

The clinical spectrum of Malaysian patients with chronic inflammatory demyelinating polyneuropathy

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Abstract

Chronic inflammatory demyelinating polyneuropathy (CIDP) is now increasingly thought to be heterogeneous with several clinical patterns being described. We describe the clinical spectrum of a series of 45 Malaysian patients with CIDP recruited from 1993 to 2003. There were five clinical subgroups – classical CIDP with symmetrical motor-sensory, proximal more than distal weakness; symmetrical distal sensorimotor demyelinating neuropathy; asymmetrical (multifocal) pure motor neuropathy; asymmetrical sensorimotor neuropathy and pure sensory neuropathy. The subgroups had some differences in terms of age of onset, sex ratio, functional severity, response to immunotherapy and pattern of outcome. Patients with classical CIDP had poorer function at nadir but responded well to treatment. Distal symmetrical sensorimotor neuropathy patients were older, were more often men, functionally less severe but responded less well to immunotherapy. Therefore, subclassifying CIDP patients has clinical, functional, therapeutic and prognostic implications. Further evaluation of patients from different populations may help indicate pathogenic differences and provide greater understanding of the possible immunological mechanisms underlying this disease.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is classically described as a symmetrical predominantly motor neuropathy involving both proximal and distal muscles, associated with hyporeflexia (or areflexia) and a chronic progressive or relapsing course.¹⁻³ The clinical significance of diagnosing this disorder has been the fact that the condition is immune-mediated and responds to immunomodulatory therapy including corticosteroids, intravenous immunoglobulin and plasma exchange.⁴⁻⁷ However, although there are widely accepted criteria for inclusion of typical patients in therapeutic trials,^{3, 8} there are as yet no practical clinical criteria which will enable to determine patients who will respond to treatment. The difficulties stem from the fact that CIDP is more clinically variable than previously thought and that strictly following criteria meant for research trials may exclude patients who may otherwise benefit from therapy. It has become clear over the last decade, the spectrum of immune-mediated neuropathies are much more heterogeneous than originally thought and include neuropathies which do not fit the widely used AAN research criteria.^{9,10} In addition, the nosological position of other neuropathies with immune aetiology i.e.

multifocal motor neuropathy and neuropathies associated with monoclonal gammopathy are uncertain. Several new classifications, based on clinical, electrophysiological as well as pathological features, have been proposed to include these various disorders under a broad umbrella of chronic acquired, immune-mediated, demyelinating neuropathy.^{10,11} Classification into certain distinct clinical subgroups may have the benefit of predicting response to therapy and prognosis.¹²

However, it is uncertain if these classification systems are universally applicable. It would therefore be important to review and evaluate series patients with chronic acquired immune-mediated neuropathies from different populations as this will help further refine the current classifications. We report the spectrum of chronic inflammatory demyelinating polyneuropathy in a series of Malaysian patients seen at the University of Malaya Medical Centre, Kuala Lumpur.

METHODS

The patients were seen at the Neurology Unit, University of Malaya Medical Centre, over a ten year period (1993 to 2003), and were recruited prospectively into a database. Inclusion criteria were the presence of chronic peripheral

neuropathy (\bullet 8 weeks duration) and one or both of the following: (i) electrophysiological features of demyelination in one motor (or two sensory nerves); (ii) response to immunomodulatory therapy. Patients were excluded if there was a positive family history of neuropathy or if there were a definite metabolic or vasculitic cause for the neuropathy.

All patients were evaluated clinically by an investigating neurologist and the following clinical features were specifically looked for – Time course of onset, acute (defined as < 4 weeks to maximal deficit) or insidious; Progression of the disorder, monophasic, progressive or relapsing-remitting (defined as at least two discrete episodes of illness, not related to reduction/change in treatment); The pattern of muscle weakness, symmetrical versus multifocal, distal versus proximal, predominant upper versus lower limb; Sensory symptoms including pain, paraesthesia, sensory ataxia and associated cranial nerve involvement. Associated systemic diseases including diabetes mellitus and malignancies were noted.

Laboratory investigations carried out included screening for diabetes mellitus (fasting blood glucose or oral glucose tolerance test where appropriate) cerebrospinal fluid (CSF) examination (if patient's consent was obtained), serum protein electrophoresis and serum anti GM1 antibody in patients suspected of having multifocal motor neuropathy.

All patients underwent peripheral nerve conduction studies and electromyography using standard techniques.¹³ These included sensory studies of the median, ulnar, radial and sural nerves; motor studies of the median, ulnar, common peroneal and posterior tibial nerves. F wave and H reflex studies were also carried out. Demyelination was diagnosed in a motor nerve if there were at least two of the following electrophysiological features viz. prolonged distal motor or F wave latency $> 125\%$ upper limit of normal (or $> 150\%$ upper limit of normal if amplitude $< 80\%$ lower limit of normal), reduced motor conduction velocity $< 80\%$ lower limit of normal (or $< 70\%$ lower limit of normal if amplitude $< 80\%$ lower limit of normal), partial conduction block with $\bullet 50\%$ amplitude drop with a $< 15\%$ change in duration (and abnormal temporal dispersion if $> 15\%$ change in duration). Demyelination was diagnosed in a sensory nerve if the conduction velocity was $< 80\%$ lower limit normal.

A functional score used for chronic neuropathy patients was used to assess the status of the patients at the nadir of their illness and their outcome after treatment (if any).¹⁴ This was as follows:- Grade 0 = asymptomatic; Grade 1 = symptoms not interfering with manual activities and walking normally; Grade 2 = minor difficulties with manual activities and walking abnormally without support; Grade 3 = unable to perform some manual activities and walking independently with support (e.g. walking stick); Grade 4 = unable to eat, dress, or wash independently and needing another person's help to walk; Grade 5 = no useful tasks performed with upper limb and wheelchair bound.

Therapy for neuropathy was variable depending on the progression of patients' symptoms, signs and disability; and included no treatment, oral corticosteroids, other immunosuppressive agents e.g. azathioprine, plasma exchange and intravenous immunoglobulin infusion. Response to therapy was regarded as an improvement in at least one functional grade from nadir to outcome.

RESULTS

There were a total of 45 patients, of which 30 (66.7 per cent) were male. The mean age of onset of the neuropathy was 50 ± 18.7 years (range 13 to 88 years). The ethnic breakdown was as follows – Chinese, 30 (66.7 per cent); Malay, eight (17.8 per cent); Indian, five (11.1 per cent) and others, two (4.4 per cent), and probably reflects the proportions of the different ethnic groups seen at our centre. Clinical onset (time to nadir) was acute in seven patients (15.6 per cent) and insidious in 38 (84.4 per cent). Mean time to maximal deficit was 16 ± 28.3 months (range one to 156 months). The clinical course in the majority was progressive or monophasic in 38 (84.4 per cent) while seven (15.6 per cent) were relapsing-remitting. The neuropathy was motor-sensory in 38 patients (84.4 per cent), pure motor in five (11.1 per cent) and pure sensory in two (4.5 per cent). It was symmetrical in 38 (84.4 per cent) and asymmetrical in 7 (15.6 per cent); predominantly distal in 14 (31.1 per cent), predominantly proximal in 12 (26.7 per cent) and involved both proximally and distally equally in 19 (42.2 per cent). The majority had involvement of both upper and lower limbs (37, 82.2 per cent) while five patients (11.1 per cent) and three patients (6.7 per cent) had predominant upper and lower limbs involvement respectively. Sensory

symptoms and signs include paraesthesia (36 patients, 80 per cent), pain (three, 6.7 per cent) and sensory ataxia (five, 11.1 per cent). Cranial nerve involvement was less common and four (8.9 per cent) each had bilateral facial palsy and bulbar palsy respectively. Associated diseases seen in the patients included diabetes mellitus (five patients, 11.1 per cent), malignancies (six, 13.3 per cent) and one patient with Acquired Immune Deficiency Syndrome. The malignancies included two patients with nasopharyngeal carcinoma, one each with Non-Hodgkin's lymphoma, alveolar cell (lung), breast and prostate carcinoma.

Forty patients underwent CSF examination and 36 (90 per cent) had raised CSF protein (> 0.45 g/L) levels. Mean CSF protein was 1.3 ± 0.96 g/L (range 0.14 to 4.81). Serum M protein was detected in three patients, IgM in two and IgG in one patient.

All patients underwent electrophysiological studies. Evidence of motor nerve conduction slowing (i.e. prolonged distal latency, slow motor nerve conduction velocity or prolonged F wave latency) were detected in 43 patients (95.6 per cent), while 22 patients (48.9 per cent) had slow sensory conduction velocity. Conduction block was present in 24 patients (53.3 per cent) while temporal dispersion was noted in 9 patients (20 per cent). However, only 75.6 per cent of patients met the electrophysiological criteria for CIDP set out by the AAN task force.³

The patients' functional status were determined at the nadir of the illness and were as follows:- Grade 1, 5 patients (11.1 per cent); Grade 2, 28 patients (17.8 per cent); Grade 3, 9 patients (20 per cent); Grade 4, 10 patients (22.2 per cent); Grade 5, 13 patients (28.9 per cent). Treatment modality was variable. Seven patients had no treatment as their deficits were mild and their clinical course stable. Corticosteroids were used in 30 patients at an initial dose of 1 mg/kg body weight, of which 27 patients responded. It is our practice to add azathioprine for its steroid-sparing effect and also in patients who may not have responded originally to corticosteroids. Twenty one patients were given azathioprine with good effect but two patients who did not respond originally to steroids, did not benefit from azathioprine either. Intravenous immunoglobulin (IVIG) infusion was the initial treatment in 18 patients, of which 12 responded (66.7 per cent). Seventeen patients underwent plasma exchange, of which 13 responded (76.5 per cent). Six patients had both IVIG and plasma exchange

treatment. Two patients (both with classical symmetrical sensorimotor CIDP) who failed IVIG, responded to plasma exchange while one patient (with multifocal motor neuropathy) who failed plasma exchange, improved with IVIG therapy. Two others responded to both treatments during different relapse episodes. The majority of these patients were subsequently maintained on oral prednisolone and/or azathioprine. One patient required repeated plasma exchanges to maintain remission, which was subsequently achieved on oral immunosuppressive medication. Patients with underlying malignancy underwent chemotherapy and/or radiotherapy. After treatment and/or at follow up, of the 14 patients with grade 5 function at presentation 11 improved – seven (50 per cent) markedly (more than two grades), three (21.4 per cent) moderately (two grades) and two (14.3 per cent) mildly (one grade) while one remained the same and one died; of the nine patients with grade 4 function, seven improved – four (44.4 per cent) markedly, two (22.2 per cent) moderately and one (11.1 per cent) improved one grade while one remained the same and one died; of the nine patients with grade 3 function four improved – 2 (22.2 per cent) markedly and 2 improved one grade while three remained the same and two died. Those with minor disability (grade one and two initially) did not improve as much but did not worsen. Of those with grade 2 function, five of eight improved – 25 per cent became asymptomatic and 37.5 per cent improved by one grade. All five patients with grade 1 function remained the same. Four patients (8.9 per cent) died - three patients had underlying malignancies while the other died of sepsis.

Based on clinical features, several distinctive neuropathy syndromes could be identified viz. symmetrical motor-sensory predominantly proximal (or proximal=distal) neuropathy (classical CIDP); Symmetrical sensorimotor predominantly distal (or distal>proximal) neuropathy, asymmetrical (multifocal) pure motor neuropathy, asymmetrical sensorimotor neuropathy, and pure sensory neuropathy. Table 1 summarises the clinical and electrophysiological features of the various subgroups.

Classical CIDP

This accounted for the majority of patients and had a pattern of involvement which was more motor than sensory and weakness which was more proximal than distal. Cranial nerve involvement was uncommon, mainly facial and bulbar weakness. The main sensory complaints

Table 1: Summary of the subgroups of chronic inflammatory demyelinating polyneuropathy

	Classical CIDP	Distal sensorimotor demyelinating neuropathy	Multifocal motor neuropathy	Asymmetrical sensorimotor neuropathy	Pure sensory neuropathy
No. of patients (%)	27 (60)	9 (20)	5 (11.1)	2 (4.4)	2 (4.4)
Mean age (yr)	48.2	59.9*	40.0	57.5	44.9
M:F ratio	1.08:1	3.5:1	All males	All males	All males
Acute onset (%)	15.5	22.2	Insidious	Insidious	50
Relapsing course	28.0% relapsing	Progressive	Progressive	Progressive	Progressive
Pattern of weakness	Proximal • distal	Distal > proximal	Distal; distal > proximal	Distal	N.A.
Motor vs. sensory symptoms	Motor • sensory	Sensory • motor	Pure motor	Motor > sensory	Pure sensory
Upper vs. lower limb symptoms	Lower = upper limbs	Lower • upper limb	Upper limb (60%); upper=lower limb (40%)	Upper limb	Lower = upper limb
Sensory ataxia (%)	None	44.4	N.A.	None	50
Pain (%)	3.7	11.1	N.A.	None	100
Paraesthesiae (%)	81.5	100	N.A.	None	100
Facial palsy (%)	11.1	11.1	None	None	N.A.
Bulbar palsy (%)	7.4	22.1	None	None	N.A.
Mean CSF protein (g/L)	1.29	1.40	0.95	0.90	1.83
Fulfill AAN electro-physiological criteria (%) ³	88	77.8	40	50	0
Motor nerve slowing (%)	100	100	80	100	N.A.
Motor conduction block (%)	66.7	11.1	100	100	N.A.
Sensory nerve slowing (%)	55.6	55.6	N.A.	50	50
Poor function (grade • 3) at nadir (%)	88**	44.4	40	50	50
Response to therapy(%)	85.2***	62.5	60	50	50

N.A. = not applicable

* P = 0.042, ** P = 0.002, *** P = 0.045

were paraesthesiae rather than pain or sensory ataxia. This group of patients had both acute (15.5 per cent) as well as insidious onset. Twenty eight per cent had a relapsing-remitting course. Electrophysiologically, 88 per cent fulfilled the AAN criteria for CIDP.³ Four patients had underlying malignancies of which 3 were diagnosed simultaneously with the neuropathy. M-protein was detected in two patients, IgG and IgM respectively, the latter patient having underlying non-Hodgkin's lymphoma. Most (88 per cent) had poor function (grade 3 or more) at the nadir of their illness but the majority (23 patients, 85.2 per cent) responded to immunomodulatory therapy. Of those who responded, 21 patients (91.3 per cent) remained well on follow up. Two patients who failed to respond had underlying malignancies as did another patient who worsened after responding to treatment initially. Two further patients were lost to follow up.

Distal sensorimotor demyelinating neuropathy

There were nine patients in this subgroup, who were on the whole significantly older than the rest of the patients. Male:female ratio was higher than for classical CIDP. Symptoms and signs were progressive or monophasic, more distal than proximal, sensory more than motor and lower limb more than upper limb. Paraesthesiae (100 per cent) and sensory ataxia (44.4 per cent) were prominent. 77.8 per cent fulfilled the AAN electrophysiological criteria.³ Two patients had a history of malignancy but these were diagnosed several years before the neuropathy making it unlikely that there is a clear relationship between the two. One patient had IgM monoclonal gammopathy of uncertain significance (MGUS). Fewer patients (44.4 per cent) had a poor functional grade but fewer patients responded to immunomodulatory treatment (62.5 per cent). However, the clinical course is stable, the majority remaining stable without further treatment.

Multifocal motor neuropathy

These patients had a progressive, asymmetrical pure motor neuropathy, predominantly involving the upper limbs. Anti GM 1 antibody was tested in four patients of whom one had a positive titre of anti GM 1 IgM antibody. Conduction block was detected in at least one motor nerve in all patients and only 40 per cent fulfilled the AAN electrophysiological criteria.³ Four patients underwent IVIG infusion; and three improved,

two are on continued treatment. The other patients have remained stable functionally without treatment.

Asymmetrical sensorimotor demyelinating neuropathy

There were two patients in this grouping whom symptoms were predominantly upper limb, motor more than sensory, distal more than proximal. One patient was treated with oral corticosteroids with improvement while the other declined treatment and has remained stable.

Pure sensory neuropathy

The two patients in this group had different presentations – one with marked sensory ataxia; the other with severe paraesthesiae. Both had raised CSF protein but sensory slowing was detected only in the latter patient. The former patient showed some response to plasma exchange therapy, while the latter did not respond to steroid therapy.

DISCUSSION

Diagnosis of acquired immune-mediated inflammatory neuropathies largely depends on electrophysiological and/or histological evidence of demyelination, as there are few specific immunological markers available. However, the various proposed electrophysiological criteria, primarily designed for clinical studies^{3,8,15,16,17}, have had varying sensitivities and have been understandably designed to be very specific. Adopting these criteria in the clinical setting may result in missing patients who may otherwise benefit from immunotherapy. Not all patients thought to have CIDP will fulfil the AAN electrodiagnostic criteria.^{3,18} Correlation between electrodiagnostic and histological criteria have also shown a lack of agreement, with patients meeting the latter but not the former responding to immunomodulatory therapy.¹⁹ Furthermore, although specific immune-mediated syndromes with distinctive clinical and investigative features have been described, most are considered a form of CIDP, with some features of demyelination and response to treatment.

Therefore, as we sought to determine the clinical spectrum of the disorder in Malaysian patients, we adopted broader and less selective criteria in patient selection. Clinically, we considered only the temporal duration of the polyneuropathy and its response to treatment, if

any, and did not emphasise its pattern of involvement, so as to be as comprehensive as possible in describing its clinical spectrum. Electrophysiologically, we adopted looser criteria for demyelination, requiring only two of four criteria in at least one motor nerve only or slowing of conduction velocity in two sensory nerves indicating demyelination. Similar criteria have been adopted by other authors previously, when describing the clinical spectrum in their own series of patients.^{9,10} As we did not routinely carry out sural nerve biopsies, we did not include histological evidence for demyelination in our criteria.

We found our patients to be heterogeneous and were able to classify them into several clinical subgroups based on clinical features. The majority of patients (60 per cent) had clinical features typical of classical CIDP with symmetrical predominantly motor more than sensory and proximal more than or equal distal limb involvement. In a series from the Oxford Peripheral Nerve Clinic, the patients were classified as chronic or subacute motor-sensory demyelinating and constituted 70 per cent of their patients.^{9,11} The clinical course in our patients demonstrated variability with an acute or insidious presentation and a progressive or a relapsing-remitting course. Even in this subgroup, only 88 per cent fulfilled the AAN electrophysiological criteria.³ These patients had a poorer functional status at the nadir of their illness compared to other subtypes but on the whole responded well to immunomodulatory treatment. Those that did poorly had severe concomitant illnesses such as underlying malignancy.

The next most common subgroup (20 per cent) had distal more than proximal, sensorimotor involvement, (usually more typically seen in length-dependent axonal neuropathies). These patients were older and more were males than females. Unlike classical CIDP, sensory symptoms and signs were more prominent including paraesthesiae and sensory ataxia suggesting significant involvement of the large sensory fibres. They were on the whole less functionally disabled but responded less well to treatment. This subgroup is now well described, constituting from 17 per cent of patients in ones series⁹ to 56.6 per cent of symmetrical acquired demyelinating neuropathies in another.²⁰ These patients, termed distal acquired demyelinating symmetrical neuropathy (DADS) has been found in the majority to have an M-protein, mostly anti myelin associated glycoprotein (MAG).^{9, 20}

However, only one of our nine patients had IgM M-protein.

Multifocal motor neuropathy was seen in 11.1 per cent of our patients. Compared to the series from Oxford, in which 13 per cent had multifocal motor neuropathy, we did not, in addition, find patients with pure motor symmetrical demyelinating neuropathy.^{11,12} Asymmetrical sensori-motor demyelinating neuropathy is another variant that we recognised (4.4 per cent of our patients compared to 6 per cent from the Oxford series). Also called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis Sumner syndrome, it differs from the more typical multifocal motor neuropathy in that there is additional involvement of the sensory nerves, raised CSF protein and response to corticosteroid treatment.^{10, 21-23} We had two patients whom we labelled as sensory CIDP, having no clinical or electrophysiological evidence of motor abnormalities, one of which had marked sensory ataxia. Sensory ataxic neuropathy was reported in 5 per cent patients in the Oxford series, but some of these patients had mild motor weakness.¹¹ Pure sensory CIDP is a disputed entity some authors have opined that most have coexistent minor motor abnormalities and that it likely represents one end of a spectrum which also includes distal symmetrical sensorimotor neuropathy with sensory ataxia.¹⁰

As can be seen from the earlier description, subclassifying CIDP patients clinically may have practical clinical, therapeutic and prognostic implications. The clinical subgrouping of patients in this series generally conforms in terms of clinical features and frequency to what has been previously described^{10,11}, indicating the universal applicability of this approach. However, there may be some minor differences which may need further study e.g. the distal symmetrical sensorimotor neuropathy subgroup in this series had fewer patients with M-protein compared to other series, suggesting possible differences in the inciting immune mechanism. The association between malignancies and CIDP also needs further investigation – the exact relationship is unknown but it would appear that the neoplasms are directly related to neuropathy in those who belong to the classical CIDP group. The association confers a poorer response to therapy and prognosis.

This study did not set out to systemically study the response of various subgroups to different immunomodulatory treatments. However, identifying certain subgroups will indicate the appropriate treatment modality as

well as predicting their response. Classical CIDP patients respond well to steroids and other immunomodulatory treatment better than the other subgroups. The others may have a more stable clinical course and be functionally better off even without continued immunotherapy.

The most rational classification of a disease is based on its pathophysiology. However, at present, we have no clear understanding of these processes in CIDP. Its clinical heterogeneity would suggest variable antigenic targets, immunological mechanisms and possible inciting events. Continued detailed clinical characterisation in different populations will certainly contribute to understanding these mechanisms.

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