Long term prognosis of chronic inflammatory demyelinating polyneuropathy: a five year follow up of 38 cases

S Kuwabara, S Misawa, M Mori, N Tamura, M Kubota, T Hattori

Background: Little is known about long term prognosis and course after immune treatments in chronic inflammatory demyelinating polyneuropathy (CIDP).

Objective: To study long term outcomes and prognostic factors in patients with CIDP.

Methods: Clinical and electrophysiological findings, responses to immune modulating treatments, and outcomes five years after the start of treatment were reviewed in 38 CIDP patients.

Results: Patients were treated with corticosteroids (89%), immunoglobulin infusion (45%), or plasmapheresis (34%), and 58% received combined therapy. Five years after treatment was begun, 10 (26%) of the patients had complete remission (lasting >2 years with normal nerve conduction studies), and 23 (61%) had partial remission (able to walk) with (26%) or without (34%) immune treatments. The remaining five patients (13%) still had severe disability (unable to walk) or treatment dependent relapses. Patients with complete remission more often had subacute onset, symmetrical symptoms, good response to initial corticosteroid treatment, and nerve conduction abnormalities predominant in the distal nerve terminals. In contrast, insidious onset, asymmetrical symptoms, and electrophysiological evidence of demyelination in the intermediate nerve segments were associated with refractoriness to treatment or treatment dependent relapse.

Conclusions: The long term prognosis of CIDP patients was generally favourable, but 39% of patients still required immune treatments and 13% had severe disabilities. Mode of onset, distribution of symptoms, and electrophysiological characteristics may be prognostic factors for predicting a favourable outcome.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a diagnostic term dependent on pattern recognition, and is based on clinical symptoms and signs, electrodiagnostic studies, and other laboratory tests. CIDP is therefore likely to be a heterogeneous disorder with a wide range of clinical phenotypes, a variable course, and different responses to immune modulating treatments. Most CIDP patients are treated with corticosteroids, immunoglobulins, or plasmapheresis, but there is no standard first line therapy. Accordingly, CIDP patients have received variable or combination of treatments. The long term outcome of patients with CIDP after receiving these immune modulating treatments is unclear. There are various reports investigating long term course and outcome of CIDP patients, but follow up periods were variable among the studies, including patients with only a few years of follow up. There is no report with a uniform time point for long term follow up. Moreover, whether specific clinical, electrophysiological, and laboratory features are associated with prognosis of CIDP patients is not well understood. The extent of axonal loss has been reported to be the major prognostic factor in CIDP, but this would not be prominent in the early stage of the disease. Distribution patterns of demyelination have been suggested to correlate with clinical profiles, including response to treatments, but long term prognosis was not investigated. We therefore carried out an analysis of five year follow up after the initiation of immune modulating treatments on our CIDP patients to investigate long term outcomes and prognostic factors.

METHODS

Patients

Clinical and laboratory data were reviewed for 38 patients seen at first visit to Chiba University Hospital between 1990 and 2000, and their detailed clinical, laboratory, and electrophysiological findings were followed at least five years after the start of treatments. The inclusion criteria were as follows:

- follow up period for at least five years;
- clinical assessment at least every two months;
- electrodiagnostic evaluation in four or more motor nerves at least once a year;
- no concomitant systemic disease such as severe diabetes and malignancy.

We excluded patients with monoclonal gammopathy, anti-myelin associated glycoprotein antibody, or multifocal motor neuropathy, because their clinical and immunological profiles and response to treatment appear to be somewhat different from those with idiopathic CIDP. Neurological examinations were made at least every two months, and nerve conduction studies were carried out at least once a year. Clinical evaluation included Hughes grade (see below), grip strength, muscle strength in four muscle groups (deltoid, wrist flexors, iliopeas, and tibialis anterior muscles), tendon reflexes, and pin prick, touch, and vibratory sensations. At entry, their condition fulfilled the research criteria for diagnosis of CIDP. A functional assessment was undertaken using the Hughes functional grading scale: 0, normal; 1, able to run with minimal symptoms and signs; 2, able to walk 5 metres independently; 3, able to walk 5 metres with aids; 4, chair or bed bound; 5, requiring assisted ventilation; 6, dead. We focused on the asymmetry of symptoms, which was defined as differences in muscle strength by one or more...
MRC scales in the homonymous muscles. Regarding mode of onset, the classification “subacute” was used when immune treatment was begun within six months of onset because of difficulty in carrying out daily activities.

**Treatment**

During the follow up period, all the 38 patients received immune modulating treatments; 34 (89%) were treated with high dose corticosteroids, 17 (45%) received intravenous immunoglobulin therapy, and 13 (34%) were treated with plasmapheresis. Azathioprine was given to two patients, and cyclophosphamide to two. Treatment was considered effective when the patient’s condition improved by 1 or more on the Hughes grade.

**Electrophysiological studies**

Motor nerve conduction studies were carried out in the median, ulnar, tibial, and peroneal nerves using conventional procedures. Antidromic sensory nerve conduction studies were conducted in the median and sural nerves. According to the electrophysiological criteria for demyelination, the presence of demyelinating conduction abnormalities of the median and ulnar nerves was determined in the distal nerve segments (distal to the wrist) or intermediate nerve segments (wrist to elbow), or both. Patients were classified as having “distal”, “intermediate”, or “diffuse” demyelination, as detailed elsewhere. The terminal latency index was used to compare the distal segment with the intermediate segment and was calculated using the formula\(^1\): distal conduction distance (mm)/forearm conduction velocity (m/s)/distal latency (ms).

In sensory nerve conduction studies, we focused on the involvement patterns of the median and sural sensory nerve responses. The pattern of “abnormal median–normal sural sensory responses” has been reported to suggest demyelinating predominant in the distal nerve terminals, and is specifically seen in patients with CIDP or Guillain–Barré syndrome.\(^3\)

**Statistical analyses**

Differences in proportions were tested by \(\chi^2\) or Fisher’s exact test, and differences in medians by Mann–Whitney U test. The logistic regression method was used to analyse categorised outcome variables: first, univariate regression analyses were carried out, and when two or more factors had significant correlation with outcome, multivariate logistic regression analyses were done.

**RESULTS**

**Outcomes (five year follow up)**

All 38 patients had a clinical evaluation at least every two months and electrodiagnostic studies at least once a year during the follow up period of five years. Table 1 shows the Hughes grade of the CIDP patients at entry (before treatment), and five years after the initial treatment was begun; at five years, 10 (26%) of the patients were in complete remission (Hughes grade 0), which had lasted for two years or more after treatment was stopped, and their nerve conduction studies were normal. In a further 10 patients, a period of progression ranging from 11 weeks to six months (mean 3.6 months), with progression of neuropathic symptoms, continued until immune modulating treatment was begun. These findings eliminated the possibility that patients with acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome) had been included in the cohort.

The course of the patients with complete remission was generally monophasic; nine of the 10 patients with complete remission were treated with corticosteroids, and the remaining patient with intravenous immunoglobulin therapy. Two patients treated with corticosteroids experienced relapse when the dose was reduced (at five and 11 months, respectively, after the start of treatment), but their condition improved with plasmapheresis and an increased dose of corticosteroids, resulting in complete remission for all 10 patients within three years. Clinical remission continued and nerve conduction study results remained normal for the last two years of the five year follow up.

Twenty three (61%) had partial remission (Hughes grade 1 or 2; able to run or walk). In 13 of the 23 patients, immune modulating treatment had been stopped, but the remaining 10 required continuous or intermittent treatment, usually oral corticosteroids. Five patients (13%) still had severe disability (Hughes grade 3 or more; unable to walk) or treatment dependent relapse five years after treatment was begun. A 76 year old male patient who had been treated with repeated intravenous immunoglobulin therapy, had experienced frequent treatment dependent relapses and died of pneumonia when he was tetraplegic five years after the start of initial intravenous immunoglobulin therapy. During the five year follow up, this patient was the only one to die from CIDP. The most recent visit by the patients ranged 6 to 15 years (mean 10.5 years) after entry, and at the end of follow up the outcomes were similar to those at five years: Hughes grade 0, 26% (all the patients were the same as those with Hughes grade 0 at five years); grade 1, 42%; grade 2, 18%; grade 3, 5%, grade 4, 5%; grade 5, 0%; grade 6, 3%.

**Responses to immune modulating treatment**

Of the 38 patients, treatment was started with high dose corticosteroids in 33 (87%), intravenous immunoglobulin therapy in five (13%). None had plasmapheresis as initial therapy. When the initial therapy was ineffective, or only transiently effective, the second treatment was employed; during the five year follow up period, 89% of patients were eventually treated with corticosteroids, 45% with intravenous immunoglobulin therapy, and 34% with plasmapheresis; 58% received combined therapy. Improvement by 1 or more Hughes grade within two months after each treatment was introduced was found in 70% of the patients treated with corticosteroids, 82% of the patients treated with intravenous immunoglobulin therapy, and 58% of the patients receiving

<table>
<thead>
<tr>
<th>Hughes grade at entry</th>
<th>Hughes grade at 5 years</th>
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<tr>
<td></td>
<td>0</td>
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<tr>
<td>1</td>
<td>1</td>
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<td>3</td>
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<tr>
<td>3</td>
<td>1</td>
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<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (100%)</td>
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</table>
plasmapheresis. Five years after the start of treatment, 15 (39%) were still receiving immune modulating treatment (corticosteroids 29%, intravenous immunoglobulin therapy 5%, and plasmapheresis 5%). Azathioprine and cyclophosphamide were given to two patients but did not appear to be effective in either of them.

**Prognostic factors**

Table 2 shows correlation of clinical and electrophysiological profiles and the rate of complete remission at five years after entry. On univariate analyses, age, sex, and Hughes grade at entry did not correlate with outcome. Muscle strength at entry was not related to outcome at five years; the MRC scale entry did not correlate with outcome. Muscle strength at entry. On univariate analyses, age, sex, and Hughes grade at entry did not relate to outcome at five years; the MRC scale entry did not correlate with outcome.

For multivariate logistic regression analyses, three factors (mode of onset, response to steroid treatment, and motor electrodiagnostic features) were used because “symmetrical symptoms” and “no muscle atrophy” were significantly cross correlated with “mode of onset” (p = 0.001 and 0.011, respectively), and therefore were not considered to be independent factors. Table 3 shows results of multivariate logistic regression analyses; using three factors (mode of onset, response to steroid treatment, and motor electrodiagnosis), the probability of complete remission at five years was 89.5%, and only motor electrodiagnostic features were statistically significant (p = 0.029).

Patients were classified as having the distal (n = 10), intermediate (n = 14), or diffuse patterns (n = 14), according to the distribution of demyelinating conduction abnormalities; the distal pattern was associated with a higher rate of complete remission than the other patterns. Conversely, none of the patients with the intermediate pattern had complete remission; in most of these patients, serial nerve conduction studies showed conduction block or abnormal temporal dispersion in the same intermediate nerve segments (for example, the forearm segments of the median or ulnar nerves) without distal nerve conduction abnormalities. They were generally refractory to corticosteroid treatment. Patients with the diffuse pattern were often responsive to treatment but had treatment dependent relapse and therefore less often had complete remission at five years after entry. In sensory nerve conduction studies, the presence of “abnormal median–normal sural responses” was associated with the higher remission rate (54% v 15%; p = 0.02).

Table 4 compares nerve conduction study results at entry between patients with complete remission at five years and the other CIDP patients. Longer distal latencies, relatively faster conduction velocities, and lower terminal latency indices for patients with complete remission suggest that demyelination was more predominant in the distal nerve segments, presumably in the distal nerve terminals. Amplitudes of median sensory nerve action potentials were significantly smaller for patients with complete remission.

**Features of patients with a poor prognosis**

Five years after entry, five patients (13%) had severe disability (n = 3) or treatment dependent relapses (n = 2). Three of these developed extensive axonal degeneration evidenced by prominent muscular atrophy, and low or not recordable motor and sensory nerve responses after distal stimulation, and became less responsive to immune treatments. The remaining two were dependent on intravenous immunoglobulin therapy or plasmapheresis; their condition responded well to intravenous immunoglobulin, but the effects continued only for two to five months. Accordingly, they experienced tetraplegia and partial remission for five years. One patient died of pneumonia during relapse at age 76 years. Although the number of patients was small, development of axonal degeneration and long lasting disease activity appeared to be related to a poor outcome.
DISCUSSION

Our five year follow up study showed that the long term prognosis of Japanese CIDP patients was generally favourable; 87% of the 38 patients were able to walk five years later, and 26% experienced complete remission lasting for more than two years without treatment. However, 39% of the patients still required immune treatments, and 13% had severe disability. Further follow up for six to 15 years showed similar results, suggesting that the prognosis of CIDP may be determined by the course and response to treatment in the first five years.

CIDP patients with complete remission more often had subacute onset, symmetrical symptoms, a good response to initial treatment with corticosteroids, and nerve conduction abnormalities predominant in the distal nerve terminals than the other patients. These factors can be predictors of long term outcome. Mode of onset or progression time from onset to nadir is an important prognostic factor. All 10 patients with complete remission had a subacute onset. The possibility that these patients had acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome) could be eliminated because they definitely had a progression time of over two months. Moreover, none of the 10 patients were obviously responsive to corticosteroids, and this is not the case for Guillain–Barré syndrome.

Our findings also showed that asymmetrical symptoms were associated with refractoriness to treatments or treatment dependent relapse. As described below, the distribution was associated with demyelinating nerve conduction abnormalities in the intermediate nerve segments. Distal nerve terminal, as well as nerve roots, where the blood–nerve barrier is anatomically deficient, are preferentially involved in immune mediated neuropathies such as Guillain–Barré syndrome and CIDP.7 18 Substantial increases in distally evoked CMAP amplitude can be seen after successful immune treatment; because the effects were rapid and large, it is likely that resolution of conduction block in the distal nerve terminals was the probable mechanism for improvement.19 Distal latencies were longer and distal CMAPs were smaller in patients with complete remission than in other CIDP patients, whereas nerve conduction velocities did not differ significantly. The disproportionately prolonged distal latencies were consistent with a smaller terminal latency index and the presence of an abnormal median–normal sural sensory pattern, all of which suggest demyelination preferentially in the distal nerve terminals. The pattern of distribution of lesions is similar to that of Guillain–Barré syndrome, suggesting that the pathophysiology of this subgroup of CIDP may partly common to that of the Guillain–Barré syndrome, whereas disease activity apparently lasts longer, over several months. Differentiating this subgroup may be important because such patients are obviously steroid responsive, and this study showed that they could have long lasting complete remission without drug treatment, and that corticosteroids could be the first line of treatment for this subgroup of CIDP patients.

In contrast, patients without complete remission often had involvement of the intermediate nerve segments and therefore were classified as having the intermediate or diffuse pattern. The involvement of the intermediate segments would be associated with breakdown of the blood–nerve barrier, possibly caused by local activation of cell adhesion molecules, cytokines, matrix metalloproteinases, or other inflammatory substances.20 21 There appear to be two subgroups not achieving complete remission. Patients with focal conduction block/abnormal temporal dispersion in the nerve trunk without distal terminal lesions often had a chronic course, asymmetrical symptoms, upper limb predominant weakness, and refractoriness to treatment. The other subgroup of CIDP without complete remission was characterised by involvement of both the distal and the intermediate nerve segments, and thus had demyelination that was diffusely distributed along the course of the nerve. This subgroup of patients had similar clinical features to those of the subgroup with complete remission, such as subacute onset, symmetrical symptoms, proximal as well as distal muscle weakness, and responsiveness to immune treatments, but eventually had a treatment dependent course for several years, suggesting more prolonged disease activity. At present, there is no standard regimen to treat for such CIDP patients. More effective or intensive treatments are required to improve the prognosis of these patients.

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**Table 4 Nerve conduction study results and outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete remission (n = 10)</th>
<th>Others (n = 28)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Motor Median</td>
<td></td>
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</tr>
<tr>
<td>Distal latency (ms)</td>
<td>9.9 (1.2)</td>
<td>6.8 (0.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>40.6 (2.5)</td>
<td>34.5 (2.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>CMAP amplitude (mV)</td>
<td>5.0 (1.3)</td>
<td>6.7 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
<td>39.9 (2.8)</td>
<td>46.4 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Terminal latency index</td>
<td>0.021 (0.003)</td>
<td>0.042 (0.004)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tibial Median</td>
<td></td>
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<td></td>
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<tr>
<td>Distal latency (ms)</td>
<td>10.3 (0.9)</td>
<td>7.4 (0.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>36.7 (2.3)</td>
<td>33.8 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>CMAP amplitude (mV)</td>
<td>3.2 (0.6)</td>
<td>6.2 (0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>F wave latency (ms)</td>
<td>68.4 (4.4)</td>
<td>70.0 (2.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Terminal latency index</td>
<td>0.017 (0.001)</td>
<td>0.024 (0.002)</td>
<td>&lt;0.001</td>
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<tr>
<td>Sensory Median</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conduction velocity (m/s)</td>
<td>42.2 (2.2)</td>
<td>47.9 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>SNAP amplitude (µV)</td>
<td>3.0 (1.1)</td>
<td>11.8 (2.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sural Median</td>
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<td></td>
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<tr>
<td>Conduction velocity (m/s)</td>
<td>43.7 (1.7)</td>
<td>45.1 (0.1)</td>
<td>NS</td>
</tr>
<tr>
<td>SNAP amplitude (µV)</td>
<td>7.6 (1.6)</td>
<td>9.0 (1.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (SEM).
CMAP, compound muscle action potential; SNAP, sensory nerve action potential.
REFERENCES

20. Hall SM, Redford EJ, Smith KJ. Tumor necrosis factor-α has few morphological effects within the dorsal columns of the spinal cord, in contrast to its effects in the peripheral nervous system. J Neuroimmunol 2000; 106:130–136.