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Quantitative Sensation and Autonomic Test Abnormalities in Transthyretin Amyloidosis Polyneuropathy

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Abstract

This study assesses the value of standard quantitative autonomic (QAT) and sensation (QST) tests in detecting, characterizing, and quantitating the severity of transthyretin amyloid polyneuropathy (TTR-A-PN). This information is needed for prospective therapeutic trials, epidemiologic surveys and medical practice. We reviewed thirty six patients with TTR-A-PN who were evaluated between 1997 and 2007. They had neurologic, genetic, electrodiagnostic, and autonomic reflex screen evaluations and allowed their medical records and test results to be evaluated for research purposes. Of these, 22 patients had also been tested by quantitative sensation tests (QSTs). The median symptom duration was 4 years (range 1 to 30 years). Among quantitative nerve tests evaluated, composite scores of nerve conduction (Σ 5 NC nds), a composite score of QSTs (Σ3QST nds), and quantitative autonomic tests (QSART, $HR_{db,}$ and CASS) gave high frequencies of abnormality. These results show that peripheral autonomic and small fiber sensory dysfunction is prominent and characteristic of most of the patients we studied. However this involvement was not selective for small-diameter sensory and autonomic nerve fibers; large motor and sensory fibers were also shown to be dysfunctional. Dysfunction of large fibers was approximately as frequent as that of small fibers. This study provides a rationale for use of QAT, QST, and Σ 5 NC nds as standard, objective and quantitative measures for quantitating the severity of TTR-A-PN in epidemiologic surveys, therapeutic trials and medical practice.

Keywords

transthyretin; hereditary amyloidosis; polyneuropathy; quantitative sensation test; autonomic reflex screen

INTRODUCTION

Transthyretin amyloidosis (TTR-A) is an autosomal dominant disorder resulting from amino acid substitutions in the TTR molecule. Although Val30Met is the most common amino acid substitution, approximately 100 other mutations have been described.3 Most cases of TTR-

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A-PN begin with sensorimotor or autonomic peripheral neuropathy symptoms. Later, symptoms evolved related to involvement of other fiber classes and organs, e.g., heart, eye or kidney.10, 19 Differences in the natural history and pattern of tissue involvement have been described.2 The phenotypic heterogeneity has been most extensively studied for the Val30Met mutation.5, 8, 22, 23, 33, 37 Although median nerve involvement due to the carpal tunnel syndrome may occur initially or subsequently in TTR-A-PN, we did not study this complication in this study.

Several studies have emphasized preferential involvement of small diameter sensory and autonomic nerve fibers in TTR-A-PN.12, 36, 44 But in another study, less selective involvement of small fibers was reported.7 In a recent study, QSTs demonstrated elevated thermal thresholds before nerve conduction abnormalities (a large fiber function).18 Evaluation of sympathetic skin responses has also been advocated for characterizing small fiber neuropathies.9, 38 The need therefore remains to systemically and comprehensively evaluate the nerve fiber class vulnerability in TTR-A-PN using standard, objective and quantitative autonomic (QAT) and sensation (QST) tests for which reference values corrected for applicable variables of age, gender, height and weight are available.4, 22, 33, 35

There has been an increasing interest in therapies directed at preventing unfolding of precursor proteins involved in the formation of beta pleated sheets of amyloid fibrils.20, 21, 24 To test these new treatments there is a need, therefore, to find standard, objective, and quantitative neuropathy endpoints not only to detect but also to track severity of TTR-A-PN for use in epidemiologic surveys and in prospective controlled therapeutic trials. Here we assess the frequency and severity of symptoms, signs and abnormalities of standard nerve tests, including nerve conduction studies (NC), quantitative sensation tests (QSTs), and quantitative autonomic tests (QATs) for the purpose of detecting, characterizing and scaling the severity of neuropathic abnormalities. Since reference values corrected for applicable variables are available for NCs, QSTs, and QATs, it is possible to determine frequency of abnormalities at a set sensitivity and specificity value of ~ 0.95. This study allowed us to test sensitivity for detection of polyneuropathy in a cohort of TTR-A patients evaluated at Mayo Clinic in the last 10 years. With approval of our protocol studies from our IRB, we only assessed the medical records of patients who had given permission to allow their medical records to be used for research purposes.

MATERIALS AND METHODS

Patients with TTR-A-PN evaluated at Mayo Clinic between 1997 and 2007 were retrospectively identified from diagnostic registries. Of 103 tissue proven cases of amyloidosis, 36 patients were identified as having TTR-A-PN (the type of amyloidosis and polyneuropathy based on evidence of an amino acid substitution in the TTR molecule or in earlier years by a characteristic pattern of neuropathy, evidence of amyloid in tissue, familial occurrence of neuropathy, lack of a monoclonal protein and evidence of polyneuropathy based on clinical examinations, and electrodiagnostic, quantitative sensation and autonomic tests). All patients with different types of TTR-A-PN were assessed as a group, because we did not have sufficient numbers of patients (with specific amino acid substitutions) to compare difference among different gene mutations. Of this group, 21 also had been tested by QST, and 18 had been evaluated by thermoregulatory sweat distribution tests. QSTs and QATs were prospectively performed using standard tests and validated algorithms of testing expressed as normal deviates (from percentiles corrected for applicable variables). Some of the patients (n = 6) were later enrolled in a prospective controlled double-blind trial of Diflunisal versus placebo (principal investigator, John Berk, M.D., Boston University).

The Mayo Clinic Neurology record sheets of these patients were abstracted to determine the frequency of neuropathic motor, sensory, and autonomic symptoms and findings. Information from the general medical record was abstracted for constitutional and specific parenchymatous organ dysfunction. A distinction was made between negative (loss of sensation) and positive ("asleep numbness", "prickling", cold sensations, and varieties of neuropathic pain, i.e. burning, lancinating and deep aching) sensory symptoms and positive and negative autonomic symptoms.

Typically nerve conduction measures were available for median, ulnar, tibial and peroneal motor nerve fibers, and for median, ulnar and sural sensory nerve fibers (antidromic recordings) obtained by standard methods in the EMG laboratory at Mayo Clinic. All attributes of nerve conduction were expressed as measured values and as normal deviates from percentiles corrected for applicable variables of age, gender, height and weight. The composite nerve conduction score used here was Σ 5 NC nds, which consists of the summated normal deviates (from percentiles corrected for applicable variables) of peroneal motor nerve amplitude, velocity, and distal latency, tibial motor nerve distal latency, and sural sensory nerve amplitude. In the derivation of this score, all abnormalities are expressed in the upper tail of the normal distribution, values are summed, divided by the number of measurable variables and multiplied by 5.13, 34 The 95th percentile of Σ 5 NC nds was ascertained from a study of 330 healthy subjects in the RDNS-HS cohort.13 Σ 5 NC nds was chosen, because, as we reported earlier,15 "…nerve conduction abnormality is objective (results cannot be willed by the patient), provides a quantitative measure over a wide range of magnitudes, has been shown to be as (or more) sensitive and specific for sensorimotor polyneuropathy than other nerve conduction criteria, is more reproducible than most individual attributes of nerve conduction, and generally correlates well with neuropathic impairment, and its components include several nerves of the legs and representative attributes (conduction velocities, latencies, and amplitudes)."

Autonomic function tests consisted of the autonomic reflex screen, which evaluates the severity and distribution of postganglionic sudomotor, adrenergic, and cardiovagal function, 25, 26 and the thermoregulatory sweat test (TST). Except for the TST, all QAT results were also expressed as normal deviates from percentiles and as corrected for applicable variables. For the TST, normal values are given by the surface distribution of anhidrosis, expressed as a percent of body surface area.16 The use of these tests in research and neurologic practice has been extensively documented.27, 30–32 Sympathetic postganglionic cholinergic function is assessed using the quantitative sudomotor axon-reflex test (QSART), which quantitatively evaluates the postganglionic sympathetic sudomotor axon at the forearm and three lower extremity sites. Sympathetic adrenergic function is assessed by beat-to-beat blood pressure and heart rate responses to head-up tilt and the Valsalva maneuver. Cardiovagal function is evaluated by the heart rate responses to deep breathing and the Valsalva maneuver. Results are compared to a normative database of 557 normal subjects.25 Based on the results of the autonomic reflex screen, a 10-point composite autonomic severity score (CASS) is generated that corrects for the confounding effects of age and gender.29 The 10-point total CASS score is divided into three subscales: adrenergic (range = 0–4), sudomotor (range = 0–3), and cardiovagal (range = 0–3). Generally, a total CASS score ≤ 3 indicates no or mild autonomic failure; scores from 4–6 indicate moderate autonomic failure; and scores from 7–10 indicate severe autonomic failure. Orthostatic hypotension was defined as a fall in systolic BP ≥30 mm Hg at 1 minute of head-up tilt, which corresponds to ≥ 97.5 percentile of controls.25

The QST evaluated with CASE IVb (WR Medical Electronics, Inc., Stillwater, MN) included: vibratory (VDT) and cooling (CDT) detection threshold, and an intermediate severity of heat-pain response (HP 5.0), heat-pain detection threshold (HP 0.5), and the

stimulus-response slope between HP 5.0 and HP 0.5 (HP 5.0-0.5).14 All values of QST were given as normal deviates from percentiles corrected for applicable variables of age, gender, height and weight when applicable.13, 34 When the composite score of QST (Σ3QST nds, the summated normal deviates of VDT, CDT, and HP 5.0) were used, all abnormalities were expressed in the upper tail of the normal distribution and the 95th percentile line was based on assessment of 330 healthy subjects also drawn from Olmsted County.13, 34

Statistical analysis

Descriptive statistics were used to express dichotomous data. The abnormality of each test was set at 5th or 95th percentile and the abnormal criterion of Neuropathy Impairment Score (NIS) (as described in Reference 10) was equal to or greater than 2 points. Spearman correlation coefficients were used to evaluate the relationship between NIS, and composite scores of nerve conduction studies (Σ 5 NC nds), QST (Σ3QST nds), and QAT (total CASS). Statistical significance was defined as p-value <0.05.

RESULTS

Genetic abnormalities

The most common genetic mutations and in order of decreasing frequency were: Val30Met (38%), Thr60Ala (14%), Asp38Ala (5%), Gly47Glu (5%), Ser77Tyr (5%), Pro24Ser (3%), Phe33Leu (3%), Als45Asp (3%), Phe64Leu (3%), and Ala109Ser (3%). However, in 7 patients evaluated at an earlier time when we only tested for 4 point mutations, the specific gene mutation was not identified.

Clinical features

Patient and disease characteristics are shown in Table 1 and Table 2. There was a strong male predominance in our cohort (92%). This was somewhat higher than the male predominance in cases referred to the Mayo Clinic. Age of symptom onset of generalized polyneuropathy was quite variable, (18–75 years) with a median value of 53 years. The most frequent initial symptom was one or more of positive neuropathic sensory symptoms, i.e. “prickling,” “asleep numbness” or various pains (64%), followed by motor (17%), autonomic (11%), cardiac (6%) and weight loss (3%) symptoms. At our first evaluation, positive neuropathic sensory symptoms occurred in 100%, autonomic symptoms in 91%, and motor symptoms in 61% of patients. On physical examination, motor weakness was found in 67%, and decreased sensation in 89%. The anatomic distribution of clinical findings showed the following patterns: distal and proximal involvement of lower and upper limbs (44%); distal lower and upper limbs (31%); and distal lower limbs (17% only) (Table 2).

Based on the abstracted information of neurologic records, positive neuropathic sensory symptoms were: “prickling” (72%), “asleep numbness” (69%), burning pain (22%), deep aching pain (17%), cold discomfort (11%), and lancinating pain (6%). Based on neurologic examination, the most common neurologic abnormality was decreased or absent loss of sensation. By modality, vibration loss was most frequent (72%), followed by impairment of pin prick (69%), temperature and touch (each 55%), and joint movement (47%) sensation. Autonomic symptoms at our first examination included gastrointestinal symptoms such as nausea, vomiting, and diarrhea (55%), orthostatic hypotension (44%), secretomotor (sweating, salivation, lacrimation; 42%), sexual dysfunction - inability to have a penile erection (33%), urinary (28%), sleep disturbance (3%), and vasomotor (3%) symptoms. The lower limbs were involved earlier than the upper limbs (median duration of lower and upper limb symptoms: sensory, 2.3 and 1.5 years; motor, 2 and 1.3 years, respectively). The median duration of autonomic symptoms was 2.0 years (range, 0.3 – 7). The median NIS (a

summated score of neurologic signs described in Reference 10) was 33.5 points (range, 0 – 142.5 points), and the sensitivity of NIS was 90% (abnormal, NIS ≥2 points) (Table 3).

Electrodiagnostic tests

The most common electrodiagnostic findings were consistent with a length-dependent axonal sensorimotor polyneuropathy (72%). The composite score of nerve conduction (Σ 5 NC nds ≥ 95th percentile) was abnormal in 81% of our cohort (Table 3). The median values of median, ulnar, peroneal, and tibial compound muscle action potentials were 6.9, 5.8, 0.3, and 0.8 mV. The median values of sensory nerve action potential amplitudes of median, ulnar, and sural nerves were 3.0, 3.0, and 0 uV. Evidence in keeping with carpal tunnel syndrome was observed in 8 patients.

Quantitative autonomic tests

Abnormal postganglionic sympathetic sudomotor dysfunction was found in 74%, and the typical pattern was length-dependent in 18 patients (47%) followed by diffuse and patchy involvement in 5 patients (13%). The HR_{db} was abnormal in 25 (69%) of 36 persons. Thirteen patients (36%) had orthostatic hypotension (OH) with a median systolic blood pressure fall of 36 mmHg at 1 minute (range, 32–80 mmHg) (Table 3). The total CASS scores were normal in 6, mildly abnormal in 4, moderately abnormal in 5, and severely abnormal in 21 patients. The median total CASS score was 7 (range, 0–10), which is an indicator of severe involvement of autonomic function. The TST was performed in 18 patients. The median percent of anhidrosis was 18.5% (range, 0–99) showing a distal distribution in 7 patients, mixed (focal and distal) in 5, focal in 1, regional in 1, global in 1, hyperhidrosis in 1, and normal in 2.

Quantitative sensory testing

The median percentile value of each of VDT, CDT, and HP 5.0 of the foot were all > 95th percentile, indicating a severe pan-modality sensory loss. The most sensitive indicator of QST abnormality of the foot was Σ3QST nds ≥ 95th (86%), followed by HP5.0 ≥ 95th (76%), VDT > 95th (67%), and CDT ≥ (57%) (Table 3).

Correlation of nerve tests

Highly significant correlations were found between NIS and a composite score of nerve conduction (Σ 5 NC nds), and QSTs (Table provided on written request).

DISCUSSION

This study, of a cohort of TTR-A-PN patients referred to a tertiary medical center between 1997 – 2007, focuses on results of standard quantitative sensations (QSTs) and autonomic (QATs) tests, but it also provides information about the natural history, inferred anatomical distribution of neuropathic involvement, class of nerve fibers affected, and endpoints which might be used in prospective controlled trials of therapy.

Early involvement of small diameter sensory and autonomic nerve fibers has been emphasized in many earlier studies,[12, 36, 44] which we also found here, but the present study finds a more generalized involvement of all nerve fiber classes even from early stages of the disease. This more generalized involvement of all classes of nerve fibers was recognized by use of specialized endpoints, i.e., Σ 5 NC nds and vibration detection threshold of QSTing (large fiber involvement) and CDT and HP thresholds of QSTing and QATing (small fiber involvement).

Among early manifestations of the disease in our cohort was the occurrence of “prickling” and feelings of “asleep numbness” and, in a few cases, gastrointestinal symptoms. The composite nerve conduction score (Σ 5 NC nds ≥ 95th), QSTs and QATs also provided early evidence of involvement in many cases. Therefore, although there may be cases with selective involvement of small sensory and autonomic nerve fibers (e.g., cases reported by several authors),[12, 44] the usual pattern is of involvement of all classes of peripheral nerve fibers. However, the prominent involvement of small sensory and autonomic fibers is a useful criterion for the diagnosis of this variety of neuropathy.

Our studies also confirm results from earlier studies that initial symptoms tended to begin in the feet and/or in hands and later progressed to more proximal limb involvement.

Our studies provide useful information about QST and QAT abnormalities in a cross-sectional cohort of TTR-A-PN patients. All QST modalities provided high frequencies of abnormalities; the highest frequency was a combination of all modalities, i.e., Σ3QST nds (86%). Similarly, QAT gave high frequencies; the highest frequency was the QSART (78%), followed by HR_{db} (69%) and OH (36%). By comparison, the composite score of 5 attributes of nerve conduction (Σ 5 NC nds, $\geq 95^{th}$) that indicate large fiber dysfunction gave an even higher frequency of abnormality (81%).

Do our clinical and test evaluations provide information about the distribution of tissue amyloid deposition? We infer from our results that amyloid deposition must be distributed widely and affect both proximal and distal levels of nerves and all classes of nerve fibers, i.e., motor, sensory (both small and large) and autonomic fibers of various types. This is in keeping with deposition of amyloid in nerve roots, ganglia and proximal to distal levels of nerves.[17, 33, 39, 43]

What information do our studies provide about the usefulness of the clinical examinations and tests studied here for the conduct of therapeutic trials to prevent or improve TTR-A-PN? For the conduct of trials, standard, objective and quantitative endpoint measures that give monotonic results over time are needed.[10, 11, 13, 15] We infer that assessment of symptoms, neurologic signs, QSTs, QATs and nerve conduction test results (e.g., Σ 5 NC nds) might be appropriate endpoints for such trials. Although we did not test QSTs and QATs for their change with time, the tests are suitable by the criteria of being standard, quantitative, sensitive, and reference values are corrected for applicable variables. The tests of attributes of nerve conductions are objective tests in the sense that result can not be willed by the patient. The QST are not as objective as are nerve conductions and QAT, but abnormalities due to inattention, drowsiness, malingering, or depression are recognizable and in any case not found to be a problem in previous controlled trials, evaluations considered here, or in epidemiologic surveys. The QSTs and QATs employed here have been used in prospective controlled trials and epidemiological surveys over periods of years and have been found to give monotonic results.[11, 28] Therefore, we conclude that the Σ 5 NC nds, QST, and QAT tests used here would be suitable measures in therapeutic trials.

The early and generalized involvement of different classes of nerve fibers must be considered when thinking about the putative mechanisms and distribution of nerve fiber involvement in TTR-A-PN. Three pathogenic mechanism of fiber dysfunction have been postulated, i.e. ischemia, compression, and metabolic derangement.[12, 17, 36, 44] The lack of a clear cause and effect relationship between amyloid deposition and fiber degeneration raised the possibility of generalized metabolic derangement affecting the nerve or toxicity of amyloid itself.[6] Recent studies suggest that this toxicity may relate to immature amyloid fibrils, i.e. non-fibrillar aggregates.[1, 40–42] Non-fibrillar aggregates are present in nerve prior to fibril formation.[40]

The current study has limitations. The sample size is not as large as desirable, and it may not be representative of TTR-A varieties in a future study population. Although 36 TTR amyloidosis polyneuropathy patients had nerve conduction and QAT tests done, QSTing was done in only 22 patients. Finally the gene abnormality was not characterized in all patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CASS	Composite Autonomic Severity Score
CDT	cooling detection threshold
HP	heat-pain
HR_{db}	heart rate decrease with deep breathing
NC	nerve conduction
NIS	Neuropathy Impairment Score
QAT	quantitative autonomic test
QSART	quantitative sudomotor axon reflex test
QST	quantitative sensation test
TST	thermoregulatory sweat distribution test
TTR-A-PN	transthyretin amyloidosis polyneuropathy
VDT	vibratory detection threshold

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Table 1

Patient and Disease Characteristics of the Transthyretin Amyloidosis Cohort

Number	**36**
Male gender (number, %)	31 (86%)
Weight (kg), median (range)	74 (38.1 – 122.5)
Height (m), median (range)	1.77 (1.58 – 1.96)
Body mass index (kg/m^2), median (range)	24.1 (15.4 – 38.8)
Age at initial symptom onset (years), median (range)	53 (18–75)
Below 50 year old, cases (%)	16 (44%)
Above 50 year old, cases (%)	20 (56%)
Age at first Mayo Clinic evaluation (years), median (range)	59 (23 – 78)
Duration from symptom onset to first Mayo Clinic evaluation (years), median (range)	4 (1 – 30)
History of clinical or electrophysiologic CTS, cases (%)	14 (39%)
History of carpal tunnel release, cases (%)	9 (25%)
Gene mutations, cases (%)	
Val30Met	14 (39%)
Thr60Ala	5 (14%)
The others*	11 (28%)
Not detected†	7 (19)

CTS, carpal tunnel syndrome

*Asp38Ala, Gly47Glu, and Ser77Tyr, 2 cases respectively; Pro24Ser, Phe33Leu, Als45Asp, Phe64Leu, and Ala109Ser, 1 case respectively

†Patients who could not be identified on genetic test because of limitation of TTR mutant genes tested.

Table 2

Clinical and Neurophysiologic Findings of Transthyretin Amyloidosis Patients

Case	NIS	Symptoms			Signs		Tests			Distribution			
		M	S	A	M	S	Σ 5 NC nds	Total CASS	Σ 3 QST nds	D_L	D_LU	D_U	DP_LU
1	0	−	+	−	−	−	−	−	−	−	−	−	−
2	0	−	+	+	−	−	+	−	+	−	−	−	−
3	4	−	+	+	−	+	−	+	+	−	+	−	−
4	4	−	+	+	−	+	−	+	−	+	−	−	−
5	4	−	+	+	−	+	+	+	+	+	−	−	−
6	6	−	+	−	−	+	+	−	−	+	−	−	−
7	8	−	+	+	−	+	+	+	+	+	−	−	−
8	14	+	+	+	+	+	+	+	+	+	−	−	−
9	35	+	+	+	+	+	+	+	+	−	−	−	+
10	38	−	+	+	+	+	+	+	+	−	+	−	−
11	39	+	+	+	+	+	+	+	+	−	+	−	−
12	41	+	+	+	+	+	+	−	+	−	+	−	−
13	61.5	+	+	+	+	+	+	+	+	−	−	−	+
14	64	+	+	+	+	+	+	+	+	−	−	−	+
15	71.5	+	+	+	+	+	+	+	+	−	−	−	+
16	81	+	+	+	+	+	+	+	+	−	−	−	+
17	92	+	+	+	+	+	+	+	+	−	−	−	+
18	97	+	+	+	+	+	+	+	+	−	−	−	+
19	98	+	+	+	+	+	+	+	+	−	−	−	+
20	115.5	+	+	+	+	+	+	+	+	−	−	−	+
21	121	+	+	+	+	+	+	+	+	−	−	−	+
22	0	−	+	+	−	−	−	+		−	−	−	−
23	2	−	+	+	−	+	−	−		+	−	−	−
24	3	+	+	+	−	+	+	−		−	+	−	−
25	5	−	+	+	−	+	+	+		−	+	−	−
26	11	+	+	+	+	−	−	+		−	+	−	−
27	14	−	+	+	−	+	−	−		−	+	−	−

Case	NIS	Symptoms			Signs		Tests			Distribution			
		M	S	A	M	S	Σ 5 NC nds	Total CASS	Σ 3 QST nds	D_L	D_LU	D_U	DP_LU
28	14	−	+	+	+	+	+	+		−	−	−	+
29	18	+	+	+	+	+	+	+		−	−	−	+
30	21	−	+	+	+	+	+	+		−	+	−	−
31	32	+	+	+	+	+	+	+		−	+	−	−
32	50	+	+	+	+	+	+	−		−	+	−	−
33	57	+	+	+	+	+	+	+		−	−	−	+
34	57	+	+	−	+	+	+	+		−	−	−	+
35	70	+	+	+	+	+	+	+		−	−	−	+
36	142.5	+	+	+	+	+	+	+		−	−	−	+

+, abnormal; −, normal; NIS, neurologic impairment score; M, motor; S, sensory; A, autonomic; Σ 5 NC nds, the composite score of nerve conduction studies; Total CASS, total Composite Autonomic Severity Score; Σ3QST nds, the composite score of quantitative sensation tests; D_L, distal lower limbs; D_LU, distal lower and upper limbs; D_U, distal upper limbs; DP_LU, distal and proximal lower and upper limbs

Table 3

The Sensitivity of Nerve tests in TTR Amyloidosis Cases Evaluated at Mayo Clinic

	N = 36		N = 21	
	Abnormal cases	**%**	**Abnormal cases**	**%**
NIS, ≥2 points	33	92%	19	90
Σ 5 NC nds, ≥95th	29	81%	18	86
VDT, ≥95th	-	-	14	67
CDT, ≥95th	-	-	12	57
HP 5.0, ≥95th	-	-	16	76
HP 0.5, ≥95th	-	-	13	62
HP 5.0-0.5, ≥95th	-	-	14	67
Σ 3QST nds, ≥95th	-	-	18	86
QSART, ≤5th	28	78%	16	76
HR_{db}, ≤5th	25	69%	14	67
OH*	13	36%	7	33
Total CASS, ≥2 points	29	81%	17	81

NIS, Neuropathy Impairment Scale; Σ 5 NC nds, The summated normal deviates of peroneal motor nerve amplitude, velocity, and distal latency, tibial motor nerve distal latency, and sural nerve amplitude; VDT, Vibration detection threshold (CASE IV_b, toe); CDT, Cooling detection threshold (CASE IV_b, dorsal foot); HP 5.0, Intermediate severity of heat-pain response (CASE IV_b, dorsal foot); HP 0.5, Heat-pain detection threshold (CASE IV_b, dorsal foot); HP 5.0-0.5, Stimulus-response slope between HP 5.0 and HP 0.5 (CASE IV_b, dorsal foot); Σ 3QST nds, The summated normal deviates of VDT, CDT, and HP 5.0; QSART, Quantitative sudomotor axon reflex test; HR_{db}, Heart rate response to deep breathing; OH, Orthostatic hypotension; Total CASS, total Composite Autonomic Severity Score.

*a fall in systolic blood pressure greater than or equal to 30 mmHg at 1 minute of standing or on head-up tilt