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Clinical and electrophysiologic attributes as predictors of results of autonomic function tests

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Autonomic dysfunction is a feature of some neuropathies and not others. It has been suggested that some clinical and electrophysiologic attributes are predictable of autonomic impairment detected using laboratory testing; however, clear guidelines are unavailable. We evaluated 138 relatively unselected patients with peripheral neuropathy who underwent neurologic evaluation, electromyography (EMG), nerve conduction studies, and autonomic function tests to determine which variables were predictive of laboratory findings of autonomic failure. The variables evaluated were 1) clinical somatic neuropathic findings, 2) clinical autonomic symptoms, and 3) electrophysiologic findings. Autonomic symptoms were strongly predictive (R_s = 0.40, $p < 0.001$) of autonomic failure. Among the non-autonomic indices, absent ankle reflexes were mildly predictive ($R_s = 0.19$, $p = 0.022$) of autonomic impairment, but all others were not (duration, clinical pattern, severity, weakness, sensory loss). Electrophysiologic changes of an axonal neuropathy predicted autonomic impairment while demyelinating neuropathy did not. We conclude that autonomic studies will most likely be abnormal in patients who have symptoms of autonomic involvement and those who have an axonal neuropathy.

Keywords: neuropathy, autonomic, EMG, symptoms, laboratory.

Peripheral nerve is composed of motor, sensory, and autonomic nerve fibers [1]. Patients with neuropathy have involvement of these fiber populations in different proportions. Conventional electromyography (EMG) and nerve conduction studies (NCS) mainly evaluate functions of the large-myelinated fast-conducting somatic motor and sensory fibers [2,3]. On the other hand, autonomic function tests evaluate function conducted by small myelinated or unmyelinated nerve fibers [4]. With the availability of the autonomic laboratory, the clinician wishes to refer those patients who have the greatest likelihood to have autonomic failure. Currently, guidelines are unsatisfactory. There is limited quantitative information on whether autonomic symptoms are predictive of autonomic deficits. There is also limited information on which, or whether, attributes of nerve conduction or neuropathic symptoms are predictive of finding autonomic deficits in the laboratory.

With this background, we evaluated conventional electrophysiologic, somatic neuropathic, and autonomic neuropathic symptoms in patients with neuropathy and determined if these indices were predictive of the severity and distribution of autonomic failure. Since many clinical centers lack an autonomic function laboratory, the identification of parameters that are associated with autonomic impairment should help identify the patients who should undergo autonomic tests, and possibly serve as surrogate indicators of autonomic involvement.

Material and methods

Patients and inclusion criteria

We reviewed 138 cases of patients with peripheral neuropathy referred from the Department of Neurology to its Clinical Autonomic and Electromyography (EMG) Laboratories in order to evaluate which clinical and EMG indices were predictive of laboratory findings of autonomic failure. We followed the following procedure: all patients seen at the Mayo Clinic Autonomic Laboratory were assigned a "diagnostic code" after the tests were done. From 1993 to 1995, a total of 615 patients were coded with "neuropathy." We reviewed the histories of all 615 patients and chose the cases that fulfilled the following criteria: 1) electrophysiologically definite generalized peripheral neuropathy; 2) completed both EMG and autonomic reflex screen (ARS). We excluded patients with focal neuropathy (including radiculopathy), amyotrophic lateral sclerosis, or generalized small fiber neuropathy of known etiology. We defined small fiber neuropathy as being characterized by the disproportionate impairment of pain and temperature perception and the presence of clinical autonomic failure. A total of 138 patients out of the original 615 cases fulfilled the inclusion criteria.

Autonomic function tests

Autonomic tests were performed as previously described [5] and comprised an evaluation of postganglionic sudomotor, cardiovagal, and adrenergic functions.

Quantitative sudomotor axon-reflex test (QSART), which quantitatively evaluates the postganglionic sympathetic sudomotor axon [6], was routinely recorded from four sites (the forearm, the proximal lateral leg, the medial distal leg, and the proximal foot over the extensor digitorum brevis muscle). The stimulus was iontophoresed acetylcholine, and the responses were recorded in a compartment of a multicompartmental sweat cell that was separate from the stimulus

compartment. The axon reflex is mediated by postganglionic sympathetic sudomotor fibers [4]. Control values were derived from studies on 223 normal subjects aged 10 to 83 years [4].

Heart rate response to deep breathing (HRDB) and Valsalva ratio (VR) evaluated cardiovagal function and were performed as previously described [4,5]. HRDB was the heart rate range in response to forced respiratory sinus arrhythmia, with the subject supine and breathing at six breaths per minute. For the Valsalva maneuver, the subject, rested and recumbent, was asked to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is the ratio of the maximal to minimal heart rate. Control values were based on 157 healthy subjects aged 10 to 83 years [4].

Adrenergic function was evaluated by the blood pressure and heart rate responses to the Valsalva maneuver and head-up tilt. Adrenergic failure is indicated by reductions in late phase II (mainly peripheral adrenergic) and phase IV (mainly cardiac adrenergic) [7] and by changes in blood and pulse pressure in response to head-up tilt. Beat-to-beat blood pressure was monitored using a continuous BP Monitor (Finapres Monitor, Ohmeda, Englewood, CO) and input into a computer console that displayed systolic (SBP), diastolic (DBP), and mean blood pressure (MBP) continuously [7]. Blood pressure was also recorded using a sphygmomanometer cuff and mercury manometer over the brachial artery.

CASS (Composite Autonomic Scoring Scale). The results of the ARS were corrected for the confounding effects of age and gender and semi-quantitatively graded from 0 (no deficit) to 10 (maximal deficit). CASS consisted of three subscores: sudomotor (CASS_sudo; 0–3), cardiovagal (CASS_vag; 0–3), and adrenergic (CASS_adr; 0–4) [8]. The score with its subsets provided an evaluation of the severity and distribution of autonomic failure.

Electromyography and nerve conduction studies criteria

Electromyography (EMG) and nerve conduction studies (NCS) were done using standardized methods of the Mayo EMG laboratory. A *demyelinating* neuropathy was accepted if the following findings were observed in motor or sensory conduction studies: 1) Conduction slowing $\geq$ 30%, with amplitude within the normal range and no fibrillation potentials, or 2) conduction velocity less than 50% of the normal range with amplitude greater than 50% of normal and minimal fibrillation potentials, or 3) the presence of at least two of the following:

- Distal latencies $>$ 50% above the normal range, with normal amplitude
- Progressive dispersion and amplitude reduction of the CMAP with more proximal sites of stimulation (including conduction block)
- F-wave latency slowed out of proportion to nerve conduction slowing
- Conduction velocities less than 10% of normal
- Blink reflex latency (R_1 component) greater than 16 ms

An *axonal* neuropathy was accepted if any of the following three criteria were satisfied: 1) Motor amplitude 50% to 70% of normal with normal conduction velocity and latency; no amplitude reduction between stimulation sites; clear cut fibrillation. 2) Motor amplitude less than 50% of normal with conduction velocity greater than 70% of normal, no amplitude reduction between stimulation sites; prominent fibrillation. 3) Absent sensory potentials with normal motor conduction and/or fibrillation potentials.

If the results fulfilled both criteria it was classified as a "mixed" neuropathy (axonal/demyelinating). If a mixed neuropathy shows any of the demyelinating criteria, it was classified as "mixed, predominant demyelinating neuropathy."

The following electrophysiologic and clinical information were collected: age; type of neuropathy (sensorimotor, polyradiculoneuropathy, pure motor, pure sensory); the presence of fibrillation potentials on EMG; summed peroneal and tibial compound muscle action potentials; sural sensory nerve action potential; duration of symptoms in years; the presence of clinical autonomic symptoms; lower extremity muscle strength; large fiber sensory function; small fiber sensory function; the presence of deep tendon reflexes in the lower extremity.

Clinical autonomic evaluation

The clinical autonomic symptoms evaluated were failure or dysfunction in: vasomotor, secretomotor, gastrointestinal, bladder, sexual function (male less than 65 years old), pupillomotor functions, or the presence of orthostatic intolerance [9]. We grade the symptoms as absent (Score = 0), mild when only one system was involved, or without orthostatic intolerance (Score = 1). If at least two systems were involved it was graded as moderate involvement (Score = 2). The patients with significant orthostatic hypotensive symptoms were rated as severe involvement (Score = 3).

Statistical analysis

Univariate associations between CASS and explanatory variables was performed using Spearman rank correlations, because some of the data were highly skewed. Stepwise regression for identifying the most important associations was performed, stepping up, and using Kendall's tau for the correlation matrix. Comparisons between groups were performed using a rank sum test. All tests are two-sided. We separated the patients into two polar groups. The first was "demyelinating" neuropathy comprising patients with pure or mixed neuropathy, where demyelination predominated. The second group was designated "axonal" neuropathy, comprising patients with pure or mixed neuropathy with predominant axonal neuropathy. We then repeated the same analytic procedure in each group. Data were expressed as mean $\pm$ SD. $p < 0.05$ was considered significant.

Results

Clinical characteristics

The clinical characteristics of the neuropathy are shown in Table 1. There was a male preponderance (85:53). The age

Table 1. Clinical characteristics of patients with neuropathy

Number of patients	138
Gender (men : women)	85 : 53
Age in years (mean ± SD)	Men, 60.7 ± 10.9
	Women, 55.8 ± 13.6
Cause of neuropathy	
Unknown	52
Diabetes mellitus	32
Hereditary	22
AIDP or CIDP	13
Sensory neuronopathy or ganglionopathy	7
Idiopathic autonomic	5
Collagen vascular disease	2
Miscellaneous	5

AIDP, Acute inflammatory demyelinating polyradiculoneuropathy; CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy.

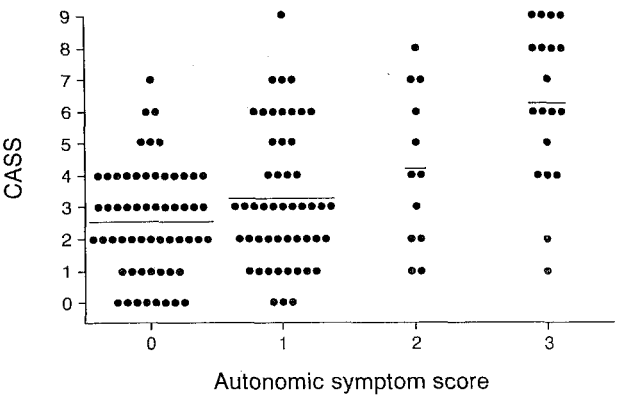

Figure 1. Scattergram relating Composite Autonomic Scoring Scale (CASS) to clinical autonomic symptom scores.

distribution was not significantly different by gender. The cause of neuropathy was unknown in 38% of patients (Table 1). The most common known causes were diabetes (23%), inheritance (16%), and immune-mediated (9%).

Electrodiagnostic

The electrodiagnostic pattern of neuropathy was sensorimotor neuropathy (101), polyradiculoneuropathy (26), pure motor neuropathy (1), and pure sensory neuropathy (10). The distribution of fibrillations and their qualitative grade are shown in Table 2.

Autonomic

Clinical autonomic symptoms in these 138 patients were most commonly absent (n = 57; 41%) or mild (n = 50; 36%). Nineteen patients (14%) had severe autonomic dysfunction and 12 had moderate dysfunction (9%; Fig. 1).

Composite Autonomic Scoring Scale scores showed a higher percentage of patients with autonomic impairment compared to the presence of symptoms. The distribution of CASS score were: 0 (normal study; 11/138; 8%); 1–3 (mild impairment was seen in 68/138 (49%); moderate failure (4–6; 42/138; 31%); severe failure (≥ 7, 17/138; 12%). Although the majority of asymptomatic patients (autonomic symptom score = 0 in Fig. 1) had only mild autonomic failure (CASS 1–3), some patients with moderate failure were also asymptomatic (Fig. 1).

In evaluating the predictive value of clinical and EMG laboratory indices of autonomic failure (CASS), the best predictor was the presence of clinical autonomic symptoms (R_s = 0.40, $p < 0.001$; Table 3) and less robustly the absence of ankle jerks (R_s = 0.19, $p = 0.027$). These were also the only variables that were significant in the multivariate analysis.

Table 2. Electrodiagnostic features of neuropathy

Number of patients	138
Pattern of neuropathy	
Sensorimotor neuropathy	101
Polyradiculoneuropathy	26
Pure motor neuropathy	1
Pure sensory neuropathy	10
Fibrillation potentials grade	
0 (No fibrillation)	11
1 (Foot only)	19
2 (Lower Extremities)	38
3 (Lower & Upper Extremity)	70

Demyelinating versus axonal neuropathies

We separated the patients into two polar groups, one with demyelinating or mixed neuropathy where demyelination predominated (n = 13) and the other group with axonal or mixed neuropathy where axonal neuropathy predominated (n = 125), and repeated the same analytic procedure. Only clinical autonomic symptoms were significant in the axonal neuropathy group. For the demyelinating group no variables predicted autonomic failure, although the number of cases was much smaller. We next compared the two groups, using non-parametric analysis (Table 4). The axonal group had significantly higher CASS ($p < 0.001$), sudomotor index ($p = 0.01$), and adrenergic index ($p < 0.01$). Symptom score was marginally higher ($p = 0.05$) in the axonal groups. The axonal group's mean age was significantly older ($p < 0.01$).

Table 3. Predictive value of clinical or laboratory indices of autonomic deficit (CASS Score) in 138 neuropathic patients

Variable	p Value	Spearman R
Clinical features		
Age	0.485	0.06
Type of Neuropathy	0.172	0.11
Duration of Neuropathy	0.464	0.06
Clinical ANS involvement	<0.001	0.40
Lower extremities muscle strength	0.107	0.14
Large fiber type sensory loss	0.977	0.00
Small fiber type sensory loss	0.830	0.02
Knee jerk	0.268	0.10
Ankle jerk	0.027	0.19
Electrophysiologic features		
EMG fibrillation scale	0.307	0.09
Summated motor amplitudes	0.636	0.04
Sural sensory amplitudes	0.662	0.04

Table 4. Comparison of axonal versus demyelinating neuropathies

Variable	Axonal	Demyelinating	p Value
Age (years)	59.6 ± 12.4	51.2 ± 7.9	0.0066
CASS (0–10)	3.7 ± 2.3	1.5 ± 1.5	0.0009
CASS_sudo (0–3)	1.2 ± 1.0	0.5 ± 0.8	0.0130
CASS_vag (0–3)	1.1 ± 1.1	0.6 ± 0.7	0.2643
CASS_adr (0–4)	1.4 ± 1.2	0.5 ± 0.7	0.0051
Fibrillation scale (0–3)	2.2 ± 1.0	2.6 ± 0.9	0.0612
Motor amplitudes (mV)	5.3 ± 5.6	3.5 ± 4.7	0.1105
Sensory amplitudes (μV)	1.9 ± 2.9	3.2 ± 4.3	0.3481
Duration (months)	69.6 ± 88.6	51.0 ± 62.2	0.4882
ANS symptoms (0–3)	1.0 ± 1.0	0.4 ± 0.5	0.0515
Muscle strength (0–3)	1.0 ± 1.0	1.5 ± 1.3	0.1311
Large sensation (0–3)	1.5 ± 0.9	1.6 ± 1.3	0.6559
Small sensation (0–3)	1.5 ± 1.0	1.5 ± 1.0	0.7826
Knee Jerk (0–2)	0.9 ± 0.8	1.2 ± 0.8	0.2621
Ankle Jerk (0–2)	1.5 ± 0.7	1.5 ± 0.7	0.9416

Discussion

The main findings of this study are that autonomic impairment is more common than autonomic symptoms, that autonomic symptoms are predictive of laboratory findings of significant autonomic failure, and that axonal neuropathies are more likely than demyelinating neuropathies to result in a laboratory-detected autonomic deficit.

The composition of the patient cohort significantly affects the likely outcome. If only polar groups (autonomic neuropathies with generalized autonomic failure vs mild neuropathies without autonomic symptoms) were considered [8], the correlation between symptoms and autonomic function tests and between electrophysiologic studies and autonomic function tests would be enhanced. Since the Mayo laboratories attract a significant number of autonomic disorders, possibly resulting in an over-representation of cases with autonomic failure, we have attempted to reduce the bias by excluding patients with florid autonomic neuropathies. The resultant group is likely to more closely resemble patients seen in other EMG laboratories.

The clinical features of somatic neuropathy were not predictive of the presence or severity of laboratory findings of autonomic impairment. We evaluated such important characteristics as age of the patient, duration of neuropathic symptoms, clinical motor, sensory, and reflex deficits, and except for the mild predictive value of absent ankle reflexes, no correlations were found. Part of the explanation for the lack of an effect of age relates to the design of CASS, which corrects for the confounding effects of age and gender. However, we did not know whether age conditioned autonomic fibers to neuropathy-induced autonomic failure. This study provides some evidence that they do not appear to do so. Interestingly, the clinical findings of small fiber sensory loss, including pin-prick and thermal sense, were also not related to autonomic failure ($p = 0.8299$). This observation needs to be validated by more quantitative sensory testing; if correct, it suggests that neuropathic involvement may be selective by system (autonomic vs somatic) rather than by fiber type (large vs small).

In contrast to a lack of predictive value of somatic symptoms, the presence of autonomic symptoms was strongly predictive of laboratory autonomic failure. Although it is known that symptoms of severe autonomic failure are predictive of laboratory evidence of autonomic deficits, quantitative information is unavailable. Specifically lacking have been methods to quantitate autonomic deficits, and the availability of a large patient cohort with a range of autonomic deficits. Also lacking is information on the threshold deficit for the development of autonomic symptoms. We used a relatively crude evaluation of autonomic symptoms that does have the advantage of simplicity, in contrast to more complicated autonomic symptom profiles that we have developed [10]. The approach used here is available to all clinicians. The regression of CASS against symptoms provides some insights into the relationship. A threshold deficit of 2.5 on the CASS score is evident (Fig. 1).

This study also addresses an important hitherto unanswered question of whether neuropathic symptoms predict autonomic failure by fiber type. It has been useful to divide neuropathies into large and small fiber types. Within small fiber involvement, somatic and autonomic failure often coexist, so that there has been a tendency to lump these latter deficits together. What has been lacking is a large study such as this, with a data set of a relatively unselected group of patients, to address the question of whether somatic neuropathic features are predictive of autonomic laboratory deficits or whether this is confined to patients with autonomic symptoms. The latter notion appears to be correct.

In this study, we have focused on the electrophysiologic characteristics of axonal degeneration and demyelination rather than on etiologic groups. While clear differences in the severity of axonal degeneration exist among the many causes of axonal and demyelinating neuropathies, most of these differences are reflected in the electrophysiologic characteristics [11], and hence we have chosen not to subdivide the patients into etiologic groups. Relatively pure demyelination is relatively uncommon ($n = 13$) in chronic progressive neuropathies.

The study does demonstrate that electrophysiologic evidence of axonal degeneration is associated with an increase in autonomic symptoms and an increase in laboratory deficits, whereas demyelination per se is not. Although patients with axonal neuropathy were older, age is not likely to be responsible for the difference, since the CASS scoring scale corrects for the confounding effects of age. A similar observation has been made by others [12,13]. Demyelination without significant axonal degeneration does not result in significant autonomic failure [12]. The apparent exception of Guillain-Barre syndrome likely relates to the concomitant involvement of autonomic fibers in the condition [14]. Presumably, axonal degeneration and not demyelination results in disconnection of autonomic end-organs in addition to muscle fibers, and hence autonomic failure is more common. The fewer cases with demyelination seen in the Autonomic Lab could reflect the uncommon development of autonomic symptoms in these patients with pure demyelination. The lack of a particularly strong connection confirms the notion that EMG and ARS are dealing with different parts of the

peripheral nervous system; EMG evaluates large myelinated nerve fibers while ARS evaluates small unmyelinated fibers. Previous workers have reported that autonomic tests are correlated with H-reflex, distal ulnar and peroneal motor conduction velocities [15], and sural sensory action potentials [16]. We suggest the following reasons for the discrepancy. The number of patients studied in these studies were relatively small and all were diabetic patients, in whom the process is almost always axonal. The severity of autonomic failure were not graded. There were also some internal inconsistencies in these observations. For instance, results were only suggestive of a correlation of the severity of neuropathy with the autonomic dysfunction in some nerves but not all. Shahani *et al.* [13] showed that sympathetic skin reflexes were more related to the unmyelinated axonal loss, but not to the clinical evidence of dysautonomia [13]. They did not use a comprehensive autonomic screen.

In conclusion, EMG and ARS evaluate different components of peripheral nervous system. Type and severity of somatic neuropathic findings clinically or on EMG are not adequate surrogate measure of autonomic function. Instead autonomic symptoms are important predictors for laboratory detection of autonomic deficits recognizing that mild and sometimes moderate autonomic failure may be unassociated with autonomic symptoms. In demyelinating neuropathy autonomic dysfunction is less severe than in axonal neuropathy.

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