Chronic idiopathic axonal polyneuropathy
Comparison of patients with and without monoclonal gammopathy


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Summary
In order to study whether axonal polyneuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) is a distinct entity, we prospectively studied the clinical, electrophysiological and pathological features of 16 patients with chronic idiopathic axonal polyneuropathy (CIAP) with MGUS (CIAP-MGUS) and compared them with those of 71 patients who had CIAP without MGUS. In patients with CIAP-MGUS the arms were more frequently affected and the disability was worse. On electromyography there was more evidence of denervation in patients with CIAP-MGUS. All other clinical symptoms, signs, nerve conduction parameters and nerve biopsy findings, showed no differences between both groups. Antibodies against myelin associated glycoprotein (MAG), GM1-ganglioside and chondroitin sulphate were not present. Only one patient with an immunoglobulin M (IgM)-MGUS and a sensory neuropathy had antibodies against sulphatide. In conclusion, axonal polyneuropathy in patients with and without MGUS are essentially indistinguishable rather than different, suggesting that the MGUS may be coincidental in most patients.

Keywords: axonal; neuropathy; gammopathy

Abbreviations: CIAP = chronic idiopathic axonal polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; DML = distal motor latency; Ig = immunoglobulin; MAG = myelin associated glycoprotein; MGUS = monoclonal gammopathy of undetermined significance

Introduction
The association of polyneuropathy and MGUS is well established (Gosselin et al., 1991; Yeung et al., 1991; Suarez and Kelly, 1993; Notermans et al., 1994c; Smith, 1994). Antibodies to glycoconjugates of the peripheral nervous system have been found in 50–65% of the patients with a polyneuropathy associated with IgM-MGUS, suggesting a role for the monoclonal protein in the pathogenesis of the disease (Abrams et al., 1982; Melmed et al., 1983; Mendell et al., 1985; Takatsu et al., 1985; Tatum, 1993; Nobile-Orazio et al., 1994). However, if no antibodies to glycoconjugates are found, a relationship between MGUS and polyneuropathy is still debatable. The association of polyneuropathy and MGUS may be coincidental as monoclonal protein can be demonstrated in 0.1–3% of the healthy population increasing with age (Axelsson et al., 1966; Kyle et al., 1972; Kahn et al., 1980).

In previous studies demyelinating polyneuropathy associated with MGUS has been distinguished from chronic inflammatory demyelinating polyneuropathy (CIDP) (Simmons et al., 1993). However, whether the axonal type of polyneuropathy associated with MGUS is a separate disease entity is still unknown. Therefore, we compared the clinical, electrophysiological and pathological features of 16 patients with CIAP-MGUS with 71 patients who have CIAP without MGUS (Notermans et al., 1993, 1994d).

Material and methods
Patients
In a prospective study between 1987 and 1990, 87 patients were diagnosed as having a CIAP with or without gammo-
Ataxia was quantified using a tapping test, as described previously, which included history, physical examination, quantitative strength and sensory testing, extensive biochemical and haematological screening, assays for autoantibodies, chest X-ray and a total body scintigraphy (Notermans et al., 1991). No cause for the axonal polyneuropathy was found in any of the 87 patients. Seventy-one of the 87 patients did not have a monoclonal gammapathy. These patients were classified as CIAP (Notermans et al., 1993; Notermans et al., 1994d). A monoclonal gammapathy was present in the remaining 16 patients: 11 IgG (nine IgGk, two IgGλ ) and five IgMk. In these patients malignant plasma cell dyscrasias (multiple myeloma, lymphoma, Waldenström’s macroglobulinemia or amyloidosis) were excluded by haematological evaluation, radiological skeletal survey, including bone marrow examination (Notermans et al., 1994c). These 16 patients were classified as CIAP-MGUS.

Evaluation
All patients were seen by the same neurologist (N.C.N.). The neurological deficit was quantified as follows:

**Strength (using the Medical Research Council grading system).** Six muscles of each arm (deltoid, biceps and triceps brachii, finger extensors, finger flexors and first dorsal interosseous) and six muscles of each leg (iliopsoas, quadriceps femoris, hamstrings, anterior tibial, gastrocnemius and peroneal) were tested. Summation of test results could lead to a maximum motor sumscore of 120.

**The sensory function.** The touch and pinprick sense: normal = 4, distal to wrist/ankle abnormal = 3, distal half forearm/leg abnormal = 2, distal to elbow/knee abnormal = 1, distal to axilla/groin abnormal = 0. Vibration sense: tuning fork perception (128 Hz) on middle finger/hallux = 4, ulnar styloid/medial malleolus = 3, elbow/knee = 2, clavicle/iliac crest = 1, no perception = 0. Joint position sense of middle finger/hallux: normal = 2, diminished = 1, absent = 0. Summation of all sensory modalities could lead to a maximum sensory sumscore of 56.

**Ataxia.** Ataxia was quantified using a tapping test, as previously described (Notermans et al., 1994b). This test uses a device consisting of two push buttons placed on a fixed distance of 35 cm apart, connected to an automatic counter. The patient is asked to push the left and right buttons alternately with the dominant limb as fast as possible. Counting starts as soon as the first button is pushed and stops after 15 s. In addition, the Romberg test was quantified (Notermans et al., 1994b). We measured the time from the moment the patient closed the eyes until he/she opened them or was likely to fall. This test was limited to a maximum of 60 s.

**Disability.** Disability was determined with the modified Rankin disability scale (van Swieten et al., 1988).

To measure progression, the motor and sensory sumscores were repeated after 5 years of follow-up.

**Laboratory analysis**
Electrophoresis of serum was performed on cellulose acetate membrane and the monoclonal component was quantified with densitometry. Immuno-electrophoresis was performed by utilizing monospecific antisera to IgM, IgG, IgA, k and l. In addition, immunofixation with monospecific antisera was performed. Serum antibodies to MAG were detected by thin-layer chromatography, using the glycolipid sulphated glucuronyl paragloboside (kindly performed by Dr N. Latov, Columbia University, New York, USA) (Latov, 1990). Serum antibody titres to the GM1 ganglioside, sulphatides and chondroitin sulphate C were measured by enzyme-linked immunosorbent assay (van den Berg et al., 1992, 1993; Nemni et al., 1993). These tests were performed in all patients.

In patients with a gammapathy, bone marrow aspirates or biopsies from the crista iliaca posterior were obtained with a Yamshidi needle. Aspirates were stained with May–Grunwald–Giemsa. Bone marrow biopsies were embedded in paraffin and stained with haematoxylin–eosin. Patients with >10% plasma cells or >30% lymphoid cells were excluded from the study.

**Electrophysiological assessment**
On entry into the study axonal polineuropathy was confirmed by electrophysiological examination. Nerve conduction was investigated by means of surface electrodes using standardized techniques described elsewhere (Notermans et al., 1994a). The ulnar and median nerve (motor, sensory and F waves) in one arm, the tibial nerve (motor) and the sural nerve in one leg and the H-reflex of the soleus in the opposite leg were investigated. In all patients concentric needle examination was performed in the tibial anterior muscle and the first interosseus muscle. Skin temperature was maintained at 36°C with an infrared heat lamp.

Axonal degeneration was considered to be present when there was (i) spontaneous EMG activity such as fibrillation potentials, positive sharp waves or complex repetitive discharges on concentric needle examination; (ii) reduction of the amplitude of the compound muscle action potential or of the sensory nerve action potential on distal stimulation. Demyelination was considered to be present when (i) motor or sensory conduction velocity was decreased below 70% of the lower limit of normal in our laboratory (Ad Hoc Subcommittee of the American Academy of Neurology, 1991); (ii) the distal motor latency (DML) was increased above 150% of the upper limit of normal in our laboratory; (iii) there was evidence of conduction block or abnormal temporal dispersion in ulnar or median nerve motor fibres according to the criteria of Lange et al. (1992); (iv) the
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Table 1

<table>
<thead>
<tr>
<th></th>
<th>CIAP-MGUS (n = 16)</th>
<th>CIAP (n = 71)</th>
<th>p*</th>
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<tbody>
<tr>
<td>Age at onset of polyneuropathy in years (SD)</td>
<td>58 (9)</td>
<td>57 (6)</td>
<td></td>
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<tr>
<td>Onset symptoms entry into study in years</td>
<td>4</td>
<td>6</td>
<td></td>
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<tr>
<td>Presenting symptoms (sensorimotor:sensory)</td>
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<td>3:2</td>
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<tr>
<td>Men: women</td>
<td>3:2</td>
<td>3:2</td>
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<tr>
<td>Median score tapping test arm</td>
<td>30</td>
<td>34</td>
<td>0.02</td>
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<tr>
<td>Median score tapping test leg</td>
<td>35</td>
<td>35</td>
<td>0.6</td>
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<tr>
<td>Median motor sumscore</td>
<td>115</td>
<td>118</td>
<td>0.06</td>
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<tr>
<td>Median sensory sumscore</td>
<td>42</td>
<td>44</td>
<td>0.2</td>
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<tr>
<td>Rankin score</td>
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<td>35</td>
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<td>13</td>
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*Value between CIAP-MGUS and CIAP (Wilcoxon rank sum test).

minimal F wave latency of 20 F waves was increased above 150% of the upper limit of normal or when F waves were not obtainable.

Histological studies
Sural nerve biopsy was performed under local anaesthesia at the level of the lateral malleolus. One-micrometre Epon sections were stained with toluidine blue or p-phenylendiamine for light microscopical examination and quantification. A second piece of nerve was fixed in 2% glutaraldehyde, put fixed in 1% osmium tetroxide and infiltrated with Epon. Thin material single fibres were teased out for light microscopical examination. A third piece of nerve was snap-frozen in isopentane cooled with liquid nitrogen. Kryostat sections were prepared for routine histology and histochemistry (haematoxylin–eosin, periodic acid–Schiff, acid phosphatase, Congo red) and for demonstration of IgG, IgM, IgA and complement using immunofluorescence.

Statistical analysis
For the statistical analysis, the results of sumscores and tapping tests can be considered as an ordinal scale, and presented in percentiles. The non-parametric Wilcoxon rank sum test was used to test differences between both groups. The significance of the differences in nominal-scale data was determined by Fisher’s exact test. Values of P < 0.05 were considered significant.

Results

Patients
The mean age at onset of the polyneuropathy was 58 years (SD = 9) for those with CIAP-MGUS and 57 years (SD = 6) for those with CIAP. The mean time from onset of symptoms to entry into the study was 4 years for those with CIAP-MGUS and 6 years for those with CIAP (Table 1).

Symptoms
Thirty-three percent of the patients with CIAP-MGUS presented within 12 months after onset of the initial symptoms, whereas this was 15% for the CIAP patients (Fisher’s exact test, P = 0.09). All patients had sensory symptoms: numbness, tingling, paraesthesias or unsteadiness of gait. Weakness was a more common complaint in the CIAP-MGUS group (71%) than in the CIAP group (50%) (Fisher’s exact test, P = 0.1). No patient had bladder or bowel dysfunction, nor cranial nerve involvement.

Neurological evaluation
Neurological examination revealed a pure sensory neuropathy in 28% of the CIAP-MGUS patients and in 39% of the CIAP patients (Fisher’s exact test, P = 0.9). In patients with CIAP-MGUS, the arms were more frequently affected (70%) than in patients with CIAP (30%) (Fisher’s exact test, P = 0.05). In all patients there were abnormalities in vibratory sense and light touch sense was diminished in a stocking-like distribution. The majority of patients in both groups had diminished or absent lower extremity reflexes. The sensory and motor sumscores did not differ significantly between both groups (Table 1).

The tapping test scores for the arms of the CIAP-MGUS patients were significantly lower than in CIAP patients (Wilcoxon rank sum test, P = 0.02) (Table 1). The tapping test scores for the legs showed no difference (Wilcoxon rank sum test, P = 0.06) (Table 1).

In both groups the clinical course of the polyneuropathy between entry and end of the study as determined by the sumscores was progressive (Wilcoxon rank sum test, P < 0.001). The median motor sumscore was 115 on entry and 113 after 5 years of follow-up for CIAP-MGUS and 118 on entry and 116 at the end of the study for CIAP; the sensory sumscore was 42 on entry and 40 after 5 years of follow-up for CIAP-MGUS and 44 on entry and 42 at the end of the study for CIAP.
Disability
The disability measured by the modified Rankin scale was significantly worse in patients with CIAP-MGUS than in the CIAP group (Wilcoxon rank sum test, P < 0.001) (Table 1). On entry into the study 11 (69%) of the CIAP-MGUS patients and 22 (31%) of the CIAP patients needed devices. At the end of the follow-up, 12 of the CIAP-MGUS patients (75%) needed ankle braces or walking canes, whereas in the CIAP group 35 patients (50%) needed devices (Fisher’s exact test, P = 0.09).

Individual data of CIAP-MGUS patients
In the CIAP-MGUS patients, no significant differences were found between patients with IgM-MGUS and IgG-MGUS (Table 2). Three of the 16 patients had a worse disability score, these three patients scored also worse on the tapping test, motor and sensory sum scores. These three patients were treated with immunosuppressive treatment (cyclophosphamide, 4 days 300 mg daily/month, during 6 months; prednisone, 5 days 40 mg daily/month, during 6 months) because of their worse disability score. After 6 months of treatment two patients stabilized and one patient deteriorated.

Laboratory results
In the CIAP group none of the patients had antibodies against MAG, GM1 ganglioside and sulphatides. Of the patients with CIAP-MGUS, one patient with IgM-MGUS had antibodies against sulphatides (Table 2). This patient complained about painful nocturnal paraesthesias in the legs, disturbing sleep and causing restlessness. On neurological examination there was impairment of all sensory modalities distally in the legs and impairment of the vibration sense in the hands. Minor weakness was only found in the extensor hallucis muscle and there was areflexia. Extensive electrophysiological examination and sural nerve biopsy were compatible with axonal degeneration, no evidence of demyelination was found and deposits of IgM or amyloid were absent. In the other 15 patients with MGUS no antibodies against MAG, GM1 ganglioside and chondroitin sulphate C were present.

Electrophysiological assessment
Comparison of median, ulnar and tibial nerve conduction data did not reveal significant differences between both groups (Table 3). Concentric needle examination showed fibrillations and positive sharp waves in all 16 MGUS and in 45 (60%) CIAP patients (Fisher’s exact test, P = 0.003).

Histological studies
Sural nerve biopsies were performed in 12 patients with CIAP-MGUS and 31 patients with CIAP. No signs of demyelination, inflammation or amyloidosis were found. All nerve biopsies showed axonal degeneration. There was no significant difference in densities of myelinated nerve fibres between both groups (CIAP-MGUS, 3880 mm², SD = 1600; CIAP, 4170 mm², SD = 1450). In the nerve biopsies of patients with CIAP-MGUS no deposition of IgM, IgG or IgA was demonstrated. Although a diffuse background staining for IgG was evident in the endoneurium, this was no greater than for controls. No deposition of complement was detected.

Discussion
Several studies have shown an association between polyneuropathy and the presence of a serum monoclonal gammopathy (Abrams et al., 1982; Melmed et al., 1983; Mendell et al., 1985; Takatsu et al., 1985; Latov, 1990;
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Table 3 Median values of electrophysiological parameters of CIAP-MGUS and CIAP patients

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<th>CIAP-MGUS (n = 16)</th>
<th>CIAP (n = 71)</th>
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<tr>
<td>Ulnar nerve</td>
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<td>Motor</td>
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<td>DML (ms)</td>
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<td>CV (m/s)</td>
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<td>Amp. (mV)</td>
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<td>F-M</td>
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<td>Sensory</td>
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<td>CV (m/s)</td>
<td>16</td>
<td>14</td>
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<td>Amp. (μV)</td>
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<td>Median nerve</td>
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<td>Motor</td>
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<td>Amp. (mV)</td>
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<tr>
<td>F-M</td>
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<td>Sensory</td>
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<td>CV (m/s)</td>
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<tr>
<td>Amp. (μV)</td>
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<td>Tibial nerve</td>
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<td>CV (m/s)</td>
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<td>Amp. (mV)</td>
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<td>Sural nerve</td>
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<td>Amp. (μV)</td>
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n = number of patients in whom the investigations were done; o = number of patients in whom a compound muscle action potential, sensory nerve action potential or F wave was obtainable; amp. = amplitude of a compound muscle action potential or sensory nerve action potential on distal stimulation; CV = conduction velocity; DML = distal motor latency; F-M = minimal F wave latency minus M-response latency; SD = standard deviation. *Value between CIAP-MGUS and CIAP (Wilcoxon rank sum test).

Tatum, 1993; Nobile-Orazio et al., 1994). However, most research has focused on demyelinating polyneuropathy associated with MGUS (Abrams et al., 1982; Melmed et al., 1983; Mendell et al., 1985; Takatsu et al., 1985; Tatum, 1993; Kaku et al., 1994; Nobile-Orazio et al., 1994; Smith et al., 1994). In ~50% of the patients with a demyelinating polyneuropathy associated with an IgM-MGUS, the MGUS showed antibody activity to the myelin antigens MAG and Po, while substantial evidence for a role of anti-MAG antibodies in the pathogenesis of demyelinating polyneuropathy has been found (Melmed et al., 1983; Mendell et al., 1985; Latov, 1990; Tatum, 1993; Nobile-Orazio et al., 1994). Recently, CIDP has been distinguished from CIDP associated with MGUS (IgM, IgG, IgA) (Simmons et al., 1993). Simmons et al. (1993) found that patients with CIDP-MGUS (26 patients) had a more indolent course, less severe weakness and less functional impairment than patients with CIDP (77 patients). Bleasel et al. (1993), however, described five patients with a demyelinating neuropathy associated with IgG-MGUS whose clinical, electrophysiological and pathological features were similar of that of a CIDP.

Little is known of the role of MGUS in axonal neuropathy. Antibodies to glycoconjugates such as GM1, sulphatide or chondroitin sulphate have been detected in only a minority of the patients with axonal neuropathy associated with MGUS (Nobile-Orazio et al., 1994). Moreover, in contrast to anti-MAG antibodies in demyelinating neuropathy, evidence for a pathogenic role of these antibodies is scarcely available. To study more extensively the role of MGUS in axonal neuropathy we have compared the clinical, electrophysiological and pathological and pathological features of CIAP with and without MGUS. Three significant differences between both groups were found: (i) in CIAP-MGUS patients the arms were more frequently affected than in the CIAP group; (ii) the Rankin score was significantly worse; (iii) there was a higher frequency of denervation on electrophysiological examination in patients with CIAP-MGUS. These few differences between both groups suggest that CIAP-MGUS and CIAP might be different entities and that the monoclonal protein might play a pathogenic role, especially in the three patients with a worse Rankin score. However, it cannot be ruled out that the significant differences between both groups are due to chance alone. The clinical presentation of symptoms, the sensory and motor signs, the nerve conduction parameters and the sural nerve biopsies were not different in both groups. This indicates that CIAP and CIAP-MGUS are essentially indistinguishable, suggesting that the MGUS is coincidental in most patients, as monoclonal proteins are.
present in 0.1% of the population over 25 years, increasing to 3% in persons older than 70 years. This may be especially so in the IgG-MGUS group as, with increasing age, 88% of the benign M-proteins happened to be IgG (Axelsson et al., 1966).

As CIAP usually presents at middle or old age, its pathogenesis might be related to ageing of the peripheral nervous system or ischaemia due to vascular abnormalities, leading to axonal degeneration (Notermans et al., 1993, 1994d). Basically, a polyneuropathy can only be classified as idiopathic after exclusion of all known possible causes. A genetically determined axonal neuropathy of late onset cannot completely be excluded such as (sporadic) hereditary motor and sensory neuropathy type 2, which may present in up to 15% of patients after the age of 50. The family history and follow-up of the CIAP patients, however, do not support a hereditary pathogenesis of the polyneuropathy (Harding and Thomas, 1980; McLeod et al., 1984; Notermans et al., 1993, 1994d). On theoretical grounds the presence of a MGUS in serum of patients with CIAP suggests an immune-mediated pathogenesis. Similar to the anti-MAG antibodies in demyelinating polyneuropathy, the MGUS may bind to axonal antigens (Li et al., 1991; Mamoli et al., 1992; Nobile-Orazio et al., 1994). However, in our study only one patient with CIAP-MGUS had elevated antibody titres to sulphatide compared with normal and disease controls. Moreover, biopsy studies showed no differences between CIAP and CIAP-MGUS patients and no deposition of IgM or IgG was noted in the biopsies of CIAP-MGUS patients.

In conclusion, axonal polyneuropathy in patients with and without MGUS are essentially indistinguishable rather than different, suggesting that the MGUS may be coincidental in most patients.

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