

# **CORRELATION OF DEMYELINATING AND CLINICAL FEATURES IN PATIENTS WITH NEUROPATHY OF OTHERWISE UNKNOWN ETIOLOGY**

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## **ABSTRACT**

**PURPOSE:** To correlate the electrodiagnostic and clinical features of patients with demyelinating abnormalities and neuropathy of otherwise unknown etiology. **METHODS:** We examined the records of patient with demyelinating abnormalities and no other cause for neuropathy that were evaluated in our electrophysiology laboratory over the course of a year, to correlate the clinical and electrodiagnostic features. **RESULTS:** Eight percent of all patients had one or more demyelinating abnormalities. Demyelinating features were significantly more numerous in generalized or asymmetric neuropathy than in distal polyneuropathy. The peroneal nerve was the most commonly affected in all phenotypes, and none of the patients with distal neuropathy had F-wave prolongation in the demyelinating range. **CONCLUSIONS:** The number and type of demyelinating abnormalities in patients with polyneuropathy vary with the clinical phenotype. The clinical presentation should be considered in developing or evaluating electrodiagnostic criteria for demyelinating neuropathies.

**Search terms:** neuropathy, demyelinating, electrodiagnostic features, chronic inflammatory demyelinating polyneuropathy, CIDP, clinical phenotype

## **INTRODUCTION**

Neuropathies are routinely classified as demyelinating or axonal, based on the presence or absence of demyelinating abnormalities on electrodiagnostic testing. The presence of demyelination in patients with compatible clinical presentations provides a clue to such diagnoses as chronic inflammatory demyelinating polyneuropathy (CIDP) (Koller, 2000). There is little or no data, however, regarding the type or distribution of demyelinating lesions in patients with various clinical phenotypes. We reviewed the records of patients with demyelinating abnormalities and unexplained neuropathy, to correlate the clinical and electrodiagnostic features.

## METHODS

All patients with polyneuropathy whose electrodiagnostic studies exhibited one or more features of demyelination, seen in our electrophysiology laboratory over a 1-year period were evaluated. The clinical presentation and results of electrodiagnostic studies were reviewed. Patients with known causes for neuropathy, including family history of neuropathy or immunoglobulin M (IgM) monoclonal gammopathy, were excluded. Patients typically were screened for other causes of acquired neuropathy including diabetes, infection, nutritional or rheumatologic disorders, or tumors, and MRI imaging was performed in cases that were clinically warranted. The study was approved by the Institutional Review Board of the Weill Medical College of Cornell University.

The following segments were considered for analysis: tibial (ankle and popliteal fossa), peroneal (ankle and below the fibular head), ulnar (wrist and below elbow), and median nerve (wrist and elbow). Electrodiagnostic changes that were considered features of demyelination were similar to those proposed by the American Academy of Neurology (AAN) committee (AAN, 2001), but with more stringent criteria for partial conduction block/temporal dispersion (CB/TD) (Magda, 2003). They included: 1) Conduction velocity (CV) slowing of  $<80\%$  of the lower limit of normal with a compound muscle action potential (CMAP) amplitude  $\geq 80\%$  of the lower limit or normal, or of  $<70\%$  of the lower limit of normal with a CMAP amplitude  $<80\%$  of the lower limit of normal in any motor nerve. 2) Partial conduction block/temporal dispersion (CB/TD):  $>30\%$  amplitude decline with  $<30\%$  increase in CMAP duration/proximal-distal CMAP duration increment increase of  $\geq 30\%$ , in the ulnar, median, and distal peroneal nerves. 3) Distal latency (DL) prolongation of  $\geq 125\%$  with a CMAP amplitude  $\geq 80\%$  of the lower limit of normal, or of  $\geq 150\%$  with a CMAP amplitude  $<80\%$  the lower limit of normal in peroneal, tibial, or ulnar nerves, and 4) F-wave minimal latency prolongation of  $>120\%$  of the upper limit of normal with a CMAP amplitude that is  $\geq 80\%$  the lower limit of normal; or  $>150\%$  the upper limit of normal with a CMAP amplitude of  $<80\%$  of the lower limit of normal in any motor nerve; or absent F-waves in median or ulnar nerves with distal CMAP amplitudes of  $\geq 75\%$  the lower limit of normal. 5) Distal CMAP (DCMAP) duration of  $\geq 9$  milliseconds in any motor nerve (Thaisetthawatkul, 2002).

These abnormalities were considered to be indicative of demyelination, as they were beyond the ranges that occur secondarily to axonal degeneration, based on studies of patients with motor neuron disease. With respect to partial CB, some investigators advocate using a CMAP amplitude reduction of  $>50\%$ , based on mathematical modeling studies (Rhee, 1990), but studies in patients with motor neuron disease show that loss of large axons does not produce an amplitude reduction of  $>30\%$  (Cornblath, 1992; Cappellari, 1997), so that a CMAP amplitude reduction of greater than 50%, in the absence of compression, is more likely to result from demyelination than axonal degeneration.

Patients with electrodiagnostic features of demyelination were divided into three clinical phenotypes based on the neurological examination (McCombe, 1987; Rotta, 2000). For purposes of analysis, patients with generalized neuropathy were defined as exhibiting either symmetric proximal weakness, or proximal plus distal weakness of major muscle groups. The distal neuropathy phenotype was defined as exhibiting symmetric distal large fiber vibratory loss on sensory testing, with or without distal weakness. The asymmetric neuropathy phenotype was defined as exhibiting motor asymmetry of 1/2 grade point difference in at least 1 muscle group, excluding intrinsic hand or foot muscles, based on the medical research council scale (MRC) scale.

Patient charts were reviewed to determine whether they were treated, and whether the neuropathy improved, progressed, or remained stable, based on the neurological examination within 6 months after the initial evaluation. Patients did not routinely undergo spinal tap. The spinal fluid protein is frequently elevated in patients with generalized CIDP (Koller, 2005), but in less than 50% of patients with the distal

or asymmetric phenotype (Mygland, 2003; Verschueren, 2005). In general, patients were observed rather than treated if their physician considered their neuropathy to be mild or non-progressive.

The 3 groups (asymmetric, generalized, and distal neuropathy phenotypes) were compared using Student's t-test. Statistical significance was established at a probability <0.05.

## RESULTS

Of 235 patients evaluated in our electrodiagnostic laboratory over a 1-year period, 19 (8%) with polyneuropathy of otherwise unknown etiology exhibited one or more demyelinating abnormalities. Twelve were men and 7 women, with an age range of 27-89, and a median age of 59. 14 had electrodiagnostic studies of 1 arm and 2 legs, and 5 had studies of one arm and one leg only. The clinical phenotype and results of the electrodiagnostic studies for each patient are presented in Table I. The table also lists whether immunomodulatory therapy was given and the response, for each of the patients.

The clinical phenotypes of the 19 patients were as follows: distal 7 (36%), asymmetric 6 (32%), and generalized 6 (32%). The average age of patients in each of the groups was distal (68), asymmetric (51), and generalized (54). Of the 6 patients with the asymmetric phenotype, 5 patients had a 1-point MRC difference in one muscle (with values between 3-5) or 3 muscles with a ½ point MRC difference. The remaining patient had a ½ point difference in hip flexion, which was considered significant by the examiner.

The number and types of demyelinating abnormalities observed for each of the 3 clinical phenotypes is presented in Table 2. The average number of demyelinating abnormalities per nerve tested was significantly greater in patients with the generalized (0.77) or asymmetric phenotype (0.72), than in the distal phenotype (0.389) ( $p<0.05$ ). Partial conduction block/temporal dispersion was the most common demyelinating feature observed in all phenotype subgroups (generalized 0.27, asymmetric 0.22, and distal 0.15). F-wave minimal latency demyelinating range abnormalities were not observed in any of the nerves from patients with the distal phenotype, regardless of the total number of demyelinating lesions.

In Table 3, the frequencies of demyelinating abnormalities observed in each motor nerve, per nerve, are presented for each phenotype. In all phenotypes, demyelinating abnormalities were most commonly observed in the peroneal nerve, which was the sole nerve affected in 6 patients; in 1/6 with the generalized phenotype, 2/6 with the asymmetric phenotype, and 3/7 with the distal phenotype. Only 1/6 of patients with the asymmetric phenotype, 2/6 with the generalized phenotype, and none with the distal phenotype had no demyelinating peroneal nerve features. In 2 of these 4 patients, (1 asymmetric, 1 generalized phenotype) both tibial nerves had demyelinating range abnormalities.

The number of nerves or limbs per patient that exhibited demyelinating abnormalities, for each phenotype, is presented in Tables 4 and 5 respectively. Demyelinating range abnormalities were restricted to the upper extremity in 1 of the 6 patients with the generalized phenotype. Seventeen to 57% of the patients, depending on the phenotype (Generalized 17%, asymmetric 33%, distal 57%), had only one nerve or one limb that exhibited demyelinating features, with the highest percentage found in patients with the distal phenotype. All the patients with only 1 nerve/limb affected had pre-treatment electrodiagnostic studies, with 3 limbs studied.

**TABLE 1  
CLINICAL PHENOTYPE AND DEMYELINATING ABNORMALITIES IN 19 PATIENTS**

Pt	Phenotype	# limbs tested	RP	LP	RT	LT	RU	LU	RM	LM	Treatment/Response
1	AS	2	B				B, C, F		B		CC/ IMP
2	AS	3	B								IVIG/PR
3	AS	3		B					C		IVIG/S
4	AS	2	D,F		C, D, EF		B,C,D,F		F		PE, IVIG/IMP
5	AS	3		B,C							IVIG/IMP
6	AS	3			E	E					L
7	GN	2		A(52%) F		D,F				F	IVIG/PE/P PR
8	GN	3			C,E	C	A(33%) E,F		A(40%) C,E,F		IVIG/IMP
9	GN	2	B				D				IVIG/IMP
10	GN	3	B	E		E					L
11	GN	3	B								P/IMP
12	GN	2						A (36%)		B	IVIG/IMP
13	DS	3	F,D			D					IVIG/S
14	DS	3		A (31%) B	E	E					NT/S
15	DS	3		B							NT/S
16	DS	3		D,F		E					IVIG/IMP
17	DS	3	B								NT/S
18	DS	3	B								NT/S
19	DS	3	D,F				A(42%)		B		PE/IMP

Pt = patient, AS = asymmetric, GN = generalized, DS = distal, RP = right peroneal, LP = left peroneal, RT = right tibial, L= left tibial, RU = right ulnar, LU = left ulnar, RM = right median, LM = left median. .  
 A=CB >30%, with a duration increase of less than 30%, B= TD ≥ 30% duration increase, C=F wave prolongation, D=DL prolongation, E=DCMAP prolongation, F=CV slowing.  
 CC=cellcept, IVIG=intravenous gammaglobulin, PE=plasma exchange, P=prednisone, L=lost to follow-up, NT=not treated, S=stable, IMP=improved, PR=progressed.

**TABLE 2  
NUMBER AND TYPE OF DEMYELINATING ABNORMALITIES FOR EACH PHENOTYPE**

<b>Pheno- type</b>	<b># of nerves tested</b>	<b># of pts tested</b>	<b>Total # of Dem Abn (per nerve)</b>	<b>CB/TD Total # of Dem Abn (per nerve) [% amplitude decline ]</b>	<b>CV Total # of Deml Abn (per nerve)</b>	<b>DL Total # of Dem Abn (per nerve)</b>	<b>DCMAP Total # of Dem Abn (per nerve)</b>	<b>F-WAVE Total # of Dem Abn (per nerve)</b>
<b>GN</b>	30	6	23(.77)	8(0.27); TD-4, CB-4 [40%, 33%, 52%, 36%]	5(.17)	2(.07)	5(.17)	3(.10)
<b>AS</b>	32	6	23(.72)	7(0.22); TD-7	5(.16)	3(.09)	3(.9)	5(.16)
<b>DS</b>	42	7	16 (.38)	6(0.14); TD- 4, CB-2 [31%, 42%]	3(.07)	5 (.11) 4 (.10)	3(.07)	0(0)

GN = generalized, AS = asymmetric, DS = distal, pts = patients, Dem Abn = demyelinating abnormalities. The % amplitude decline is given for each CB.

**TABLE 3  
FREQUENCY OF DEMYELINATING ABNORMALITIES PER NERVE,  
FOR EACH PHENOTYPE**

<b>Phenotype</b>	<b># of Patients Tested</b>	<b>PERONEAL # Dem Abn/ # Nerves (# / Nerve)</b>	<b>TIBIAL # Dem Abn/ # Nerves (# / Nerve)</b>	<b>ULNAR # Dem Abn/ # Nerves (# / Nerve)</b>	<b>MEDIAN # Dem Abn/ # Nerves (# / Nerve)</b>
<b>GN</b>	6	5/9 (0.55 )	4/9 (0.45 )	3/6 (0.50)	3/6 ( 0.50)
<b>AS</b>	6	5/10 (0.50)	3/10 (0.30 )	2/6 (0.33)	3/6 (0.50)
<b>DS</b>	7	7/14 (0.50)	4/14 (0.28 )	1/7 (0.14)	1/7 (0.14)

GN = generalized, AS = asymmetric, DS = distal, Dem Abn = demyelinating abnl.

**TABLE 4**  
**NUMBER OF NERVES EXHIBITING DEMYELINATING FEATURES PER PATIENT, FOR EACH PHENOTYPE**

<b>PHENOTYPE</b>	<b># of Patients</b>	<b># of Nerves Tested</b>	<b># Nerves with Dem Abn</b>	<b># of Nerves with Dem Abn, per Patient; Range (average)</b>	<b># of Patients with Only 1 Nerve Affected; # (%) of patients, Nerve Affected</b>
<b>GN</b>	6	30	15	1-4 (2.5)	1 (17%), Peroneal
<b>AS</b>	6	32	13	1-4 (2.2)	2 (33%), Peroneal
<b>DS</b>	7	42	13	1-3 (1.9)	3 (43%), Peroneal

GN = general, AS = asymmetric, DS = distal, Dem Abn = demyelinating abnormalities

**TABLE 5**  
**NUMBER OF LIMBS PER PATIENT EXHIBITING DEMYELINATING ABNORMALITIE, FOR EACH PHENOTYPE**

<b>Pheno-type</b>	<b># of Patients</b>	<b># Limbs Tested</b>	<b># Limbs with Dem Abn</b>	<b># of Limbs with Dem Abn, per Patient Range (Average)</b>	<b># of Patients with Only 1 Limb Affected # (% of Patients)</b>	<b>Limb Affected</b>
<b>GN</b>	6	15	11	1-3 (1.8)	1 (17%)	1-LEG 1-ARM
<b>AS</b>	6	16	10	1-2 (1.6)	2 (33%)	2-LEG
<b>DS</b>	7	21	10	1-2 (1.4)	4-(57 %)	4-LEG

GN = generalized, AS = asymmetric, DS = distal, Dem Abn = demyelinating abnormalities

Four of the 5 patients with the generalized phenotype, for which information is available, and that were treated, improved with immunomodulatory therapy. Five of the 6 patients with the asymmetric phenotype were treated, leading to improvement in 3, stabilization in 1, and worsening in 1. Of the 7 patients with the distal phenotype, 2 of 3 that were treated showed improvement, and one remained stable. Four patients were not treated and remained stable at follow-up 3 to 6 months after the evaluation.

## DISCUSSION

Approximately 8% of patients in this series had electrodiagnostic changes with at least one demyelinating feature. However, this may not be reflective of the incidence in a general neuropathy population, as patients with known diagnoses would be less likely to be referred to a tertiary center.

All three groups of patients shared CB/TD as the most common demyelinating feature, and the peroneal nerve was most commonly involved regardless of presentation. Patients with the distal phenotype, however, were older, as was reported for CIDP (Hattori, 2001), and had fewer demyelinating features, with rare abnormalities in CV or DCMAP. None of the patients with the distal phenotype exhibited F-wave prolongation in the demyelinating range, consistent with distal accentuation of the neuropathy. It is not known, however, whether these phenotypes represent distinct disorders, or part of a spectrum of demyelinating neuropathy, as patients may evolve from an initial asymmetric or distal presentation to a generalized phenotype (Berger, 1997; Dyck, 2000; Viala, 2004). It may be that the presentations reflect the type, number, and distribution of the demyelinating lesions rather than distinct pathophysiologic processes, as is the case, for example, in multiple sclerosis. This, however, needs to be further investigated.

The results of the study are not directly comparable to some others such as Nicolas (2000), as proximal stimulation was not examined, and 8 motor nerves were not routinely tested. This is because proximal stimulation is rarely done in routine practice or outside research centers, due to technical difficulties and ambiguities in interpretation of supramaximal stimulation. However, Nicolas (2000), and Van den Bergh (2004) also found that CB/TD was the most frequent type of demyelinating abnormality in their patients with CIDP.

Six of the 19 patients, including one of six patients with the generalized phenotype, 2 of 6 patients with the asymmetric phenotype, and 3 of 7 patients with the distal phenotype, exhibited demyelinating changes in only one limb or nerve. Three of the 6 were treated, and 2 of those 3 improved, as in CIDP. In all 6, 3 limbs or 6 motor nerves were tested, and all had temporal dispersion in the peroneal nerve. As such, it may be necessary to examine at least 3 limbs, and in particular both peroneal nerves, when looking for evidence of demyelination in a particular patient. It may be, however, that additional demyelinating lesions might have been detected if proximal segments were examined, or some demyelinating lesions could be masked by secondary axonal degeneration (Hanemann, 2002).

The diagnosis of CIDP depends on the diagnostic criteria that are used, with the number of demyelinating abnormalities per patient required by proposed criteria ranging from one to five (Rajabally, 2005; Joint Task Force, 2005). The data presented in this paper suggests that the clinical phenotype needs to be considered when developing or testing proposed criteria for demyelinating neuropathy.

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