Quantitative sensory testing in a large cohort of neuropathy patients: QST in Neuropathy

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Introduction

Quantitative sensory testing (QST) is a set of largely painless, noninvasive techniques developed more than 30 years ago to determine specific patient threshold to accurately calibrated sensory stimuli.[1,2,3,4] QST can measure small- and large-fiber function in the peripheral and central somatosensory pathways, including warming, cooling, heat-pain sensation and vibratory perception, but cannot distinguish between central and peripheral impairment. The most commonly tested modalities are vibratory perception and thermal pain. Although QST is a psychosocial measure derived from subjective responses, there is good reliability and reproducibility of QST results on both an individual and population level.[5,6]

QST may have some use as a diagnostic, staging and outcome measure in peripheral neuropathy (PN) research, but its usefulness in the routine clinical setting is unclear.[4] PN is typically diagnosed based on a combination of clinical and electrophysiological data, with slowly progressive, distally predominant sensory loss being the most common clinical pattern.[7,8] QST may provide evidence of peripheral nerve pathology in the setting of normal nerve conduction studies (NCS) and electromyography (EMG) and may be particularly helpful in small-fiber pathology as routine electrophysiologic studies do not detect small-fiber sensory dysfunction.[9] The utility of QST, however, to distinguish between types of peripheral neuropathy is not established.

Although up to 30% of PNs referred to specialty clinics do not have a clear etiology identified and are ultimately categorized as cryptogenic sensory PN (CSPN), most PNs are categorized to a variety of etiologies.[4,10] The most common cause in the United Status of acquired PN is diabetes mellitus. Other causes of PN include infection (e.g., leprosy, HIV), toxic (e.g., alcohol-induced), nutritional (e.g., B12 deficiency) in addition to autoimmune etiologies (e.g., chronic inflammatory demyelinating polyneuropathy [CIDP]) and hereditary neuropathies (e.g., Charcot Marie Tooth [CMT] disease).[11] While different forms of PN at times present with unique clinical patterns and electrodiagnostic signatures on NCS/EMG, the neurological examination and electrophysiological studies may not distinguish different etiologies of PN, especially when of predominantly axonal pathophysiology. A non-invasive method to distinguish between types of PN would be helpful in differential classification and management.

The objective of this study was to retrospectively evaluate patterns of QST findings among different categories of neuropathy in a large cohort of PN patients evaluated at the University of Texas Southwestern Medical Center from 1995-2000.

Methods

This retrospective study consists of patients who presented to the University of Texas Southwestern Medical Center PN tertiary clinic between 1995 and 2000. Patients who were diagnosed with any form of neuropathy underwent routine QST using the Computer-Assisted Sensory Examination system (CASE IV, WR Medical Electronics, Stillwater, MN) using a 4, 2, and 1 stepping protocol.[12] This test typically lasts approximately one hour. The CASE IV system used during the enrollment period had age-matched control values for vibration and cooling sensory thresholds. Thresholds for heat-pain had not been fully validated. Abnormal results were established at the greater than 95th percentile for age. Patients were categorized by a single etiology of neuropathy as diagnosed by neuromuscular medicine specialists.

All analyses were performed in R (version 4.0.5). Chi-squared tests were used to compare the prevalence of abnormal responses between tests. Due to the limited number of observations and normal results for some diseases, Fisher's Exact test was used to perform pairwise comparisons of the prevalence of abnormal tests between diseases for each test. To account for multiple comparison, false detection rate (FDR) adjusted p-values are reported. The FDR-adjusted p-values were computed independently for each set of pairwise comparisons. For instance, FDR-adjusted p-values were computed for the pairwise comparisons of the abnormal cold test amongst diagnoses and the abnormal vibration test.

To determine the impact of disease and test on the prevalence of abnormal responses, meta regression was implemented with a logit link function. Meta regression was performed independently for the cold and vibration tests and the pure thermal and pure vibration tests due to the

greater proportion of abnormal cold and vibration results relative to pure thermal and pure vibration results.

Results

A total of 559 QST studies were performed in this study. The average age of patients (n=557) was 60 years with a male-to-female ratio of 1:1. The most common diagnosis was CSPN (n=294), followed by CMT disease (n=84) (Table 1).

Meta-regression of cold and vibration indicate that the expected proportion of abnormal responses is less for the vibration test (p = 0.0002), relative to the cold test (Figure 1). However, no differences were observed between diagnoses, as previously found in Table 5. Meta-regression indicate that the expected proportion of pure vibration is less than the pure thermal (p < 0.0001); however, no differences were observed between diagnoses, as previously found in Table 5 (Figure 2).

Vibration and cold detection thresholds were measured in all patients, whereas heat-pain was measured in 284 patients (Table 2). In this cohort, patients were more often abnormal for cold sensation testing relative to vibration (p < 0.0001) and heat (p < 0.0001). Additionally, the data suggest that more subjects were abnormal for vibration relative to heat (p<0.0001) (Table 3).

Table 1: Patient characteristics and diagnoses

Total patients	557
Men	277
Women	280
Mean Age (range) [years]	60 (14-93)
Diagnoses	
CSPN	294 (53%)
CMT	84 (15%)
CIDP	39 (7%)
Diabetic	39 (7%)
B12 deficiency	18 (3%)
Leprosy	11 (2%)
Alcoholic	7 (1%)
Other	65 (12%)

Other includes several diagnoses with a small number of cases. These diagnoses include: amyotrophic lateral sclerosis, primary lateral sclerosis, distal acquired demyelinating symmetric neuropathy, monoclonal gammopathy of undetermined significance associated neuropathy, various rheumatologic etiologies (Sjögren's syndrome, vasculitis, other connective tissue diseases), paraneoplastic neuropathy, Guillain-Barré syndrome, multifocal motor neuropathy.

Table 2. Distribution of abnormal responses by test for entire sample

	Abnormal	Total
Cold	534 (95.53%)	559
Vibration	404 (72.27%)	559
Heat	99 (34.86%)	284

Table 3. Results of pairwise comparison of abnormal results by test with FDR-adjusted p-values

Groups Compared	Adjusted p-value
Cold vs. Vibration	< 0.0001
Cold vs. Heat	< 0.0001
Vibration vs. Heat	< 0.0001

Figure 1. Forest plot of the meta-regression results for the cold and vibration tests by PN diagnosis

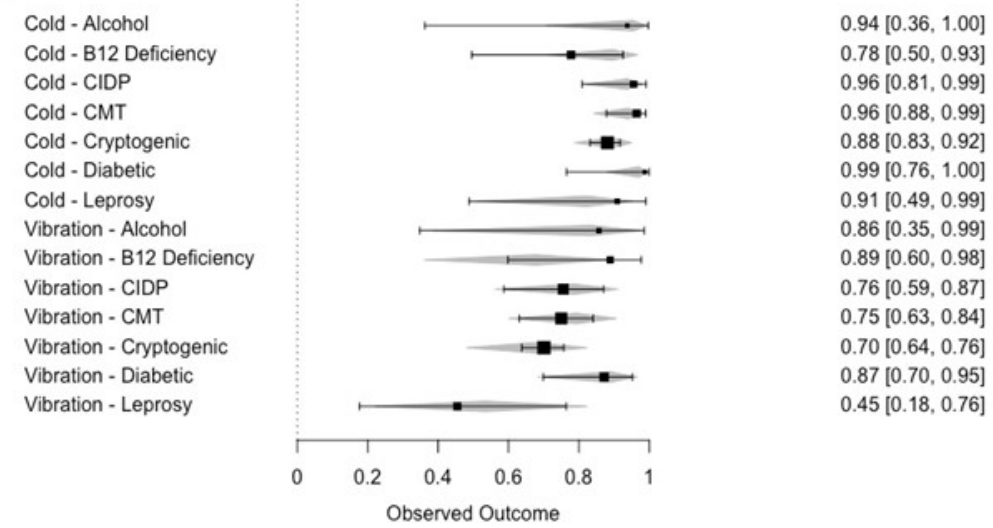

Figure 2. Forest plot of the meta-regression results for the pure thermal and pure vibration tests by PN diagnosis

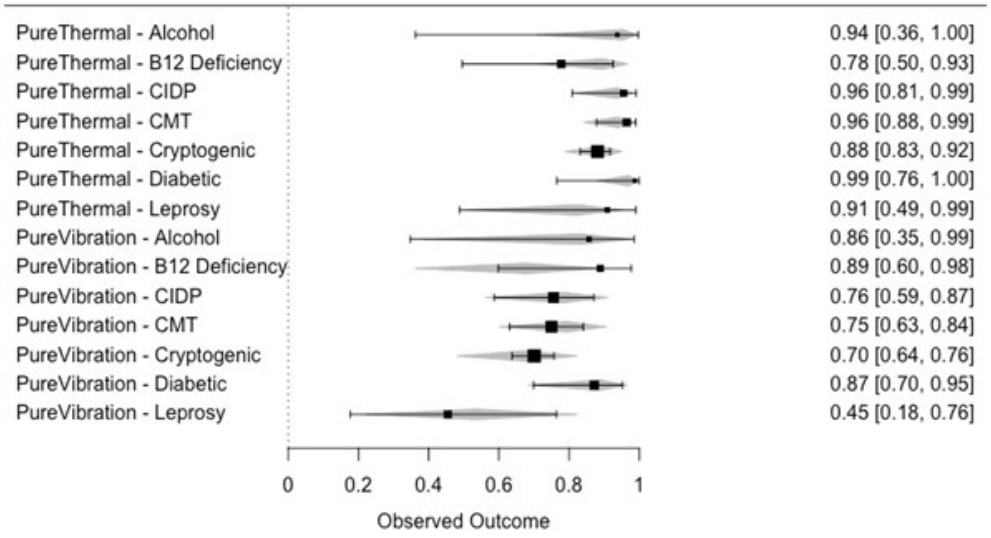

Table 4. Prevalence of abnormal results by PN diagnosis and test.

	Cold	Vibration	Abnormal	Pure Thermal	Pure Vibration	Total
Alcohol	7	6	7	1	0	7
B12 Deficiency	14	16	17	3	3	18
CIDP	43	34	44	12	3	45
CMT	81	63	84	20	3	84
CSPN	259	206	275	68	21	294
Diabetic	39	34	39	5	0	39
Leprosy	10	5	10	5	0	11

Table 5. Pairwise comparison of the proportion of abnormal results for each test by PN classification with FDR-adjusted p-values

Groups Compared	Adjusted p-value				
	Cold	Vibration	Pure Thermal	Pure Vibration	Abnormal
Alcohol vs. B12 Def.	0.687	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CIDP	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CMT	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. CSPN	> 0.99	0.949	> 0.99	> 0.99	> 0.99
Alcohol vs. Diabetic	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
Alcohol vs. Leprosy	> 0.99	0.367	0.736	> 0.99	> 0.99
B12 Def. vs. CIDP	0.212	0.603	> 0.99	0.895	> 0.99
B12 Def. vs. CMT	0.123	0.613	> 0.99	0.695	0.924
B12 Def. vs. CSPN	0.678	0.329	> 0.99	0.795	> 0.99
B12 Def. vs. Diabetic	0.123	> 0.99	> 0.99	0.586	0.938
B12 Def. vs. Leprosy	0.933	0.197	0.686	0.895	> 0.99
CIDP vs. CMT	> 0.99	> 0.99	> 0.99	0.980	0.938
CIDP vs. CSPN	0.660	0.732	> 0.99	> 0.99	> 0.99
CIDP vs. Diabetic	0.869	0.557	0.686	0.895	> 0.99
CIDP vs. Leprosy	0..869	0.300	0.734	> 0.99	0.938
CMT vs. CSPN	0.123	0.670	> 0.99	0.895	0.215
CMT vs. Diabetic	0.900	0.367	0.686	> 0.99	> 0.99
CMT vs. Leprosy	0.827	0.300	0.686	> 0.99	0.924
CSPN vs. Diabetic	0.123	0.197	0.686	0.795	0.924
CSPN vs. Leprosy	> 0.99	0.329	0.686	> 0.99	> 0.99
Diabetic vs. Leprosy	0.660	0.166	0.628	> 0.99	0.924

Among the various etiologies of neuropathy and the abnormalities detected, no statistically significant differences were observed between any pair of diagnoses for any of the QST modalities (Tables 4 and 5).

Of the 294 CSPN patients, 47 patients underwent QST and NCS with 7 (15%) patients having normal NCS. QST was abnormal in 3 (43%) of these 7 patients. All the 7 patients had abnormal pinprick documented on exam. A total of 97 CSPN patients had documented sensory exams. Ten (10%) patients had only pinprick (and not vibration) deficits on exam. QST vibration and cold thresholds were abnormal in 1 (10%) and 3 (30%) of these 10 patients, respectively. In this group of 10 patients, NCS was abnormal in 5 (50%) patients.

Discussion

In our 5-year study, no pattern of QST abnormalities was useful in distinguishing between the different classes of neuropathy. The largest proportion of patients tested had CSPN, followed by CMT disease and CIDP. Due to low numbers, the generalizability of the QST findings in other common etiologies of PN, including diabetes; alcohol overuse; and B12 deficiency, is limited. The inability to separate these types of neuropathies from each other in a routine clinical setting may limit the utility of QST to research investigations.

We found that QST was abnormal in >95% of established PN patients. This high rate of abnormal QST findings is expected in patients diagnosed with PN diagnosis in a referral clinic, and reflects the high frequency of QST abnormalities in other studies.[2,13,14] Since QST is a psychosocial measure reliant on patient cooperation, it should be emphasized that abnormal QST alone should not be used to diagnose PN. Abnormal QST results should be interpreted in the context of the neurologic examination and appropriate laboratory testing such as NCS/EMG, skin biopsy and nerve biopsy, highlighted by a subset of our cohort having variable patterns of exam, NCS, and QST results.[2,13]

Since NCS only effectively measures large-fiber peripheral nerve function, there has been interest in the use of QST to determine thermal threshold changes in patients with predominantly small-fiber involvement. Vibration thresholds reflect large myelinated A-β fibers that conduct via the dorsal columns, whereas cold thresholds measure both A-δ (thin myelinated) and C fiber (unmyelinated) function that travel centrally via the spinothalamic tracts.[4,15] Heat-pain is also mediated through A-δ and C fibers, whereas warm stimuli are mediated through C fibers exclusively.

In the current study, cold detection thresholds were most frequently abnormal, followed by vibration thresholds. Heat-pain thresholds demonstrated the lowest rate of abnormality, although control values for this modality were not fully validated at the time of the study. In addition, threshold abnormalities for cold stimuli are more commonly observed than those for heat in a variety of neuropathies including those related to diabetes and alcohol abuse.[16,17] Overall, thermal threshold abnormalities were more common than those for vibration, likely reflecting the predominance of small-fiber abnormalities characteristic of the types of PN enrolled in the study. A large proportion of the cohort had a diagnosis of CSPN, in which small-fiber deficits and neuropathic pain often predominate.

A limitation of the study includes its retrospective design, with data obtained via chart review. This resulted in a minor discrepancy in the number of QST studies recorded (n=559) compared to the total number of patient diagnoses recorded (n=557). This minor difference should not have skewed the data given the large number of QST studies performed. Additionally, there was limited data comparing the QST findings to the clinical exam. Another limitation is the lack of duration the neuropathy had been present; however, the goal of the study was to distinguish forms of neuropathy with QST regardless of the duration the neuropathy was present. We realize that the tertiary nature of the PN clinic at UTSW led to skewed percentages of etiologies on PN. The low numbers of diabetes and alcohol-related PN and large population of CMT, leprosy, CSPN, and CIDP patients do not reflect a more general PN population. In particular, the larger percentage of CSPN patients compared to other studies may be due to greater recognition of etiologies, accessibility of genetic testing, and improved diagnostics for immune-mediated neuropathies. Additionally, patients were diagnosed by several neurologists without defined protocols in place to classify PN etiologies. This may have resulted in variability in the selection of laboratory testing (e.g., serologic and genetic testing) to establish an etiology for the neuropathy. However, all patients were seen by neuromuscular specialists, and QST was widely utilized during the time period of the study.

In conclusion, QST was abnormal in the vast majority of a large cohort of patients with PN encountered over a 5-year period. The utility of QST in routine practice appears limited due to its inability to distinguish between types of neuropathy, and does not meaningfully supplement information gleaned from the neurological examination and routine and more widely-available laboratory studies.

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