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Title Page

Title: Distal symmetric polyneuropathy phenotype in patients with sensory neuronopathy at the time of electrodiagnosis.

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Running Title: Sensory neuronopathy 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.

Disclosures: LD, DGN and ZNL have no relevant conflicts of interest to disclose.

Abstract

Introduction: It is unknown how often patients with sensory neuronopathy (SNN) present with a distal symmetric polyneuropathy (DSP) phenotype. In these cases, electrodiagnostic testing may discriminate SNN with a DSP phenotype from DSP.

Methods: We reviewed the records of patients who met SNN diagnostic criteria between January 2000 to February 2021 and identified patients with a DSP phenotype at the time of electrodiagnosis.

Results: Sixty-two patients fulfilled SNN diagnostic criteria. At symptom onset, 20 (32.2%) patients presented with distal symmetric sensory symptoms limited to the feet. However, most progressed rapidly over 6 months or developed asymmetric symptoms. At the time of electrodiagnosis, only 7 (11.3%) patients had a DSP phenotype. Four of these had cerebellar ataxia with neuropathy and vestibular areflexia syndrome, 1 had vitamin B6 deficiency, 1 was thought to be alcohol-induced and 1 was idiopathic.

Discussion: Patients with SNN rarely present with a DSP phenotype at the time of electrodiagnosis. The finding that a third of cases resemble DSP at onset highlights the importance of clinical monitoring. In patients with a DSP phenotype, the presence of ataxia at onset or significant progression within 6 months may suggest the possibility of SNN and should prompt additional investigations such as EDX.

Key words:

Sensory neuronopathy, distal symmetric polyneuropathy, electrodiagnostic testing

Introduction

Sensory neuronopathies (SNN) are a subgroup of peripheral nervous system disorders caused by a primary degeneration of the dorsal root ganglia (DRG) and their central and peripheral sensory axons.[1] Early detection of SNN is crucial, because some cases are caused by potentially treatable immune-mediated or nutritional mechanisms.[1–3] Validated clinical and electrodiagnostic (EDX) criteria have been established in order to facilitate and standardize the diagnosis of SNN.[4,5]

While SNN typically presents with ataxia and asymmetric, non-length dependent sensory deficits,[1–5] it less commonly presents as a chronic, slowly progressive neuropathy mimicking a pure sensory distal symmetric polyneuropathy (DSP).[6,7] In these cases, EDX may be helpful to discriminate SNN with a DSP phenotype from DSP.

The aim of this study is to evaluate the prevalence of the clinical DSP phenotype among SNN patient who met EDX criteria for SNN, at the time of electrodiagnosis. 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.

We conducted a retrospective review of University of Michigan patients diagnosed with SNN between January 2000 and February 2021. We searched for all the patients coded as SNN using both the electronic medical record and EMGPro, an institutional database of electrodiagnostic study results. We included patients older than 18 years who met ‘possible’ or ‘probable’ diagnostic criteria for SNN established by *Camdessanché, et al*.[4] All patients had to

meet EDX criteria for SNN, defined as a) at least 1 sensory nerve action potential (SNAP) absent or 3 SNAP with amplitudes < 30% of the lower limit of normal in the upper limbs, not explained by entrapment neuropathy, and b) less than two nerves with abnormal motor nerve conduction studies (NCS) in the lower limbs.[4] Patients who fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) electrodiagnostic criteria for possible, probable or definite chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) were excluded. NCS reference values established by the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) were used.[8]

We reviewed the clinical data at the time of EDX diagnosis. 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.[9] A DSP phenotype was not considered if neuropathic symptoms were non-length dependent or if they progressed rapidly over 6 months or fewer.

We classified patients according to the most likely etiology as paraneoplastic, immune-mediated, toxic, nutritional, infectious, genetic, or idiopathic.[10]

Statistical Analysis

Categorical variables were classified using frequencies and percentages, while continuous variables were described using mean ± SD and median with interquartile ranges.

Results

From January 1, 2000 through February 28, 2021, we identified 73 patients with a diagnosis of SNN. We excluded 11 patients: 7 patients did not meet EDX criteria and 4 patients had EDX performed at a different institution or the EDX data was not available, leaving a final sample of 62 patients.

Most patients were female (71%) and the median age at onset was 55 years old. Baseline characteristics are described in Table 1. Among the patients classified as immune-mediated, 10 had Sjögren's syndrome, 1 had systemic lupus erythematous, 4 had positive Fibroblast Growth Factor 3 (FGF3) antibodies, trisulfated heparin disaccharide (TS-HDS) antibodies, or both, and 1 had positive anti-GD1b IgG antibodies. Among the patients classified as paraneoplastic, 2 had positive anti-Hu antibodies, 1 had positive anti-amphiphysin antibodies, and 1 had colon cancer with lung metastasis with no detectable onconeural antibodies. In the nutritional group, 2 had vitamin B12 deficiency, 2 had copper deficiency and 2 had vitamin B6 deficiency. In the toxic group, 2 were chemotherapy-related and 1 alcohol-induced. All patients with cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) had genetic confirmation (Table 1).

Symptoms

At onset, 20 (32.2%) patients presented with distal symmetric sensory symptoms in the feet only, 17 (27.4%) had ataxia, 8 (12.9%) had distal symmetric sensory symptoms in the feet and hands, 7 (11.3%) had distal symmetric sensory symptoms in the hands only, 7 (11.3%) presented with asymmetric sensory symptoms, 2 (3.2%) had axial sensory symptoms (burning neck and trunk pain), and 1 (1.6%) had proximal sensory symptoms (thigh tingling). Only 1 (1.6%) patient reported facial sensory symptoms.

Of the 20 patients who presented with sensory symptoms in the feet only, 11 (55%) progressed within 6 months, 2 (10%) had slowly progressive symptoms which became asymmetric over time, and 3 (15%) persisted with a DSP phenotype. Four (20%) patients had stable symptoms for many years, but then, symptoms rapidly progressed within months. In 2 of these 4 patients, initial EDX showed only mild sensory neuropathy when the symptoms were stable, but after the symptoms progressed, EDX was consistent with SNN. The other 2 patients only had EDX after the progression of symptoms.

At full development, 60 (96.8%) patients reported sensory symptoms in upper and lower extremities, 55 (88.7%) patients developed ataxia, 47 (75.8%) patients had a rapid progression within 6 months, 46 (74.2%) patients had a non-length dependent pattern, and 25 (40.3%) patients had asymmetric symptoms or exam findings.

Nerve conduction studies

Sural SNAP was recorded in 61 (98%) patients (49 absent, 7 low amplitude), ulnar SNAP was recorded in 62 (100%) patients (40 absent, 20 low amplitude), median SNAP was recorded in 54 (87%) patients (40 absent, 14 low amplitude) and radial SNAP was recorded in 61 (98%) patients (36 absent, 25 low amplitude). All sensory nerves were recorded in 54 (87%) patients, out of which 25 (46%) showed absent SNAP in all nerves, 47 (87%) showed amplitude abnormalities in all nerves, and 5 (9%) showed abnormal SNAP in all the upper extremities sensory nerves but normal sural SNAP. A total of 42 (68%) patients showed normal responses in all motor nerves.

DSP phenotype prevalence at the time of electrodiagnosis

At the time of electrodiagnosis, 7 (11.3%) patients who fulfilled electrodiagnostic criteria for SNN also fulfilled clinical criteria for probable DSP based on the Toronto criteria. Four of these patients were diagnosed with CANVAS, who presented gait ataxia at onset. One patient was classified as idiopathic, but the presence of abnormal eye saccades and lower extremity ataxia suggested the possibility of CANVAS. This was never confirmed by genetic testing. One patient had vitamin B6 deficiency, and one patient was classified as alcohol-induced neuropathy.

The neurological examination of these 7 patients is described in Table 2. The median follow-up time from the EMG to the last neurological evaluation was 1.25 years (range 0 – 11.8 years).

Discussion

The prevalence of a DSP phenotype among patients with SNN at the time of EDX diagnosis is low. Previous studies have reported that inherited and idiopathic SNN can present with a chronic, slowly progressive phenotype resembling a sensory polyneuropathy, which is consistent with our findings.[3,6,7,10] We did not identify any cases of potentially treatable immune-mediated SNN with a DSP phenotype.

One third of the SNN patients presented with symmetric distal lower-extremity predominant sensory symptoms resembling a sensory polyneuropathy. However, most developed asymmetric symptoms or rapidly progressed within 6 months, which helped differentiate these cases from DSP. This emphasizes the importance of clinical monitoring in patients with a possible DSP phenotype, particularly during the first 6 months after symptom onset. It is unknown why some patients manifested a DSP phenotype for years, and only later developed

clinical and electrodiagnostic evidence of SNN. This suggests that in patients who present with a DSP phenotype, EDX may not be able to predict whether SNN will develop.

The majority of patients with SNN in our cohort presented with one of the following features: rapid progression, non-length dependent presentation, early-onset ataxia or asymmetric examination. The presence of any of these features should prompt physicians to consider additional investigations for SNN, including EDX. Most SNN patients with a DSP phenotype were diagnosed with CANVAS, and all of these patients presented with ataxia at onset, so particular attention should be paid to apparent DSP patients with early-onset ataxia.

Limitations of this study include the retrospective and single-center study design. The fact that this study was performed in a large tertiary center may limit the generalizability of our findings. It is possible that some patients classified as having 'possible' SSN may have actually had a sensory axonopathy rather than a neuronopathy, because we utilized clinical criteria to define SNN rather than pathological criteria such as a DRG biopsy.

In conclusion, patients with SNN rarely present with a DSP phenotype at the time of electrodiagnosis. However, the finding that a third of cases resemble DSP at onset highlights the importance of clinical monitoring. In patients with a DSP phenotype, the presence of ataxia at onset or significant progression within 6 months may suggest the possibility of SNN and should prompt additional investigations such as EDX. Further studies are needed to determine how prevalent ataxia is at the onset of patients with DSP.

List of abbreviations

- SNN: Sensory neuronopathy
- DRG: Dorsal root ganglia
- EDX: Electrodiagnosis

- DSP: Distal symmetric polyneuropathy
- SNAP: Sensory nerve action potential
- NCS: Nerve conduction studies
- EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society
- CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy
- AANEM: American Association of Neuromuscular & Electrodiagnostic Medicine
- FGF3: Fibroblast Growth Factor 3
- TS-HDS: Trisulfated heparin disaccharide
- CANVAS: Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome

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Table 1. Baseline characteristics of patients with sensory neuronopathy.

Characteristic	
Age, mean (SD), years	55 (14)
Female gender, n (%)	44 (71%)
Time between symptom onset and EDX diagnosis, median (IQR), months	18 (6-60)
SNN diagnostic criteria, n (%)	
Possible	43 (69%)
Probable	19 (31%)
Etiology, n (%)	
Immune-mediated	16 (25.8%)
Paraneoplastic	4 (6.5%)
Toxic	3 (4.8%)
Nutritional	6 (9.7%)
CANVAS*	5 (8%)
Idiopathic	28 (45.2%)

*Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome

Table 2. Neurological examination of SNN patients with a DSP phenotype at the time of electrodiagnosis.

Motor exam, n (%)	
Normal	6 (86%)
Proximal weakness	1 (14%)
Sensory exam, n (%)	
Small fiber involvement	7 (100%)
Large fiber involvement	7 (100%)
Facial involvement	0 (0%)
Reflexes, n (%)	
Diffuse hyporeflexia or areflexia	2 (29%)
Absent bilateral ankle jerk reflex only	3 (43%)
Absent bilateral ankle jerk and patellar reflexes only	1 (14%)
Normal	1 (14%)
Coordination, n (%)	
Gait ataxia	4 (57%)
Lower limb ataxia	3 (43%)
Upper limb ataxia	3 (43%)
Positive Romberg	4 (57%)
Abnormal pupillary light reflex, n (%)	0 (%)
Assistive device needs	
Cane	1 (14%)
None	6 (86%)