Title Page

Title: Patients who meet electrodiagnostic criteria for CIDP rarely present with a sensory predominant DSP phenotype

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Running Title: CIDP patients rarely present with a DSP phenotype

Ethical Statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Abstract

Introduction: It is unknown how often patients with electrodiagnostic evidence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a potentially treatable condition, present with a distal symmetric polyneuropathy (DSP) phenotype. *Methods*: We reviewed the records of patients who presented to our electrodiagnostic laboratory between January 1, 2011 to December 31, 2019 and fulfilled electrodiagnostic criteria for CIDP to identify those who presented with a sensory predominant DSP phenotype. *Results*: One hundred sixty-two patients had a chronic acquired demyelinating neuropathy, of whom 138 met criteria for typical or atypical CIDP. Nine of these patients presented with a sensory predominant DSP phenotype, among whom 6 were eventually diagnosed with distal acquired demyelinating symmetric (DADS) neuropathy, 1 with Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes (POEMS) syndrome and 2 with idiopathic DSP. The prevalence of acquired chronic demyelinating neuropathies among all patients presenting with a DSP phenotype was estimated to be 0.34%. *Discussion:* Patients who meet electrodiagnostic criteria for CIDP rarely present with a sensory predominant DSP phenotype, and electrodiagnostic testing rarely identifies treatable demyelinating neuropathies in patients who present with a DSP phenotype.

Key words:

Chronic inflammatory demyelinating polyneuropathy, acquired demyelinating neuropathy, distal symmetric polyneuropathy, electrodiagnostic testing

Introduction

Distal symmetric polyneuropathy (DSP) is one of the most common reasons for electrodiagnostic testing (EDX) referrals.[1-3]The value those results carry in the management of patients is controversial.[3,4] The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) published a policy statement outlining indications for EDX in DSP, one of which is recognizing alternative or unsuspected diagnoses for which effective disease-modifying therapy exists.[2] This policy statement specifically alludes to the importance of identifying chronic inflammatory demyelinating polyneuropathy (CIDP), a disabling and potentially treatable condition for which EDX is foundational to the diagnosis.[5] Other studies have shown that the prevalence of demyelinating neuropathies among patients referred for peripheral neuropathy is low.[4,6] However, this is to be expected, since CIDP is a rare disease compared to DSP.[7]

The aims of this study are to evaluate the prevalence of the sensory predominant DSP phenotype among patients fulfilling electrodiagnostic criteria for CIDP, and to estimate the prevalence of CIDP among patients presenting with a DSP phenotype. This can better inform the discussion about when to consider EDX in patients who present with a DSP phenotype.

Methods

This study and its methods were approved by the institutional review board of the University of Michigan.

The study population was obtained retrospectively from the University of Michigan EMGPRO database for studies performed from January 1, 2011 through December 31, 2019. All patients coded as a demyelinating neuropathy in EMGPRO were selected for initial review.

We included patients between ages 19 to 79 years who fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) electrodiagnostic criteria for possible, probable or definite CIDP.[5] Nerve conduction study (NCS) reference values established by the AANEM and published F-wave reference values were used.[8,9]

Two authors reviewed the medical records of each of the selected patients and excluded acute inflammatory demyelinating polyneuropathies (AIDP), suspected hereditary demyelinating neuropathies and patients with insufficient clinical data to achieve a conclusive diagnosis. We also excluded patients who had a normal neurologic examination or a DSP phenotype only after receiving immunomodulatory treatment.

We reviewed the written history and examination from the medical record to determine the phenotype at presentation and the final diagnosis. If the two assigned authors did not agree on the final diagnosis, a third author reviewed the case to establish consensus.

We classified the phenotype at presentation as typical CIDP, atypical CIDP or multifocal motor neuropathy (MMN) according to the EFNS/PNS clinical criteria.[5,10] A DSP phenotype was defined according to the Toronto criteria as a length-dependent syndrome with at least one of the following: neuropathic symptoms (decreased sensation or positive symptoms such as tingling or pain), symmetric decreased distal sensation on exam, or unequivocally decreased or absent ankle reflexes.[11] A DSP phenotype was not considered if any of the following atypical features were present: rapid progression over 6 months or less, a non-length dependent presentation, asymmetric motor or sensory exam, or weakness in muscles proximal to the toe extensors.[1]

The final diagnosis was classified as typical CIDP, distal acquired demyelinating symmetric neuropathy (DADS), multifocal acquired demyelinating sensory and motor

neuropathy (MADSAM), pure sensory CIDP, or MMN per EFNS/PNS guidelines.[5,10] Pure sensory CIDP was defined as a non-length-dependent sensory neuropathy with or without abnormal motor NCS.[12] DSP phenotype patients that did not fit or progress to the diagnoses mentioned above were diagnosed as idiopathic DSP.

Statistical Analysis

Categorical variables were classified using frequencies and percentages, while continuous variables were described using mean and medians.

To calculate the prevalence of CIDP and other acquired chronic demyelinating neuropathies among patients presenting with a DSP phenotype, we estimated the number of DSP patients seen in our electromyography lab from January 1, 2011 to December 31, 2019. To achieve that, we reviewed the last 100 patients coded as having non-demyelinating peripheral neuropathy. We then counted the number of patients who presented with a DSP phenotype and extrapolated that incidence over the entire study period. On the assumption that some patients with a DSP phenotype would have normal electrodiagnostic studies, we performed the same review on the last 100 patients coded as normal.

Results

From January 1, 2011 through December 31, 2019, we identified 361 patients fulfilling EFNS/PNS electrodiagnostic criteria for CIDP. We excluded the following patients: 122 with suspected and confirmed hereditary demyelinating neuropathy, 58 with AIDP, 15 with insufficient clinical data, 2 with a normal exam and 2 with a DSP phenotype following immunomodulatory treatment, leaving a final sample of 162 patients.

Among those included, the majority had either typical or atypical CIDP, 15 had other reasons for demyelinating findings and 2 had idiopathic DSP (table 1). The other reasons for demyelinating findings were POEMS (n = 6), vasculitic neuropathy (n = 3), chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies (n = 2), light-chain amyloidosis (n = 1), Sjögren's syndrome (n = 1), leprosy (n =1), and neuropathy associated with anti-sulfatide IgM antibodies (n = 1).

Among all the acquired chronic demyelinating neuropathies, there were a total of 9 patients who initially presented with a DSP phenotype. Among these, 6 were ultimately diagnosed with DADS, all of whom had an IgM monoclonal protein and positive anti-myelin-associated glycoprotein (MAG) antibodies. One patient had POEMS syndrome and had a known plasmacytoma prior to developing neuropathic symptoms. In the 2 patients in whom idiopathic DSP was the final diagnosis, there was no disease progression, and serum protein electrophoresis was normal. The only EDX abnormality observed in both of these patients was conduction block in one fibular motor nerve at a non-compressible site. These did not correlate with the either of the patients' symptoms, and in one of them, the conduction block improved to less than 30% on repeat testing a year later. All 9 patients with a DSP phenotype met Toronto criteria for probable neuropathy before EDX.

Among the patients who did not present with a DSP phenotype, 68.6% had a progression of 6 months or less, 30.7% had an asymmetric exam, 79% had a non-length dependent pattern and 72.5% had ankle dorsiflexion weakness during our first evaluation.

Prevalence of CIDP and other acquired demyelinating neuropathies within DSP patients

From January 1, 2011 through December 31, 2019, there were 4,769 patients in EMGPRO coded as non-demyelinating peripheral neuropathy and 14,268 patients coded as normal. A detailed review of 100 patients from each category code suggested that 34% of patients with an axonal neuropathy code presented with a sensory predominant DSP phenotype and 7% of patients with a normal electrodiagnostic study presented with a sensory predominant DSP phenotype. Most of the patients found to have an axonal neuropathy without a DSP phenotype were referred for other reasons, and the neuropathy was considered an incidental finding. Based on the above percentages, we extrapolated that there were a total of 2,629 patients who presented to our electrodiagnostic laboratory with a DSP phenotype during the study period (999 patients with a DSP phenotype from those with an EDX study labeled as normal *plus* 1,621 patients with a DSP phenotype from those with an EDX study labeled as axonal neuropathy). The 9 patients who met EFNS/PNS electrodiagnostic criteria for CIDP account for 0.34% of this total. (Figure 1)

Discussion

Our study shows that the prevalence of CIDP and other acquired demyelinating neuropathies among patients presenting with a chronic, sensory predominant DSP phenotype is very low (0.34%). This is consistent with two previous studies that showed that only 0.4% of DSP patients and 0.6% of peripheral neuropathy cases had a demyelinating neuropathy.[4,6] One prior study suggested that inflammatory and demyelinating etiologies accounted for 20% of all peripheral neuropathies, but our data do not support this finding.[13]

We found that only 5.5% of chronic acquired demyelinating neuropathy patients presented with a DSP phenotype, and none of them were ultimately diagnosed with typical

CIDP. Most were eventually diagnosed with DADS and had an IgM monoclonal gammopathy and myelin associated glycoprotein antibodies. This emphasizes that performing routine SPEP with immunofixation in all DSP may identify patients for whom EDX or subsequent laboratory evaluation may be particularly beneficial.[14] Importantly, patients with DADS are often non-responsive to immunomodulatory therapy.[15,16] In our series, 3 out of the 6 DADS patients with a DSP phenotype received immunomodulatory treatment. In all patients, clinical progression was the determining factor in the treatment decision, rather than electrodiagnostic findings. It should be noted that patients who have a DADS phenotype without a monoclonal gammopathy may be more responsive to immunotherapy.[15] It is possible that patients with this condition could present with a DSP phenotype, but we did not identify any in our series."

Considering the low prevalence of atypical CIDP in the general population[7], the low prevalence of atypical CIDP among DSP patients, and the lack of evidence to support disease-modifying treatment of atypical CIDP such as DADS, EDX has a low yield for identifying treatable acquired demyelinating neuropathies in patients with a sensory predominant DSP phenotype. EDX may still provide value in the workup of DSP when other clinical circumstances are considered, but this is beyond the scope of this study.[2]

In our study, the majority of patients with a chronic demyelinating neuropathy presented one of the following features: rapid progression, non-length dependent presentation, ankle dorsiflexion weakness or asymmetric examination. The presence of any of these features or an IgM monoclonal protein should prompt physicians to consider EDX.

Limitations include the retrospective and single-center study design. The estimated incidence of DSP cases among all patients presenting to our electrodiagnostic lab may not be accurate, because we relied on extrapolation. Because this extrapolation did not account for

patients in whom the final diagnosis was other than axonal neuropathy, demyelinating neuropathy, or a normal study, the true incidence of DSP may have been higher. The fact that this study was performed in a large tertiary center may limit the generalizability of our findings. It is possible that we underestimated the incidence of DSP in our series by requiring intact ankle dorsiflexion strength as a prerequisite for the DSP phenotype. Patients with severe, longstanding DSP may have ankle dorsiflexion weakness, but it is a rare enough feature in this population that it should raise suspicion for an alternative diagnosis.[1]

In conclusion, patients with chronic acquired demyelinating neuropathies rarely present with a chronic, sensory predominant DSP phenotype. In our series, EDX uncovered few, if any, explicitly treatable demyelinating neuropathies in patients who presented with a DSP phenotype. Further studies are needed to determine if EDX of patients with a DSP phenotype can uncover other potentially treatable diagnoses, such as mononeuritis multiplex or inflammatory sensory neuronopathy.

List of abbreviations

- CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy
- DSP: Distal symmetric polyneuropathy
- DADS: Distal acquired demyelinating syndrome
- EDX: Electrodiagnostic testing
- NCS: Nerve conduction studies
- AANEM: American Association of Neuromuscular & Electrodiagnostic Medicine
- AIDP: Acute inflammatory demyelinating neuropathy
- MMN: Multifocal motor neuropathy
- MADSAM: Multifocal acquired demyelinating sensory and motor neuropathy

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Figure 1. Total referrals to the University of Michigan electrodiagnostic laboratory with a distal symmetric polyneuropathy (DSP) phenotype between January 1, 2011 to December 31, 2019.

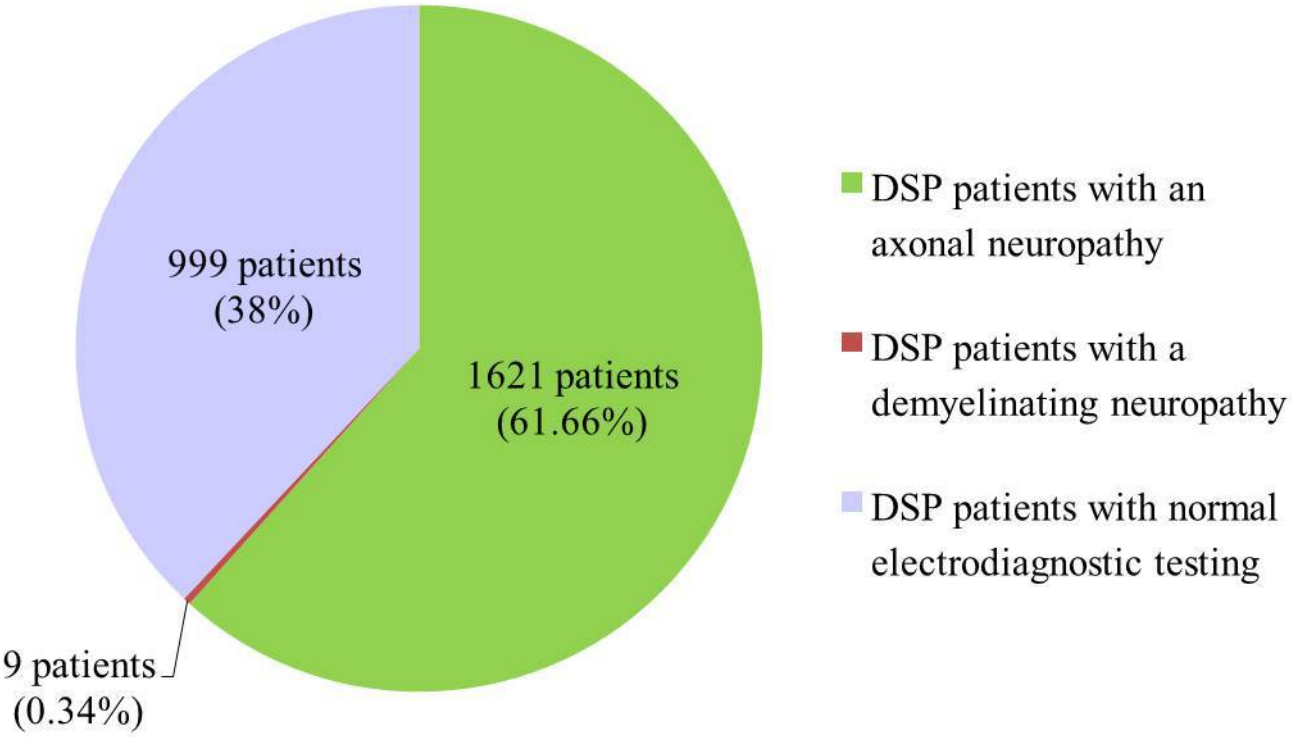

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Table 1. Baseline characteristics of patients with CIDP and MMN

Characteristic	**Typical CIDP (N=91)**	**DADS (N=29)**	**MADSAM (N=13)**	**Sensory CIDP (N=5)**	**MMN (N=7)**
Median age, yrs	58 (20-79)	60 (22-75)	52 (19-76)	47 (35-65)	67 (32-77)
Male gender	56 (61%)	18 (62%)	7 (54%)	3 (60%)	5 (71.5%)
Median time between symptom onset and first evaluation, months	11 (0.5-276)	24 (1-216)	23 (3-120)	42 (5-120)	120 (7-144)
EDX criteria (%)					
Definite	69 (76%)	17 (59%)	8 (62%)	4 (80%)	5 (71.5%)
Probable	8 (9%)	4 (14%)	3 (23%)	0 (0%)	1 (14.2%)
Possible	14 (15%)	8 (27%)	2 (15%)	1 (20%)	1 (14.2%)