has been suggested that the CSF of patients with Guillain–Barré syndrome, multiple sclerosis and CIDP may contain several factors which inhibit excitatory sodium currents resulting in impaired impulse conduction (Brinkmeier et al., 1992, 1993; Würz et al., 1995).

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