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Autonomic evaluation is independent of somatic evaluation for small fiber neuropathy

Pariwat Thaisetthawatkul [a,*], J. Americo Fernandes Filho [a,b], David N. Herrmann [c]

[a] Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, USA
[b] Neurology Section, VA Nebraska—Western Iowa Health Care System, Omaha, NE, USA
[c] Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA

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ABSTRACT

Background: The relationship between the autonomic reflex screening test (ARS) and measures of sensory function and structure (quantitative sensory testing (QST) and intraepidermal nerve fiber density (IENFD)) remains uncertain in patients with distal small fiber neuropathy (SFN). The aim of this study was to evaluate the correlations among a range of autonomic (quantitative sudomotor axon reflex test (QSART), cardiovagal and cardio adrenergic tests and the composite autonomic severity score (CASS)) and somatic sensory measures (QST of vibration, cooling and heat-pain thresholds and IENFD).

Method: 122 patients with clinically suspected sensory neuropathy without motor weakness and with normal nerve conduction studies underwent blinded autonomic reflex screening test (ARS), quantitative sensory testing (QST) and skin biopsy (IENFD) for diagnosis of SFN. The relationship between autonomic and somatic sensory measures was assessed.

Results: There was no association between autonomic function measures (QSART volume, CASS_QSART, CASS_vagal, CASS_adrenergic or total CASS) and small fiber sensory measures (IENFD, cooling or heat-pain thresholds). Weak correlations were noted among some modalities of QST (vibration and cooling thresholds) and IENFD.

Discussion: Autonomic and sensory outcomes are independent (complementary) measures of distal SFN, and should where feasible be used concurrently in the evaluation of SFN.

1. Introduction

Small fiber neuropathy (SFN) is commonly encountered in neurological practice. Patients with SFN have normal routine electrophysiological studies, such that confirmation of the diagnosis relies on an abnormality of small fiber measures including intraepidermal fiber density (IENFD) by skin biopsy, quantitative sensory testing (QST) or sudomotor function by quantitative sudomotor axon reflex test (QSART). In our previous study, addition of QSART to a combination of clinical examination, QST and IENFD increased the diagnostic yield of tests for SFN [1]. This study suggested that somatic sensory and QSART evaluations were additive in the assessment of distal SFN, leading to the hypothesis that sensory and autonomic small fiber dysfunctions occur independently and are not highly correlated in the setting of SFN. Investigations on the association of autonomic and somatic measures in SFN have yielded conflicting findings [2–6]. One study showed a significant association between the composite autonomic severity score for sudomotor function (CASS_sudo) and IENFD [6]. However, the number of the subjects was small and the patient populations were heterogeneous (a mixture of distal SFN, postural orthostatic tachycardia syndrome, and large fiber neuropathy). A further report that evaluated autonomic impairment in painful neuropathy showed no overall correlation between QSART volume, cooling threshold and IENFD [4]. However, a subgroup analysis of patients with abnormal QSART showed an inverse association between QSART and IENFD [4]. This underscores the need for further investigation of the relationships between autonomic function and somatic measures of SFN in a large cohort of strictly defined distal SFN patients.

The main goal of this study was to systematically assess the correlation between elements of the autonomic reflex screening test (ARS) and measures of small fiber somatic function and structure [vibration, cooling and heat-pain threshold (VDT, CDT and HPT respectively) just-noticeable-differences (JNDs) and IENFD] in distal SFN. Secondary objectives included an analysis of the correlation among somatic sensory measures (VDT, CDT, HPT and IENFD) in this cohort and the correlation between pain symptoms, autonomic symptoms and diagnostic measures of distal SFN.

* Corresponding author at: Department of Neurological Sciences, 988435 Nebraska Medical Center, Omaha, NE 68198-8435, USA. Tel.: +1 402 559 9953; fax: +1 402 559 9213.
E-mail address: pthaiset@unmc.edu (P. Thaisetthawatkul).

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2. Methods

All patients evaluated in the Peripheral Neuropathy Clinic at the University of Nebraska Medical Center between 2008 and 2012 underwent a standardized clinical and electrophysiological assessment of suspected neuropathic symptoms. Those patients who presented with distal sensory symptoms of pain, without muscle weakness or upper motor neuron signs and had normal nerve conduction studies and electromyography (NCS/EMG), underwent ARS (QSART, cardiovagal and adrenergic testing) with calculation of a composite autonomic severity score (CASS), QST and skin biopsy (IENFD) to assess for SFN. The protocols and procedures employed for the clinical evaluation, electrophysiological studies, QSART, QST and IENFD analysis have been previously described in a study that involved a subset of the current cohort and addressed the contribution of QSART toward diagnostic criteria for SFN [1]. For cooling and vibration thresholds, abnormality was defined as a threshold above the 95th percentile for age, height, weight and gender [1]. Heat pain threshold abnormality was defined as a value below the 5th percentile (hyperalgesia) or above the 95th percentile (hypoalgesia) [1]. A value below the 5th percentile was considered as an abnormal QSART volume or IENFD as previously described [1]. Cardiovagal and adrenergic testing and the CASS were not included in the above SFN diagnostic criteria study and are described below. The present study was approved by the Institutional Review Board of the University of Nebraska Medical Center.

2.1. Cardio-vagal testing

Cardio-vagal testing was performed as part of the ARS. This was assessed through the heart rate response to deep breathing (HR DB) and the Valsalva ratio (VR). Each subject was attached to a beat-to-beat blood pressure device (Finometer/Finapres Medical System; Amsterdam), a three-lead electrocardiogram and a chest bellow. The HR DB was obtained by having each patient breathe deeply at six breaths/minute while lying in the supine position. The procedure was repeated following a 2-minute period to ensure reproducibility and the average of 3 trials was the HR DB [7]. HR DB was defined by mean HR range (maximum–minimum) of the five consecutive largest responses among eight breathing cycles [7]. Abnormal HR DB was present if HR DB was less than the 2.5th percentile, based on healthy subjects of the same age. To obtain a VR, each patient, again lying supine, blows into a bugle with enough expiratory force to maintain a pressure of 40 mm Hg for 15 s. This was performed three times to ensure reproducibility with a 3-minute rest in between [7]. The VR was determined based on the best of the 3 trials. The VR was derived from the maximum HR divided by the lowest HR within 30 s after the maximum HR was achieved [7]. Abnormal VR was present when the VR was less than the 2.5th percentile, using normative data derived from normal subjects of the same age and gender. Normative data for both HR DB and VR were based on Low et al. [7].

2.2. Adrenergic testing

This was assessed through the beat-to-beat blood pressure response during a Valsalva maneuver (VM; see above) and a head-up tilt on a tilt table. The head-up tilt procedure was as follows. The patient was placed in the supine position for at least 20 min (this part was done last in the ARS). The blood pressure was recorded through Finometer and manually with a blood pressure cuff on a separate arm. The pulse rate was monitored through a three-lead electrocardiogram. The subject was tilted head-up at 70° for at least 5 min and a maximum 10 min while blood pressures, heart rates and electrocardiograms were monitored. At the end of the head-up tilt, the subject was tilted back into the supine position. Adrenergic function was assessed during a VM by evaluation of phase II and IV of the blood pressure response. During a VM, adrenergic impairment was present when there was reduction in mean blood pressure >25 mm Hg in early phase II, reduced or absent late phase II or pulse pressure reduction to <50% of baseline [7]. During a head-up tilt, adrenergic impairment was present when there was orthostatic hypotension (defined by reduction of systolic blood pressure by more than 30 mm Hg or reduction of mean blood pressure by more than 20 mm Hg, within the first 3 min of head-up tilt).

2.3. Composite autonomic severity score (CASS)

A CASS was computed for each patient. The CASS is a 10-point score to assess the severity of autonomic dysfunction assessed by the ARS [7]. CASS has subscores for each domain of autonomic components derived from each subtest in ARS which includes 3 main domains: sudomotor, vagal and adrenergic systems (maximum 3 points for CASS_sudo, maximum 3 points for CASS_vagal, and maximum 4 points for CASS_adrenergic). The score was normalized for the effects of age and gender. The higher the score, the more severe autonomic dysfunction is. The criteria for the scoring have been previously described [7].

2.4. Diagnosis of SFN

In this study, distal SFN was diagnosed when a patient presented with sensory symptoms without muscle weakness or upper motor neuron signs, and had normal EMG/NCS and at least 2 abnormalities of either QSART, QST or skin biopsy [1].

2.5. Statistical analysis

Linear regression analysis was performed to examine associations among neuropathy measures (IENFD, QSART volumes, QST JNDs and the total and component CASS scores) for numerical data. Fisher's exact test was used to assess difference in proportions. The Student t test was employed to assess difference in means. A p value <0.05 was considered significant.

3. Results

There were 122 patients who presented with sensory symptoms without motor weakness or upper motor neuron signs and had normal EMG/NCS. All patients underwent ARS, QST and skin biopsy. There were 84 females (69%). Mean age was 51 ± 14 years (18–85 years). The mean duration of symptoms before evaluation was 47 ± 14 months (1–240 months). Laboratory testing and previous medical histories showed that 8 patients had diabetes mellitus; 20 had impaired glucose tolerance; 23 had hypertriglyceridemia; 19 had monoclonal gammopathy; 10 had cancers; 13 had paraneoplastic antibodies (only one patient who had cancer also had a paraneoplastic antibody); 15 had a history of inflammatory disorders (5 had inflammatory bowel diseases, 3 had Sjogren's syndrome, 4 had rheumatoid arthritis, 1 had CREST syndrome, 1 had Raynaud disease, 1 had Hashimoto thyroiditis); 7 had a family history of neuropathy; 15 had a history of significant alcohol use and 2 had HIV infection. Abnormal pinprick sensation at the great toe was seen in 44 patients (36%). There were 49 patients who had abnormal vibration sense at the great toe on clinical examination. Position sensation and light touch were normal on clinical examination at the toes in all subjects.

Based on the criteria, SFN was diagnosed in 68 (57%) patients. Among these patients, 21 patients (31%) had abnormal QSART and QST, 12 (18%) abnormal QST and IENFD, 10 (15%) had abnormal QSART and IENFD, and 25 (36%) abnormality of all three measures. Overall, an abnormal IENFD, QSART and QST were found in 44 (36%), 62 (51%) and 83 (68%) of patients respectively. As a group, patients who had abnormal QSART had a higher frequency of abnormality of IENFD than those with normal QSART (Table 1). The proportion of patients with an abnormal QST did not differ between those with and without abnormal QSART.