CLINICAL CHARACTERISTICS OF PATIENTS WITH CHRONIC ACQUIRED DEMYELINATING POLYNEUROPATHY

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Abstract- Chronic acquired demyelinating neuropathy (CADP) is heterogeneous in both clinical and laboratory features. This study was performed to define the clinical, electrodiagnostic and histological findings, course and response to therapy in patients with CADP. Thirty patients (20 men and 10 women) with CADP were studied. Diagnostic criteria were based on clinical presentation, electrophysiological studies, cerebrospinal fluid (CSF) protein level and sural nerve biopsy findings. Response to treatment was assessed by changes in average muscle score (AMS). Twenty-one patients conformed to the diagnostic criteria of chronic inflammatory demyelinating polyneuropathy (CIDP) and 9 to distal acquired demyelinating symmetric neuropathy (DADS). The course was monophasic in 6 (23%), relapsing in 10 (40%) and chronic progressive in 8 (30%); 4(13%) had acute presentation with subsequent progression or relapsing course. Motor nerve conduction velocity (MNCV) of less than 70% and greater than 70% of normal were seen in 18 (60%) and 12 (40%) patients, respectively. Conduction block was observed in 14 (47%) and CSF protein levels were elevated in 19 patients (66%). Demyelination was reported in 61% and 58% of the biopsies performed in patients with MNCV < 70% and > 70% of normal, respectively. The association between MNCV and histologic findings was not significant. Twenty-one patients were treated with intravenous immunoglobulin (IVIg). Fifteen patients (83%) with CIDP had significant improvement in AMS following the initial IVIg treatment ($P = 0.01$). This study highlights the heterogeneity of clinical and laboratory findings in CADP and the importance of early treatment.

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Key words: Chronic acquired demyelinating polyneuropathy; chronic inflammatory demyelinating polyneuropathy; distal acquired demyelinating symmetric neuropathy

INTRODUCTION

In 1958, Austin first described a recurrent steroid responsive polyneuropathy (1). During the subsequent three decades, a number of authors reported their experiences with this entity under varying titles, including "recurrent and chronic relapsing Guillain-Barre polyneuritis" (2), "relapsing corticosteroid-dependent polyneuritis" (3) and "steroid responsive recurrent polyneuropathy" (4). This condition which was often referred to as chronic inflammatory demyelinating polyneuropathy (CIDP), is important since it represents approximately 21% of all initially undiagnosed neuropathies (5). In addition, a significant percentage of these patients respond to immunosuppressive therapy (3, 6, 7).

The disorder can be heterogeneous in both clinical and laboratory features (8-11). Currently, it is known under title of "chronic acquired demyelinating neuropathy" (CADP). Patients are commonly divided into the following four clinical phenotypes (11):

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1) CIDP is defined by the criteria proposed by American Academy of Neurology (AAN) in 2001: steadily progressive, chronic, monophasic or recurrent course, tendency to symmetric involvement of proximal as well as distal limb muscles and a duration of at least 2 months; electrodiagnostic studies demonstrating two of the four parameters of demyelination *i.e.,* prolonged distal latency, decrease in motor nerve conduction velocity (MNCV) to less than 70% of lower limit of normal, delayed or absent F waves and conduction block; cerebrospinal fluid (CSF) protein of more than 45 mg/dl; and nerve biopsy showing predominant features of demyelination (including demyelination, remyelination, onion bulb formation). Inflammation is not required to be present.

2) Distal acquired demyelinating symmetric neuropathy (DADS): clinical presentations of DADS include distal and symmetric sensory or sensorimotor phenotype. Despite primarily sensory signs and symptoms, electrophysiologic measures indicate demyelination of sensory and motor nerves. The majority of patients with a DADS neuropathy phenotype have a monoclonal gammapathy of undetermined significance (MGUS), which is almost exclusively IgM. Patients with DADS-M respond poorly to immunomodulating therapy; in some series only 30% showed improvement (11).

3) Multifocal motor neuropathy (MMN)

4) Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).

This study was performed to define the clinical spectrum of patients, the course of disease and the association between CADP and other diseases.

MATERIALS AND METHODS

Clinical, laboratory and biopsy records were reviewed for all patients who were admitted in Imam Khomeini Hospital over 6 years from 1996 to 2002.

Patients with concomitant systemic conditions such as central nervous system (CNS) demyelination, diabetes mellitus or hereditary neuropathy with exacerbation of symptoms were included in this study. Since hereditary neuropathies cause uniform slowing of conduction velocity without conduction block, presence of conduction block was considered as a sign of acquired neuropathy.

Mean MNCV and the presence of conduction block, CSF protein level, the relationship between nerve biopsy findings and MNCV and the response to treatment were studied.

Clinical assessment of muscle strength was performed on initial and subsequent visits using the modified Medical Research Council scale expanded to 10 point system and average muscle score (AMS) was determined (12). Muscle testing included facial muscles (orbicularis oculi), neck flexors, shoulder extensors, elbow flexors, wrist flexors and extensors, hip flexors, knee flexors, ankle dorsiflexors and ankle plantar flexors.

Routine electrophysiologic studies were performed by neurologists of Electrophysiological Department of this hospital with Tonnies EMG instrument (13). MNCV, conduction block, compound muscle action potential, degree of distal latency and F wave prolongation were monitored. MNCV was interpreted as being demyelinative if at least one of the motor nerves tested (median, ulnar, peroneal) had slowing of conduction to less than 70% of lower range of normal. We used two values in our statistical analysis: (a) the slowest motor nerve conduction and (b) the average compound muscle action potential of ulnar, median and peroneal nerves. Sensory nerve action potential was routinely measured for amplitude, latency, conduction velocity in median, ulnar and sural nerves (antidromic determination). Because of common failure to obtain an evocable sensory potential, these values could not be included in data analysis. Needle examination was performed in all patients and while motor unit potential amplitude, duration, morphologic features and recruitment were routinely evaluated, only the presence or absence of fibrillation potentials was used for data analysis.

After obtaining patients' information, sural nerve biopsy was performed through an incision extending 7-10 cm along area between Achill tendon and lateral malleulus beginning about 1 cm proximal to lateral mallelus. The specimen was processed for light and electron microscopy. Nerve biopsy assessment was standardized and consisted of the

following: a) evaluation of epineurial and endoneurial inflammatory infiltration and b) classification of changes according to the following scheme: A, indicating normal; B, demyelination (paranodal and segmental); C, remyelination; D, demyelination and remyelination; E, wallerian degeneration (14).

A consistent treatment approach had been used in the six years of observation. Twenty-one of the patients were treated with IVIg, 0.4 gr/kg for 5 days, followed by low dose prednisone (20-30 mg) and seven monthly doses of IVIg and tapering of steroid. Two of the patients not responding to the above regimen, or experiencing monetary problems, received prednisone, 100 mg daily for 2-4 weeks, and were subsequently switched over to 100 mg single-dose, alternate-day prednisone therapy with subsequent tapering for at least 2 years.

Statistical analyses, including paired and two-sample *t* test, analysis of covariance, Fisher exact test and Pearson correlation coefficient in the SAS system version 8.00, were done.

RESULTS

During the study period 30 patients (10 women and 20 men) were included. Twenty one patients had CIDP and 9 patients had DADS. They ranged in age from 16-70 years (mean 36.2 ± 13.9). In this study, there was no patient with MMN or MADSAM.

The AMS at the time of initial visit was calculated for each patient. A characteristic pattern of weakness in all patients, with the exception of DADS neuropathy cases, was the presence of proximal weakness in addition to distal weakness. Objective sensory loss of pain and temperature was seen in 57%, and of position and vibration in 93% of the patients. Twenty seven (90%) patients had loss of tendon reflexes. Three patients (10%) had facial muscle weakness. Four patients (13%) presented with acute onset (symptoms evolved in less than 4 weeks), mimicking Guillain-Barre syndrome (15), with subsequent course of relapsing-remitting or slowly progressive. Twenty six patients (87%) presented with gradual onset (more than 4 weeks for evolution of symptoms). Ten patients (40%) had a relapsing course (exacerbation and remission of symptoms), 6 (23%) monophasic and 8 (30%) had chronic progression. The course was unknown in the remaining 2 (7%).

Cases with associated systemic conditions in addition to CADP were included in this study. At the time of diagnosis, these included 2 patients with diabetic mellitus, one well controlled and the other in an uncontrolled stage. One patient had history of central demyelination (ADEM), and 2 of hereditary neuropathy with exacerbation of symptoms. No abnormal peak in immune electrophoresis was seen in any of these cases.

MNCV data revealed the following values for mean and standard deviation: median nerve, 29.1 ± 20.1 m/s; ulnar nerve, 30.8 ± 19.6 m/s; and peroneal nerve 20.5 ± 18.6 m/s. Overall, 18 (60%) patients had at least two motor nerves that were slowed to less than 70% of normal, a range compatible with demyelination, and 12 (40%) mild slowing (not less than 70% of normal). In our laboratory, this required a median or ulnar nerve MNCV below 35 m/s and a peroneal MNCV below 30 m/s. Conduction block (proximal compound muscle action potential amplitude 50% or less than distal) occurred in 14 (47%) nerves.

Nerve biopsy was performed in 23 patients. In 17 patients (74%) a profile indicative of demyelination and remyelination predominated and 6 (26%) had mixed axonal involvement and demyelination. In 7 (30%) of the biopsy specimen, small clusters of mononuclear inflammatory cells were found in epineurium and perineurium or endoneurium. The degree of MNCV slowing did not predict the findings on sural nerve biopsy (Fisher exact test, *P* value = 0.7) (Table 1). In patients with MNCV slowing to less than 70% of normal, the distribution of changes included 11(61%) biopsy specimen with demyelination and remyelination features, three

Table 1. Comparison of slowed motor nerve conduction velocities (MNCV) and sural nerve pathologic findings*

	MNCV	
Pathological findings	**< 70% of normal (n = 18)**	**> 70% of normal (n = 12)**
Demyelination	61	58
Mixed	17	17
Not done	22	25

*Data are given as percent.

(17%) patients had mixed features and in 4 patients (22%) biopsy had not been performed. Similarly, in 12 patients having only mild slowing of MNCV, 7 (58%) had biopsies with demyelination/remyelination, 2 (17%) had mixed features and in 3 (25%) nerve biopsy was not done.

CSF protein determination was performed on 29 patients; in 19 (66%) cases the CSF protein level was elevated. In 12 (41%) patients CSF protein was elevated above 100 mg/dl. Twenty-one of the 30 patients received IVIg, 2 received full doses of steroid, and 2 patients underwent plasma exchange. Fifteen (83%) of the 18 patients of the CIDP group showed initial improvement with IVIg therapy during admission.

AMS improved from 3.2 ± 0.94 at the time of initial examination to 4.35 ± 0.5 at initial improvements in case of CIDP (paired t test, mean difference = 1.15 ± 1, $P = 0.01$). In cases of DADS neuropathy, average AMS improved from 3.8 ± 0.4 to 4.33 ± 0.26 at initial improvement (paired t test, mean difference 0.55 ± 0.46, $P = 0.034$). The improvement in the two groups was not significantly different (analysis of covariance, $P = 0.5$) (Fig 1).

No change in reflexes was seen. The AMS at the time of diagnosis showed no correlation with the AMS at the time of improvement (Pearson's correlation coefficient, $r = 0.14$, $P = 0.55$). However, shorter duration of symptoms before treatment initiation was associated with greater improvement in AMS (Fig 2). The time to reach the greatest improvement in AMS varied between 1 to 57 months with repeated administration of IVIg and low dose steroids.

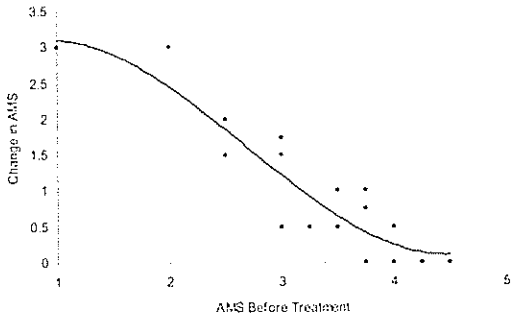

Fig. 1. Change in average muscle score (AMS) after treatment with intravenous immunoglobulin (IVIg).

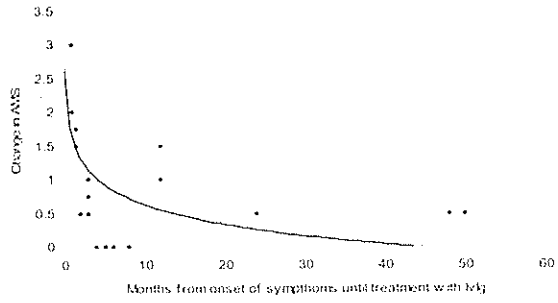

Fig. 2. Relationship between onset of symptoms and change in average muscle score (AMS) after treatment with intravenous immunoglobulin (IVIg).

DISCUSSION

The condition described by Austin in 1958 as steroid responsive neuropathy (1) and now as CADP is important since it represents approximately 21% of initially undiagnosed cases of neuropathy (5). CADP is heterogeneous in clinical and laboratory features (8-11) and can be classified as CIDP, DADS, MMN, and MADSAM.

The cardinal laboratory features of CADP have been considered to include MNCV slowing often with conduction block, inflammatory demyelinating features on nerve biopsy and elevated CSF protein levels (1, 2, 6-10). In our study, a rise in CSF protein was the most consistent laboratory abnormality (66%). MNCV slowing below 70% of normal was observed in 18 (60%) patients. Conduction block, often signifies acquired inflammatory demyelinating neuropathy, was present in 17 (47%) patients. Sural nerve biopsy in 23 of 30 patients showed demyelination in 17 (74%) patients; the remaining 6 (26%) had mixed features; there was a poor correlation between pathologic changes in sural nerve biopsy and the degree of MNCV slowing. In patients with MNCV < 70% of normal features of demyelination were reported in 11 (61%) cases, and 7(58%) patients with MNCV > 70% of normal had demyelination. These data were similar to Barhon's study (16).

Inflammatory cell infiltration in sural nerve biopsy was observed in 7 out of 23 patients (30.6%). This figure was 10.7% in the Mayo Clinic reports (16-17). These findings minimize the role of sural

nerve biopsy in diagnosis. Sural nerve biopsy may be reserved for patients whose electrodiagnostic and CSF findings are not supportive of the diagnosis, or when histological evidence of an alternative diagnosis is being sought (18). Another aspect of heterogeneity was the presence of a concurrent illness in a condition indistinguishable from CIDP in our series. Such disorders included diabetes mellitus, hereditary neuropathy and one patient with mixed peripheral and central demyelination presentation.

Responsiveness to initial treatment with IVIg was observed in 83% of CIDP patients, similar to other investigations (19, 20). Contrary to a previous study (16), there was no correlation between AMS at the time of initial examination and residual weakness, so a patient with greater weakness at initiation of treatment had similar likelihood of recovery after treatment, as a patient with less weakness.

This study highlights the heterogeneity of clinical and laboratory findings in chronic acquired demyelinating polyneuropathy and the importance of early treatment.

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