Quantitative Sensory Testing in Trigeminal Nerve Damage Assessment

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Evaluating sensory nerve damage is a challenging and often frustrating process. Diagnosis and follow-up is usually based on the patient's history and gross physical evaluation in addition to simple sensory tests such as brushing or pin prick. Based on evidence accumulated from clinical and animal experiments, quantitative sensory testing (QST) has emerged as a useful tool in the assessment of sensory nerve damage. QST has demonstrated diagnostic capabilities in temporomandibular disorders, burning mouth syndrome, oral malignancies, numb chin syndrome, posttraumatic pain, and whiplash injuries, and in elucidating mechanisms of central sensitization. In this article specific clinical uses of QST are described and its clinical applicability is demonstrated. Future studies should be directed at exploring the use of QST in the diagnosis and classification of further nerve pathologies. J OROFAC PAIN 2004;18:339–344

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The medical diagnostic process usually includes the patient's history, physical examination, and often, the use of complementary tests and equipment. These tests may include blood tests, tissue biopsy, and imaging techniques such as radiography, computerized tomography, or magnetic resonance imaging.

The diagnosis of peripheral nerve damage and the accompanying neuropathic pain is both difficult and challenging, in part because there are at present few validated complementary methods. There are no established tests or imaging techniques that provide clinically applicable information regarding the physical or functional status of the nerve and relationship between the nerve and ongoing neuropathic pain. However, pain intensity and frequency can often be accurately followed up with pain diaries and visual analog scales. Moreover, recent studies using brain imaging techniques illustrate central activity related to chronic pain syndromes[1] and neurological examination as nerve conduction tests[2] may eventually lead to methods that are able to measure pain activity.

Until recently, these additional methodologies were not available for the evaluation of nerve function in painful disorders. A growing body of evidence from clinical and animal experiments

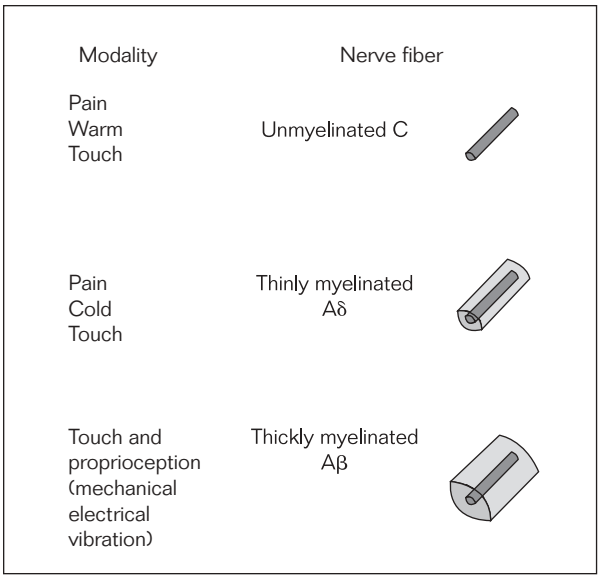

Fig 1 The assessment of primary afferent function is based on tests able to distinguish between large-diameter, thickly myelinated fibers, which normally mediate nonpainful tactile sensations, and small, thinly myelinated Aδ and unmyelinated C-fibers, which normally mediate both painful and nonpainful sensory modalities.

indicates that a group of methods collectively referred to as quantitative sensory testing (QST) may serve as a valuable tool for the evaluation of sensory nerve damage. QST methods are based on the traditional neurological examination of sensory function, psychophysical procedures, and an array of stimulus modalities that assess the functional capacity of primary afferent fibers.

QST has proved to be of high clinical value in various orofacial pathologies, including temporomandibular disorders,[3–5] burning mouth syndrome (BMS),[6–8] oral malignancies,[9] numb chin syndrome, posttraumatic pain, and whiplash injuries.[10] QST can both assess peripheral nerve function in painful conditions and mechanisms of central sensitization.[11] The goal of the present article is to describe specific clinical uses of QST and to illustrate the utility of these procedures.

QST Methods

Based on data from animal and human studies, we may assume that modality-specific and graded assessment QST can help differentiate between large-diameter, thickly myelinated Aβ fibers, thinly myelinated Aδ fibers, and unmyelinated C-fibers (Fig 1).[12–15] Traditionally a careful examination of somatosensory functions using an array of instruments (brush or cotton swab for the sensation of touch, a warm object, a cold object, and a pin for pain) has served as an initial strategy in exploring the sensory functions of a variety of afferent nerve fibers.[16]

Since the distribution of sensory abnormalities may match the damaged nerve's dermatome, the borders of the sensory dysfunction area should be carefully examined using the different modalities. This approach may identify the involved nerves, the type of pain, and the sensory aberration. The finding of pain that extends beyond the border of a dermatome and sensory aberrations indicative of altered central processing is discussed in the following paragraphs.

Tests within the defined area of abnormality provide modality-specific and graded assessment of the threshold for sensory detection and the (usually higher) threshold for pain. In abnormal cases both may be altered, or the sensory detection threshold may be absent, in which case normally painless stimulation evokes pain. The profile of altered sensory and pain thresholds across mechanical and thermal modalities provides information about the type of nerve abnormality and can be supplemented by additional tests that examine pain processing at levels above the pain threshold.[16]

For reliable results, the methods should be designed to be easily repeatable. These procedures should be applied routinely with all patients in the same order. Determination of an abnormality can be made on the basis of comparison to a set of standard control values, although comparison to a contralateral unaffected site in the same patient may be the best approach when available.[17] Common sensory modalities that are recommended for the examination and evaluation of a sensory neuropathy are:

1. Touch, or proprioceptive (mechanical, electrical, and vibratory) stimuli for the assessment of the function of thickly myelinated Aβ fibers
2. Cold detection threshold for the assessment of the function of thinly myelinated Aδ fibers
3. Heat detection threshold for the assessment of the function of thinly unmyelinated fibers.

Methods commonly used to quantify these modalities include the determination of mechanical detection and pain thresholds to both calibrated mono-filaments and to a vibrating probe. Peltier element-based equipment is commonly used for the assessment of 4 different thermal parameters (thresholds to warm and cold stimuli and heat and cold pain). The cold pain threshold is a specific test for cold allodynia, a common finding in

neuropathic pain conditions. Altered heat pain thresholds can reflect either the function of myelinated Aδ fibers or unmyelinated C-fibers, depending on the rate, location, and sequence of stimulation.

Electrical stimulation has produced conflicting and inconsistent results in a range of studies.[18–20] The authors propose reducing the interpatient variability and the inconsistency by expressing the electrical detection thresholds as the ratio between the painful and the contralateral side, ie, using the healthy side as a control for the painful side.[17]

Electrical stimulation has unique properties that are very useful for sensory assessment. Unlike the other methods, which naturally stimulate receptors of primary afferents, electrical stimuli may bypass the receptor to stimulate the axon of the primary afferent. Because of this property, the authors believe that primary afferent neurons activated by electrical stimulation do not show the same temporal profile associated with sensitization, suppression, or fatigue of the receptors. In addition, at the threshold for detection, electrical stimuli exclusively activate the thickly myelinated Aβ fibers. Thus, a comparison of the detection threshold to both mechanical and electrical stimuli can provide a differential method that isolates receptor and postreceptor processes of Aβ fibers. Changes in both or in only electrical detection indicate a postreceptor process, while changes in only the results of mechanical stimulation indicate a receptor process.

Despite the differences between trigeminal and spinal pain mechanisms,[21] evidence related to sensory assessment gathered from animal and clinical studies on spinal nerves can be useful for the clinical diagnosis of orofacial neuropathies. Mechanical nerve damage or total nerve transection is characterized by myelinated and unmyelinated afferent nerve fiber hyposensitivity that clinically can be translated to elevated detection thresholds to heat, electrical, and mechanical stimulation.[22] Partial damage may be followed by either hypo- or hypersensitivity accompanied by ongoing neuropathic pain. Similar findings have been shown in animal models of trigeminal neuropathies.[23,24]

In contrast to the neuropathic process of mechanical nerve damage, specific nociceptive processes may provide a different, identifiable sensory signature. For example, early perineural inflammation produces brief large-myelinated nerve fiber hypersensitivity that is revealed clinically by reduced detection to electrical and mechanical stimuli. This increased detection sensitivity has been demonstrated in clinical and animal spinal nerve models[5,25–28] and reproduced in a model of inflammatory trigeminal nerve neuropathy.[23]

Although the mechanisms are not clear, muscle-induced pain may result in the opposite effect, ie, reduced large-nerve fiber sensitivity reflected by elevated detection thresholds.[3,5] Other psychophysical studies evaluating pain thresholds in the trigeminal nerve territory in patients with orofacial pathologies have demonstrated mechanical hyperesthesia. For example, following injection of hypertonic saline into the masseter muscle, mechanical stimuli applied to the overlying skin induced significant increases in the verbal rating score,[29] and lowered pain thresholds to this type of stimulation have been found in patients with orofacial myofascial pain.[29,30]

In addition to the tests described, a clinical study of nerve injury pain has shown that in the presence of mechanical allodynia, a ratio between the electrical pain and detection thresholds of less than 2.0 may indicate altered central nervous system processing of A-fiber afferent input.[11] Such a result may be a sign of altered central pain modulation and central sensitization.

Combining all of the above procedures into a single methodological approach may provide a clinical decision-making tool with increased diagnostic power. The following clinical examples illustrate various clinical applications of this comprehensive QST approach.

QST and Malignancy

Even though the general concept of malignancy-induced alteration in neural function is widely documented,[31–33] there is no consensus among a number of proposed mechanisms. This article will focus on 2 of the most common explanations: inflammation and frank nerve damage.

Malignant processes produce robust inflammatory responses,[34] and the resultant inflammatory "milieu" may affect afferent nerve function in the adjacent environment. The perineural inflammation may produce neuritis with aberrant neural signals in the nerve's distal end (ie, the target organ), which is found in "benign" nerve trunk neuritis. The effects of mechanical trauma and inflammation have different time courses. In a mouse model of cancer pain, progressive compression of the sciatic nerve by the tumor mass resulted in a gradual development of hypersensitivity in the mouse paw.[35] Significant thermal hypersensitivity was detected only 10 days following the procedure, whereas mechanical allodynia occurred only 4 days following the procedure. The early phase of the process, characterized by the invasion of the

nerve trunk by immune and malignant cells and the resulting neuritis, may correlate with the development of myelinated nerve fiber hypersensitivity. Thermal hypersensitivity is observed only later; thermal hyposensitivity is observed as the malignant process within the nerve evolves with clear evidence of nerve damage. The authors propose 2 malignancy-related neuropathic pains; an early phase linked to an inflammatory process or "malignant neuritis," and a later phase, which is associated with nerve damage. In the clinical setting, sensory changes associated with the first stage of malignancy-induced neuritis may offer a diagnostic window for the early detection of malignant processes.

On the basis of these findings, the authors hypothesized that any oral cancer that produces an inflammatory response would induce sensory changes in relevant orofacial dermatomes (the innervation territory of the affected nerve). To test this, 23 patients were referred to the authors for the evaluation of oral lesions.[9] Large myelinated nerve fiber detection thresholds were assessed using electrical current tests applied bilaterally to regions innervated by the 3 main branches of the trigeminal nerve. Electrical detection threshold ratios between the affected and unaffected side were contrasted to the results of physical examination, radiographic imaging, and biopsy. Biopsy showed that the lesions in 10 of 12 patients with asymmetrical thresholds were malignant (2 cases gave false-positive results). Furthermore, the electrical detection threshold in the affected nerve was lowered by 20% or more compared to the contralateral side in all cases in which malignancy was confirmed by biopsy. No malignancy was found in the remaining 11 patients. In contrast, the detection thresholds for nerves in the territories of benign lesions were not different from those on the contralateral side. The side-to-side electrical detection ratio for nerves that were near but not directly affected by the lesions was reduced by at least 20% for 5 of the 10 malignant lesions, suggesting a possible extraterritorial effect due to central sensitization.[25,36]

These results suggest that quantifying Aβ afferent hypersensitivity may serve as a sensitive and specific indicator of soft tissue malignancy located along the passage of the nerve and that this method may aid in early detection of malignancies. Further QST studies should be aimed at characterizing the sensory changes accompanying different types of malignancies and the late malignancy phase when frank axonal damage is present.

QST and Central Processing In Relation to Nerve Damage and BMS

Nerve damage and neuropathic pain are often associated with measurable extraterritorial and contralateral (mirrorlike) hyper- or hyposensitivity.[25,36–41] These sensory changes are not frequently used as diagnostic tools in the evaluation of nerve damage. However, increasing evidence from thorough sensory assessment and carefully designed studies indicates that QST may be useful in the assessment of nerve damage and central processing of neuropathic pain.

A recent study examined the use of electrical stimulation for detection of mechanical allodynia.[11] In skin unaffected by allodynia, a ratio between the pain and detection thresholds of less than 2.0 is uncommon. In the presence of mechanical allodynia, a pain threshold detection threshold ratio of less than 2.0 may indicate altered central nervous system processing of Aβ afferent input and its contribution to allodynia. This suggests that electrical stimulation can be used to identify 2 distinct mechanisms. As stated earlier, reduced electrical or mechanical detection thresholds characterize allodynia originating from perineural inflammation, while centrally mediated allodynia is characterized by a reduced pain: detection threshold ratio. A simple test may direct treatment; for example, the administration of anti-inflammatory drugs in the former, central analgesics in the latter.

BMS is a putative centrally mediated pain that is poorly understood and treated. Patients are diagnosed as suffering from BMS only when the burning sensation is not associated with a clear pathology (local or systemic). In contrast, burning mouth symptoms are diagnosed in the presence of a known etiology for the altered sensation. BMS, an intraoral disorder most prevalent in postmenopausal women,[6,7,42] is characterized by a burning mucosal pain without major visible physical signs. Altered taste sensations have long been associated with BMS, and nearly 70% of the patients complain of accompanying dysgeusia (altered taste sensation).[42]

The application of QST in BMS patients has helped researchers identify defects in pain tolerance, altered chemosensory function, increased pain threshold to laser stimulation, and hypoesthesia related to the sensory function of large and small nerve fibers.[2,6–8,43] Accumulating evidence suggests that BMS may involve central and peripheral nervous system pathologies induced by damage to the taste system at the level of the chorda tympani nerve. This damage results in reduced

Table 1 Electrical and Mechanical QST: Suggested Interpretations

Test	Results	Interpretation
Electrical detection threshold	Elevated	Nerve damage; late-stage malignancy
	Reduced	Perineural inflammation; early-stage malignancy
Ratio of electrical pain threshold to electrical detection threshold	> 2	Normal
	< 2	In the presence of allodynia may be related to central sensitization
Ratio of tongue electrical taste detection threshold to tongue electrical itch detection threshold	> 1	Burning mouth syndrome
	< 1	Burning mouth symptom, normal
Mechanical detection threshold	Elevated	In the presence of temporomandibular disorders may be related to pain originating in the muscles
Mechanical pain threshold	Reduced	Pain originating in the muscles

trigeminal inhibition that in turn leads to an intensified response to oral irritants and eventually to oral phantom pain (ie, BMS).[44]

Electrical stimulation of the tongue can provoke 2 different sensations. One is described as an itch or tingling, and the other as an electrical taste.[45,46] In the authors' experience, electrical taste threshold in the tongue is easily recognized as a sensation usually described as a "batterylike" or sour taste. It is hypothesized that the taste sensation is conducted via the chorda tympani nerve and the itch sensation via the lingual nerve. Therefore, electrical detection thresholds of the anterior two thirds of the tongue may distinguish between the chorda tympani and lingual nerve functions.

To test this hypothesis, electrical taste and detection thresholds in patients diagnosed with BMS, patients diagnosed with burning mouth symptoms, and asymptomatic patients were compared. Forty-seven subjects were included in the study (38 female and 9 male), 23 suffering from BMS, 14 from burning mouth symptoms, and 10 healthy volunteers. Electrical detection thresholds were assessed from the mental and infraorbital nerve territories as extraoral control sites. No significant differences in electrical detection thresholds, determined at the extraoral nerve territories, were found between or within the groups. In the control and the burning-mouth symptom patients, the ratio between the electrical taste and the itch sensation on the tongue was less than 0.7 (mean ratio ± SEM 0.69 ± 0.13 for the burning-mouth symptom group and 0.59 ± 0.12 for the control group). The ratio of the electrical taste and electrical itch detection thresholds in the BMS patients was 1.39 ± 0.16, significantly higher than the burning-mouth symptom patients and the controls (P = .009 and P = .03, respectively). Typically the electrical taste threshold is lower than the electrical itch detection threshold. However, in the BMS patients, the electrical taste detection threshold was elevated above the itch threshold, suggesting chorda tympani nerve hypofunction. This result is consistent with the hypothesis that BMS is an oral phantom-type pain induced by damage to the taste system.[44] The ratio of electrical taste and itch detection thresholds may be a useful diagnostic test for BMS.

Conclusions

Quantitative sensory assessment provides a systematic analysis of sensory nerve function. The information obtained by such testing can aid diagnosis and provide accurate follow-up, as outlined in Table 1. However, further studies on various pathologies, pain conditions with either peripheral or central alterations, pain intensity, QST assessment over time, and a parallel improvement in methodology are essential to validate and establish the diagnostic value of QST for neuropathic trigeminal pain.

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