Chronic Acquired Demyelinating Symmetric Polyneuropathy Classified by Pattern of Weakness

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Objectives: To study a representative group of patients with chronic acquired symmetric demyelinating polyneuropathies, and to evaluate classification by pattern of weakness and by presence of immunoglobulin monoclonal protein (M protein).

Methods: In Vest-Agder County, Norway, an unselected population of patients with chronic symmetric polyneuropathies who fulfill electrodiagnostic criteria for demyelination are registered in a database and followed up prospectively. Data were taken from the database on April 2, 2001. Patients with proximal as well as distal weakness were classified as having chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and patients with only distal symptoms as having distal acquired demyelinating symmetric polyneuropathy (DADS).

Results: A total of 29 patients had chronic acquired symmetric demyelinating polyneuropathy; 15 had CIDP and 14 had DADS. The 2 categories differed regarding spinal protein level (mean±SD, 0.102±0.060 g/dL in CIDP vs 0.065±0.029 g/dL in DADS; P=.05); clinical course (remitting in 6 of 13 patients with CIDP vs 0 of 14 with DADS; P=.02); disability score at diagnosis (mean±SD, 3.3±1.0 in CIDP vs 1.9±0.6 in DADS; P<.001) and at peak of symptoms (mean±SD, 3.6±1.1 in CIDP vs 2.3±0.6 in DADS; P<.001); and response to immunosuppressive treatment (11 of 12 patients with CIDP vs 2 of 7 with DADS; P=.01). An M protein was detected in 8 patients (3 with CIDP and 5 with DADS). Patients with polyneuropathy with and without M protein were similar in clinical features, course, disability, and treatment response.

Conclusion: Classification by presence or absence of proximal weakness separates patients with chronic acquired symmetric demyelinating polyneuropathy into groups that are different in clinical course, disability, and treatment response.

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POLYNEUROPATHIES WITH electrophysiologic changes of demyelination and without a genetic, toxic, or metabolic cause are considered to be inflammatory and potentially treatable. Such polyneuropathies are heterogeneous, and a classification system is needed that enables clinicians to predict prognosis and response to immunologic treatment. Chronic acquired demyelinating symmetric polyneuropathies are often classified into chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and paraproteinemic polyneuropathies with circulating benign immunoglobulin monoclonal protein (M protein). The CIDP is characterized by proximal as well as distal weakness, elevated spinal protein, and a high probability of responding to corticosteroids. Paraproteinemic polyneuropathies are considered to have a more indolent course and a poor response to standard immunosuppressive treatment. The focus on M proteins is due to the fact that IgM M proteins often consist of pathogenic antibodies against myelin-associated glycoprotein (MAG). The MAG antibodies can be detected in nerve tissue and induce demyelination experimentally. From a clinical standpoint, however, a classification based solely on the presence of M protein may be confusing, since associated clinical syndromes are heterogeneous. Monoclonal proteins are detected in otherwise typical patients with CIDP, and some patients with demyelinating polyneuropathy have neither M protein nor typical CIDP features. Katz et al recently suggested classifying demyelinating symmetric polyneuropathies by the pattern of weakness into (1) CIDP characterized by proximal as well as distal weakness and (2) distal acquired demyelinating symmetric polyneuropathy (DADS) with length-dependent primarily sensory or only distal motor symptoms, and to further classify DADS into

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DADS-M (with M protein) and DADS-I (without M protein), since patients with DADS-M seemed to be older, more predominantly male, and less responsive to immunologic treatment than patients with CIDP and patients with DADS-I.3

Epidemiologic studies on chronic demyelinating polyneuropathies are limited, and the suggested phenotypic classification has so far been applied only on selected patient groups from tertiary referral centers. Our purposes were to study a representative population of patients with chronic acquired symmetric demyelinating polyneuropathy, and to examine whether classification by phenotype and M protein is clinically useful.

METHODS

PATIENTS

Vest-Agder is a county in the southern part of Norway with a population of 153,464 as of October 1, 2000. It is a geographically well-defined region with a stable population well provided with medical services. General practitioners and 1 neurology practitioner refer all patients with significant neuropathy to the Department of Neurology at Vest-Agder Central Hospital in Kristiansand, which is the only neurology department and neurophysiology center in the county. All referred patients with neuropathy are subjected to clinical or neurophysiologic examination by at least 1 neurologist with special interest in neuropathies. A diagnosis of polyneuropathy is based on the presence of symmetric motor, sensory, or sensorimotor symptoms in at least 2 extremities, associated with hyporeflexia and typical electrodiagnostic pathologic findings. The polyneuropathy is considered to be chronic when symptoms have progressed during at least 2 months. All patients with polyneuropathy are subjected to thorough causal investigation as previously described.5

Patients with chronic symmetric polyneuropathy who fulfill the criteria for demyelinating (see the “Laboratory Studies” section) and in whom underlying causes (metabolic, toxic, or hereditary) are excluded are registered in a database with clinical, serologic, and electrodiagnostic features and followed up prospectively. The patients are seen at regular intervals. Data for this study were derived from the database on April 2, 2001. The mean annual incidence was calculated from cases diagnosed in the period from January 1, 1993, through December 31, 2000. Patients with purely motor neuropathy, as in multifocal motor neuropathy, were not included in the study.

CLINICAL MEASURES AND CLASSIFICATION

Muscle strength was measured manually in abductors of shoulders, flexors and extensors of neck, elbows, wrists, fingers, hips, knees, ankles, and toes by means of the Medical Research Council (MRC) Scale. Patients with proximal weakness (MRC score <3 in shoulders or hips) or proximal as well as distal weakness (MRC score <3 in ankles, toes, hands, or fingers) were classified as having CIDP, and patients with weakness confined to ankles, toes, wrists, or fingers or only sensory symptoms were classified as having DADS. The finding of DADS with an M protein was termed DADS-M, and DADS without M protein was termed DADS-I. Polyneuropathies with normal muscle strength and only sensory symptoms despite electrodagnostic involvement of motor nerves were classified as purely sensory. The CIDP-DADS classification was based on the findings at the time of diagnosis, ie, at least 2 months after onset of symptoms. The initial classification was checked against findings at follow-up visits when diagnoses could be changed from DADS to CIDP if patients developed proximal weakness, but patients with CIDP were not reclassified if their proximal strength normalized after treatment.

Functional impairment was assessed with modified Rankin disability scale: 0, asymptomatic; 1, nondisabling symptoms that do not interfere with daily activities; 2, slight disability (unable to carry out all activities, such as running, but still able to look after themselves); 3, moderate disability (requiring assistance with some activities but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance); and 5, severe disability (totally dependent, requiring constant care).

The clinical course was classified as (1) rapidly progressive (continuous or stepwise): disability score increased to 3 during less than 6 months; (2) slowly progressive (continuous or stepwise): slower progression of disability or symptoms over at least 1 year; or (3) relapsing: fluctuating course with partial or complete recovery between relapses. Remission was defined as being asymptomatic without treatment for at least 1 year.

LABORATORY STUDIES

Standard nerve conduction studies were performed with the use of surface electrodes. Motor nerve conduction was investigated in the median and ulnar nerve from elbow to wrist, and in peroneal and tibial nerves from knee to ankle. Sensory responses were investigated in median, ulnar, radial, and sural nerves. For polyneuropathies to be classified as demyelinating and included in the study, at least 3 of the following 4 criteria had to be met: (1) conduction velocity of less than 90% of the lower limit of normal (<44 m/s in arms and 35 m/s in legs) if amplitude exceeds 50% of the lower limit of normal (5 mV in median, 4 mV in ulnar, 1 mV in peroneal, and 2 mV in tibial nerves); less than 80% of the lower limit of normal (39 m/s in arms and 31 m/s in legs) if amplitude is less than 50% of the lower limit of normal (2 more nerves); (2) distal latency exceeding 115% (4.5 milliseconds in arms and 6.4 milliseconds in legs) of the upper limit of normal if amplitude is normal; exceeding 125% (5.4 milliseconds in arms and 7.7 milliseconds in legs) if amplitude is less than 50% of the lower limit of normal (2 or more nerves); (3) a proximal to distal amplitude ratio less than 0.7 (1 or more nerves, except tibial nerve); and (4) F-wave latency exceeding 123% of the upper limit of normal (36 milliseconds in median, 38 milliseconds in tibial and peroneal nerves) or absent F-waves in 1 or more nerves.

Routine laboratory tests consisted of hemoglobin level, white blood cell count, sedimentation rate, platelets, serum electrolytes, creatinine level, liver enzyme levels, fasting blood glucose level, thyroid function tests, vitamin B12 level, folic acid level, rheumatoid factor, antinuclear antibodies, serologic examination for Lyme disease, examination of cerebrospinal fluid, and chest radiographs. Serum samples were examined with protein electrophoresis and immunofixation electrophoresis for the presence of M protein of the IgM, IgG, IgA, and κ and λ iso types. Patients with high M protein levels were examined for malignancy with bone marrow examination and radiologic skeletal survey. Serum samples from 26 of 29 patients were tested for antibodies to GMI, ganglioside and MAG. The testing was performed at the Department of Neurology, Haukeland University Hospital, Bergen, Norway.

A sural nerve biopsy was performed in 7 patients (4 with CIDP and 3 with DADS). The biopsy specimens were prepared and examined with electron microscopy and teased fibers at the Neuromuscular Center, Tromsø University Hospital, Tromsø, Norway.
TREATMENT

Patients were treated with prednisone, intravenous (IV) immunoglobulin, plasmapheresis (PE), or azathioprine. Prednisone, IV immunoglobulin, and PE were first-line treatments. The average initial dosage of prednisone was 40 mg. It was reduced when patients showed stable improvement and was discontinued if there was no significant improvement after 2 to 3 months. The initial dosage of IV immunoglobulin was 2 g/kg given over 5 days. The dose was repeated when symptoms recurred or started to progress again, or at regular intervals. The PE regimen was 5 exchanges, each removing about 2 to 4 L of plasma, performed every other day. Azathioprine was given when other treatment regimens failed and disability was significant.

Patients were classified as objective responders if they improved by at least 1 point on the Rankin disability scale or by 1 motor grade (MRC Scale) in 1 or more muscle groups after any treatment regimen. Patients were classified as subjective responders if they reported subjective improvement in function or sensory symptoms, and as nonresponders if they had no motor or subjective improvement.

MEASURES AND STATISTICS

Patients with CIDP and DADS were similar regarding age and sex ratio, and duration of symptoms at diagnosis and at the peak of symptoms (Table 2). At last follow-up, however, the disability score was similar in patients with CIDP and DADS. Four patients with CIDP were then in stable (ie, at least 1 year) remission without treatment. Three patients with CIDP had died; 1 died of CIDP and 2 died of other causes (cancer and cerebrovascular disease). None of the patients with DADS died.

Patients with CIDP and DADS were similar regarding age at onset, sex ratio, and duration of symptoms at diagnosis (Table 2). All patients classified as having DADS at presentation remained in the DADS category, ie, none of them developed proximal weakness. Eight of 14 patients with DADS had only sensory symptoms. One patient with CIDP who presented with proximal weakness had only sensory symptoms at later exacerbations. Pain was reported in 8 of 15 patients with CIDP and in 10 of 14 with DADS. The clinical course differed significantly in patients with CIDP and DADS (Table 2).

RESULTS

CLASSIFICATION

The database contained a total of 29 patients with chronic acquired demyelinating symmetric polyneuropathy; 15 had CIDP and 14 had DADS. Three patients with CIDP had died during the observation period and 4 were in remission. The prevalence of CIDP was therefore 5.1 (95% confidence interval, 1.5-8.7) per 100,000 population, and for DADS, 8.9 (4.1-13.7) per 100,000 population. The mean annual incidence was 1.2 (0.2-5.9) per 100,000 population for CIDP and 1.1 (0.2-8.8) for DADS.

An M protein was detected in 8 patients, 3 with CIDP and 5 with DADS (Table 1). The M protein was IgM in 2 patients with DADS (both λ) and 1 patient with CIDP (λ). The MAG antibodies were detected in the 2 patients with DADS IgM, making a prevalence of 0.8 per 100,000 population.

CLINICAL FEATURES

Patients with CIDP and DADS were similar regarding age at onset, sex ratio, and duration of symptoms at diagnosis (Table 2). All patients classified as having DADS at presentation remained in the DADS category, ie, none of them developed proximal weakness. Eight of 14 patients with DADS had only sensory symptoms. One patient with CIDP who presented with proximal weakness had only sensory symptoms at later exacerbations. Pain was reported in 8 of 15 patients with CIDP and in 10 of 14 with DADS. The clinical course differed significantly in patients with CIDP and DADS (Table 2). About one third of the patients with CIDP had a remitting course, whereas most of the patients with DADS had a slowly progressive course. The disability score was significantly higher in CIDP than in DADS, both at the time of diagnosis and at the peak of symptoms (Table 2). At the last follow-up, however, the disability score was similar in patients with CIDP and DADS. Four patients with CIDP were then in stable (ie, at least 1 year) remission without treatment. Three patients with CIDP had died; 1 died of CIDP and 2 died of other causes (cancer and cerebrovascular disease). None of the patients with DADS died.

Patients with DADS-M were slightly more disabled at diagnosis than those with DADS-I (mean±SD disability score, 2.4±0.5 vs 1.7±0.5; P=.03). Otherwise, comparison of patients with demyelinating polyneuropathy with and without M proteins, CIDP with and without M proteins, and DADS with and without M proteins did not show any differences regarding age at onset, sex ratio, clinical course, and disability. The 2 patients with anti-MAG had M protein of the IgM λ isotype and were classified as having DADS. They were 47 (male) and 69 (female).
male) years of age. Their distal latencies were not particularly prolonged. Patients with Gm1 antibodies did not show any distinct clinical features.

TREATMENT RESPONSES

Twelve of 15 patients with CIDP and 7 of 14 patients with DADS had been treated with immunosuppressive treatment. Four patients with CIDP had been treated with prednisolone, 1 with IV immunoglobulin, 5 with PE and prednisolone, and 1 with IV immunoglobulin and prednisolone. One patient with CIDP had been treated with prednisolone, PE, IV immunoglobulin, and azathioprine. Six patients with DADS had been treated with prednisolone and 1 with IV immunoglobulin.

Ten of 12 patients with CIDP had objective motor response to treatment as compared with 0 of 6 patients with DADS (P=.001). Subjective or objective response was reported in 11 of 12 patients with CIDP and 2 of 7 with DADS (P=.01). Prednisone was effective (subjectively or objectively) in 9 of 11 patients with CIDP and in 1 of 6 patients with DADS. Intravenous immunoglobulin was effective in 1 of 3 patients with CIDP and in 1 of 1 patient with DADS. The PE was effective in 5 of 6 patients with CIDP.

Treatment response was similar in patients with demyelinating polyneuropathy with and without M protein, and in those with CIDP with and without M protein. The 2 patients with DADS with a subjective response to treatment were in the DADS-I group, whereas none of the 3 treated patients with DADS-M responded. The 2 MAG antibody–positive patients with DADS-M did not receive immunosuppressive treatment because of mild, stable symptoms. The patient with CIDP with IgA λ responded only subjectively to prednisolone, but had a spontaneous objective remission 6 months after treatment with prednisolone was stopped.

LABORATORY RESULTS AND ELECTRODIAGNOSTIC MEASURES

The cerebrospinal fluid protein level was higher in CIDP than in DADS (Table 2). It was similar in patients with and without M protein. Sural nerve biopsy specimens from 4 patients with CIDP and 3 with DADS showed demyelination.

Electrodiagnostic findings (mean of conduction velocity, distal latency, and F-response in median, ulnar, tibial, and peroneal nerves) were similar in patients with and without M protein, in CIDP and DADS, and in DADS-I and DADS-M. Patients with IgM M protein and patients with MAG or Gm1 antibodies did not show any distinct electrodiagnostic features.

COMMENT

We studied a small but unselected population of patients with chronic acquired symmetric sensorimotor polyneuropathy and demyelinating electrodiagnostic features. We found that about half of such patients have CIDP with proximal as well as distal weakness (estimated annual incidence, 1.2 per 100000 population), whereas the other half have DADS with only distal weakness or primarily sensory symptoms (estimated annual incidence, 1.2 per 100000 population). Our CIDP prevalence was 5.1 per 100000 population. This is higher than previously reported in retrospective population-based CIDP prevalences.7,8

Our study confirms that classification by patterns of weakness is clinically useful, since patients with and without proximal weakness were different in clinical course, disability, and treatment response. In patients with CIDP the course was remitting in one third, whereas none of the patients with DADS had a remitting course. Most of the patients with DADS had a slowly progressive course, and about half had only sensory symptoms. Patients with CIDP were more disabled at presentation and peak of illness, but their disability at follow-up was not significantly worse than in DADS. This probably reflects a higher remission rate and a better treatment response in the patients with CIDP.

Most of the patients with CIDP responded to treatment; those with DADS were significantly less responsive. The 2 patients with DADS who responded to standard immunosuppressive treatment were both in the DADS-I group, whereas none of the 5 patients with DADS-M responded. This agrees with other retrospective studies showing beneficial response of prednisone in patients with “chronic sensory demyelinating polyneuropathy” without M protein,9 corresponding to our DADS-I group, but no response in patients with DADS-M.3 None of our patients with DADS-M received cytotoxic treatment. The reported beneficial effect of such treatment is based on clinically heterogeneous patient groups10,11 and does not necessarily apply to patients with DADS-M. Our treatment results must be judged with caution because of the retrospective nature of the study and the small number of treated patients with DADS. Further studies with prospective evaluation of sensory as well as motor variables are necessary to evaluate treatment response in DADS-I and DADS-M.

An M protein was detected in 20% of patients with CIDP and 36% of patients with DADS. Katz et al1 reported a higher frequency of M protein in patients with DADS (67%). The difference may reflect that our population was more unselected. Others3,12 have shown that patients with DADS with anti-MAG antibodies tend to be older than patients with CIDP. Our number of patients with anti-MAG antibodies was probably too small to show this difference. Patients with CIDP with and without M protein were similar in treatment response, course, and disability. Others3,14 have found clinical differences between these 2 groups. Their findings may be due to lumping together of patients with proximal weakness and patients with only distal symptoms. Patients with only distal symptoms and IgM M protein (DADS-M) are less treatment responsive and have a more indolent course than patients without M protein (DADS-I).3,8 Including patients with DADS-M under the term CIDP-M could therefore lead to the assumption that the whole group of patients with CIDP-M are less treatment responsive than those with CIDP-I.

Polyneuropathies associated with M protein are often termed paraproteinemic, since the M protein is consid-
erated to have a pathogenic role. There is evidence that M protein is responsible for the neuropathy in patients with IgM M proteins that react with MAG.2 There is little evidence that IgG or IgA M proteins or other antineuronal antibodies are pathogenic. In our study, the presence of M protein did not relate to clinical features, course, disability, or treatment response. However, it was hardly coincidental that our 2 patients with anti-MAG antibodies both had IgM κ and had the distal phenotype. Others have shown that DADS with IgM κ makes a distinct clinical entity characterized by male preponderance, old age, and poor response to immunosuppressive treatment.3,11,13 Patients with CIDP with IgM are different and may, as shown in our study, respond well to immunosuppressive treatment.

In conclusion, the results of our small study suggest that clinical course, disability, and response to treatment are different in patients with chronic acquired symmetric demyelinating polyneuropathy with and without proximal weakness. The presence of M protein does not seem to relate to any clinical measures in patients with proximal weakness (CIDP), but previous studies have shown that the presence of IgM M protein in patients with only distal symptoms predicts a poor response to standard immunosuppressive treatment.2 To give the best prediction of prognosis and treatment response, patients with chronic polyneuropathy should probably be approached by considering clinical findings, pattern of weakness, the presence and type of M protein, and nerve conduction findings together instead of splitting them by any one finding.

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