Overview on Tools and Methods to Assess Neuropathic Trigeminal Pain

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This article provides a brief overview of the tools and methods that may be useful to assess neuropathic trigeminal pain. Pain is a complex multidimensional and biopsychosocial experience. While the assessment of neuropathic trigeminal pain is complex, there are several meaningful ways available for the systematic assessment of neuropathic pain and its effects and manifestations. The key to such an analysis is a standardized pain history and examination and a good knowledge of pain mechanisms. Patients can be asked to provide detailed information about their spontaneous pain (ie, stimulus-independent pain), eg, quality, intensity, localization, time course, and modifying factors. Stimulus-dependent pain components can be characterized with clinical examination procedures and quantitative psychophysical techniques such as application of mechanical, thermal, chemical, and electrical stimuli. The description of the stimulus-dependent pain is important to reveal the function of the somatosensory system and to map the extent of hyperalgesia, hyperesthesia and allodynia, because the normal relationship between stimulus intensity and perceived intensity is distorted in many neuropathic pain conditions. In addition to the psychophysical techniques, a number of laboratory tests for assessment of trigeminal pain have been developed and tested, although critical information on sensitivity, specificity, and predictive values is still scarce. There is also a need for common guidelines on classification, diagnostic procedures, and management. This will require concerted international, interdisciplinary action. J OROFAC PAIN 2004;18:332–338

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Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[1] While this definition clearly has merit, it is currently also a subject of much discussion.[2] The "primary lesion" is not defined but implies definite and distinct categories of pain conditions with damage to somatosensory pathways, eg, to small fibers in the peripheral nerves or to the trigemino-thalamo-cortical pathways (for example, traumatic injuries to nerves during orthognathic surgery or removal of lower third molars, trigeminal neuralgia, brainstem infarction). However, it has been suggested that the term "dysfunction" in the current definition could apply to many more conditions that neurologists and neuroscientists traditionally do not consider neuropathic pain conditions (eg, atypical odontalgia, temporomandibular disorders, fibromyalgia, tension-type headache). Some of these conditions may in fact share similar "dysfunctional" pathological mechanisms involving peripheral

and/or central sensitization or imbalances between endogenous inhibitory and excitatory pain pathways,[3–6] but whether such conditions should be considered neuropathic types of pain is controversial.[7] The European Federation of Neurological Societies (EFNS) recently recommended the use of the more limited term "lesion" but also suggested that comparative studies should be undertaken to clarify differences between the "lesion" and "dysfunction" definitions.[2]

While the discussion of classification and the implication for assessment have already been initiated for the neuropathic pain conditions in general, they are still in their infancy with regard to neuropathic trigeminal pain. The key to the assessment of any type of pain, including neuropathic trigeminal pain, is a systematic pain analysis. Such an analysis includes a careful description of spontaneous (stimulus-independent) pain and stimulus-evoked pain. In addition, various laboratory measures, which will be described, can be used.

Spontaneous Pain

A good history-taking and examination of pain patients is a challenging and time-consuming but essential task. The reader is referred to textbooks on orofacial pain for comprehensive descriptions.[8,9] Here we will focus on some important aspects of spontaneous pain.[6,10] Patients may describe their spontaneous pains in a variety of ways. It is therefore crucial to obtain systematic information regarding quality, intensity, spatial and temporal aspects, and modifying factors.

Quality

Patients with neuropathic pain may complain of "unpleasant," "pricking," "sticking," or "shooting" sensations in parts of the face or oral cavity. They may also report "burning," "scalding," "aching," or "deep sore" pain.[10] For a comparison, toothache is often described as "sharp" or "shooting" and may in the acute stages mimic trigeminal neuralgia, for example. It is clear that "pain words" can assist in the differential diagnosis of neuropathic pain, but also that the words are not unique or entirely specific to only 1 pain condition.[11] Questionnaires such as the McGill Pain Questionnaire (MPQ)[12] can be used to standardize verbal descriptions. The MPQ is available in many different languages; however, it was not specifically developed for the assessment of neuropathic pain.[6] The MPQ has the potential to be a multidimensional pain assessment tool, since both sensory-discriminative and affective components of pain can be calculated as indices depending on the words used to describe the pain.

Intensity

Assessment of the intensity of the pain is also important to attain an understanding of the pain complaint. The most frequently used method is to ask the patient to place a mark on a 10-cm line with 0 labeled as "no pain" and 10 as "most pain imaginable." This visual analog scale (VAS) has been tested and, although very simple, can be considered the "gold standard" of pain assessment.[13] Numerous research reports have confirmed that it is a valid and sensitive technique for describing both the intensity and unpleasantness of pain.[14] For neuropathic pain conditions, both continuous and paroxysmal pain should be assessed. For some trigeminal pain conditions, especially those that are persistent, the pain can best be described by VAS assessments of different temporal aspects of the pain; for example, "how much pain right now," "how much pain during the last month," and "how much pain when it was worst."[15] These measures allow the characteristic pain intensity to be determined.[12] For neuropathic trigeminal pain conditions, it may also be useful to assess dysesthesia or paresthesia (eg, sensation of burning, needles and pins, electric shocks) on a similar 0-to-10 VAS. There are many other related pain rating scales, for example "0-1-2-3-4-5-6-7-8-9-10" (numeric rating scale), "no – mild – moderate – severe – unbearable" (categorical) or combinations of various rating scales.[13] The EFNS recommends rating the intensity and unpleasantness of neuropathic pain separately and obtaining ratings of all the different pain components that the patient may report.[2] The simplest scales are probably the best, and VAS or numerical rating scales appear to be good choices.[2] Similar guidelines need also to be established for the assessment of neuropathic trigeminal pain.

Spatial Aspects

The localization of the spontaneous pain is of course of immense importance, but it can be quite difficult for the patient to describe the exact location of the pain. In the clinic, it is useful to have the patient point to the painful area and then to ask the patient to draw a "pain map"—the distribution of pain on an anatomical map of the body.[6] For neuropathic pain patients, these maps can be

extended by somatosensory maps, ie, maps showing areas with increased or decreased sensitivity to various test stimuli (eg, mechanical or thermal stimuli).[10] The areas of the drawings or of "tattoos" on the skin can subsequently be measured, and changes over time can be established and quantified (eg, any changes in pain in response to treatment).[2] There is still a need to define the best ways to map the pain and somatosensory changes in the oral cavity.

Temporal Aspects

Neuropathic pain can, as mentioned previously, be both continuous and paroxysmal. Paroxysms normally last seconds but can be repeated with ultrashort intervals, thereby giving a false impression of continuous types of pains.[10] The MPQ also includes a description of the temporal aspects of the pain complaint.

Furthermore, the onset and duration of pain will be important for assessment. For example, was there a sudden onset (from trauma or dental treatment), or did pain gradually develop with no precipitating cause? In order to establish that the pain is neuropathic, there needs to be a relevant trauma or injury to the nervous system prior to the onset of pain.[10] There is often a description of loss of sensation before the onset of the pain, but the time delay can vary greatly (up to several months).

Modifying Factors

It is important to have a checklist to assess which orofacial functions are influenced by pain (eg, chewing, talking, yawning, swallowing) and to what extent these functions trigger painful sensations that interfere with the functional capacity. The Research Diagnostic Criteria for Temporomandibular Disorders includes such checklists, which appear to provide clinically useful information for musculoskeletal pain conditions,[15] but there may be a need to establish similar checklists for other trigeminal pain conditions.

Stress and psychological factors (eg, anger, depression, and anxiety) may also be clearly associated with pain, and several reliable and validated scales are available for assessment, for example the Beck Depression Scale, Hospital Anxiety and Depression Scale, State-Trait Anxiety Inventory, and Symptom Checklist-90, which are described in the literature on pain assessment.[2,10,15] Furthermore, pain can be associated with sleep problems, so assessment of sleep quality (eg, on a VAS or numeric rating scale) is recommended by the EFNS.[2] Pain will often impinge significantly on the patient's quality of life, and repeated measures of oral health–related quality of life may be important indicators of reduction of neuropathic trigeminal pain. The usefulness of the existing checklists and questionnaires for assessment of functional capacity, mood, sleep, and quality of life should be evaluated for neuropathic trigeminal pain conditions.

Stimulus-Dependent Pain

Many neuropathic trigeminal pain conditions have both a spontaneous component and a stimulus-dependent component, and there may be both sensory deficits (hypoesthesia or hypoalgesia) and hyperphenomena (hyperalgesia or allodynia). Hyperalgesia (the lowering of pain threshold and an increased response to noxious stimuli) and allodynia (the evocation of pain by nonnoxious stimuli) are typical elements of neuropathic pain. Three types of mechanical hyperalgesia can be distinguished[10]:

- Static hyperalgesia: Gentle pressure on the skin evokes pain.
- Punctate hyperalgesia: Punctate stimuli such as pinpricks evoke pain.
- Dynamic hyperalgesia: A light brush evokes pain.

Both cold and heat can evoke thermal hyperalgesia. The mechanism underlying cold hyperalgesia is still unclear, but cortical reorganization with central sensitization or central disinhibition due to loss of cold Aδ fibers has been suggested.[10,16] Sensitization of C-nociceptors eventually leading to a corresponding sensitization of second-order neurons has been suggested as the underlying mechanism for heat hyperalgesia.[10,16]

In the clinic, the mechanical sensitivity can be tested by a cotton swab or with special calibrated nylon filaments (von Frey filaments) applied to the facial skin or oral mucosa, which allow a quantitative assessment of Aβ fibers (Fig 1). Punctate sensations (ie, pinpricks) can be tested by a blunt needle or toothpick and will mainly assess Aδ fiber function. Thermal sensitivity can be examined by applying cooled or heated metal objects to the painful area. Cold stimuli are normally considered to test Aδ fiber function, whereas warmth stimuli reflect C-fiber function.[2,17] A convenient technique is to use as stimuli objects with temperatures that can be controlled accurately, for example, aluminum bars or thermorollers kept in the refrigerator or in a

heated bath with a preset temperature. The magnitude of the subjective responses can then be graded on a VAS or numeric rating scale. The contralateral side (ie, the nonpainful side) is usually used as a control in clinical assessment. Testing this side can help determine whether the mechanical or thermal sensitivity of the painful side is increased, decreased, or normal, but such testing does not determine the magnitude of a change. It is possible to map the areas that respond differently to mechanical and thermal stimuli as compared with normal, nonpainful areas, ie, to construct somatosensory maps.

In the laboratory, more elaborate quantitative sensory testing (QST) can be performed if the clinical examination has indicated changes in the somatosensory sensitivity.[17–19] Figure 2 shows an example of an extensive map of mechanical sensitivity in the infraorbital region and the effect of anesthetic blocks of the infraorbital nerve 30 minutes and 60 minutes following injection. Such maps indicate that both temporal and spatial aspects of trigeminal sensitivity can be reliably assessed in the laboratory.

Laboratory studies have also used radiant heat (laser stimuli) and sophisticated thermotest systems for quantitative assessment of sensory and pain thresholds to warm and cold stimuli, but such systems are expensive and sensitive to technical parameters and factors.[19] Both laser stimuli and contact-thermal stimuli can be applied intraorally, but more research and guidelines are needed.

Finally, chemical stimuli can be used in the laboratory to further assess aspects of nociceptive processing. For example, capsaicin (the burning ingredient in hot chili peppers) and menthol (the cooling agent often used in chewing gum) bind to specific receptors (TRPV1 and TRPM8) and are intimately involved in nociceptive processing.[20] These algogenic chemicals can be used in research laboratories[21] to investigate primary and secondary hyperalgesia, and in clinical studies as pain-provoking stimuli to determine the responsiveness of the patient. For example, researchers can use them to determine the degree of surviving sensitized C nociceptors as opposed to the degree of deafferentation.[10]

These various psychophysical techniques have not yet been critically assessed in terms of diagnostic sensitivity, specificity, or predictive values. However, studies on somatosensory sensitivity in the trigeminal region have reported acceptable to good test-retest variability (with coefficients of variation around 20%), whereas the interindividual variability is larger (with coefficients of variation of up to 50%).[22] A recent comprehensive review concluded that the results of QST are highly dependent on methodology, but also reasonably reproducible over days and weeks in normal subjects. However, the current literature does not allow firm conclusions on the clinical value of individual QST techniques.[19]

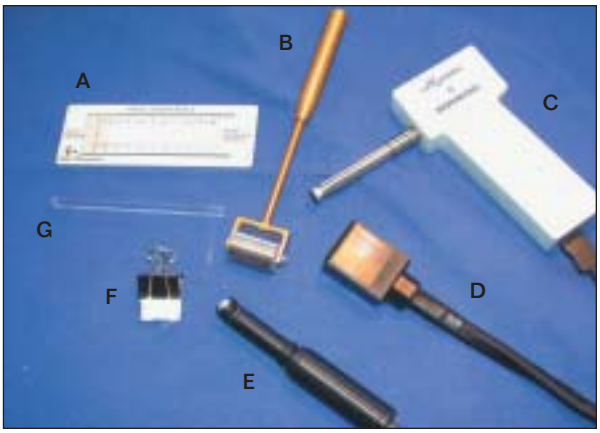

Fig 1 Tools which can be used for quantitative assessment of somatosensory function in the trigeminal region. A = visual analog scale, B = thermoroller, C = pressure algometer, D = thermotester for extraoral application, E = thermotester for intraoral application, F = cotton swab, G = von Frey nylon filament.

A characteristic and, in some cases, a central feature in many patients with neuropathic pain is, paradoxically, increased cold or heat detection thresholds simultaneous with reduced pain thresholds to the same stimuli.[7] Such response patterns reflect both a loss of afferent fibers or disturbance of central pathways and a sensitization of peripheral receptors or central neurons along the somatosensory pathway. There is a need to establish guidelines for which sensory tests should be included in the diagnostic procedures for neuropathic trigeminal pain.

Neuropathic Pain Questionnaires

A number of different scales and questionnaires (eg, Symptom Score Scale, Neuropathic Pain Scale, Leeds Assessment of Neuropathic Symptoms and Signs [LANSS]) have been specifically designed for assessment of neuropathic pain.[2] For example, LANSS has been shown to be able to discriminate neuropathic pain from nociceptive pain,[23] and similar studies will be necessary to differentiate trigeminal pain conditions. Recently, a new Neuropathic Pain Symptom Inventory has been developed and tested on the basis of 10 descriptors

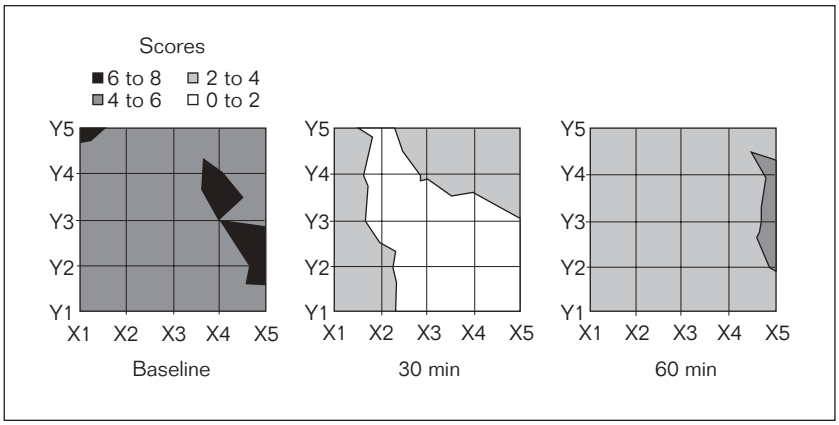

Fig 2 Assessment of mechanical sensitivity of the facial skin in a grid of 5 × 5 cm covering the infraorbital region. Each grid was stimulated with a von Frey filament (no. 7) 3 times, and each time the subject gave a rating on a 0-to-100 scale where 0 = no sensation at all, 50 = just barely painful, and 100 = most pain imaginable. The figures show the mean scores of 16 healthy subjects at baseline 30 minutes following a local anesthetic block of the infraorbital nerve and 60 minutes after the block. The very low scores clearly indicate a non-painful and barely detectable sensation evoked by this filament. The spatial and temporal changes (hypoesthesia) can be traced. (Thygesen et al, unpublished observations).

of different symptoms (burning, pins and needles, tingling, electric shocks, stabbing, pressure, squeezing, evoked by brushing, pressure, and cold stimuli) and 2 items for duration of spontaneous and paroxysmal pain.[24] Thus, there is growing evidence of the ability to systematically assess and differentiate neuropathic pain conditions from other painful conditions. However, further validation is needed and similar scales and questionnaires must be tested for neuropathic trigeminal pain conditions.

Laboratory Tests of Orofacial Pain

Since pain is more than a simple sensation, some biological markers and associated physiologic and behavioral responses can also be used as additional measures of the processing and consequences of pain. In some circumstances, these adjunctive approaches may be useful in the assessment of neuropathic trigeminal pain.

Trigeminal reflexes (eg, blink reflexes and exteroceptive suppression periods) have been suggested as objective measures or correlates of orofacial pain.[18] This is primarily based on the finding that there is a correlation between the amplitude of reflex response and intensity of the stimulus in animals (eg, jaw-opening reflex) and in humans (eg, nociceptive limb withdrawal reflex). It has also been reported that pain can influence trigeminal reflex activity. For example, experimental capsaicin-evoked skin pain in combination with tactile stimuli shortens the duration of the silent period in the masseter muscle evoked by electrical stimulation of orofacial tissues.[25] These findings indicate a connection between trigeminal reflex circuits and nociceptive pathways, but the general use of trigeminal reflex recordings for assessment of neuropathic trigeminal pain is not warranted at present since the necessary sensitivity, specificity, or prognostic value of this approach has not been established. Recordings of trigeminal reflexes may, however, be indicated if lesions of the reflex pathways (eg, stroke or degenerative diseases in the brainstem) are suspected and need to be ruled out.

Microneurography is a minimally invasive but technically demanding method that allows single-fiber recording from nerve fibers, including trigeminal nerves, in awake subjects. The physiologic characteristics of several different classes of nociceptive C-fibers have been identified using this method. Microneurography has provided important information on nociceptive mechanisms; however, this technique is far too time-consuming and difficult to be used in standard clinical settings.

The integrity of the ascending somatosensory systems has traditionally been tested with the use of electrically evoked somatosensory potentials recorded with electrodes placed on the scalp.

Studies in humans have documented that evoked potentials can also be elicited by laser stimulation of the trigeminal region.[25,26] Laser-evoked potentials appear to be a relatively easy and reliable neurophysiologic method to assess the function of the nociceptive pathways. This method is recommended by the EFNS in the study of peripheral and central neuropathic pain conditions.[2] However, the sensitivity, specificity, and predictive values have not been described for laser-evoked potentials, and the clinical utility so far is limited because the technique is available in relatively few centers.

Functional magnetic resonance imaging (fMRI), multi-channel electroencephalography, and magnetoelectroencephalography can be used in the research laboratory to assess changes in the neuronal activity of the cortex that are related to the processing of pain. Positron emission tomography (PET) is another sophisticated imaging technique that shows the patterns of neuronal activity of the living human brain while it is processing painful stimuli.[2] As these techniques are developed and the spatial resolution is enhanced, the nociceptive pathways in the brainstem may also be imaged better. PET images have also illustrated networks in the brain related to capsaicin-evoked pain and neuropathic pain.[27] At the moment, however, the clinical utility of these brain-imaging techniques is limited, and so far it is not possible to use a PET or fMRI scan to establish the precise location or type of nociceptive activity. Further studies on patients with neuropathic pain are warranted.

Autonomic parameters such as heart rate, blood pressure, sweat secretion, and temperature are also coupled to pain.[6,9] Measurement of these signs can be useful when severe autonomic dysfunction is part of the pain complaint (eg, as in complex regional pain syndromes) but have rarely been used in relation to neuropathic trigeminal pain. The general problem with many measures of autonomic function in relation to pain is that they are not specific to pain and may also change during other emotional reactions (anger, fear, aggression). Furthermore, the responses tend to habituate, ie, become smaller over time.

Finally, pharmacologic treatment also can be viewed as a laboratory tool to assess neuropathic pain.[10] Drugs with specific targets for their mode of action (eg, tricyclic antidepressants sodium channel blockers such as carbamazepine and lamotrigine, gabapentin, opioids, N-methyl-D-aspartate [NMDA] channel blockers) have been designed and tried for different pain conditions, including neuropathic pain.[28,29] From an assessment point of view, previous studies have shown that such drugs may have an action not only on pain intensity but also on specific types of pain, such as stimulus-dependent pains. Studies have shown that in patients with neuropathic pain due to nerve injury and limb amputation, NMDA receptor antagonists can block both spontaneous pain and evoked pain produced by tactile stimuli (allodynia), which indicates that these phenomena are probably produced by the same mechanism, ie, a central sensitization mediated by excess activity at NMDA receptor channels.[10] An additional example of the potential value of pharmacologic treatment as a laboratory tool could be the combined blockade by sodium channel–blocking agents and NMDA receptor–blocking drugs, suggesting that at least 2 different mechanisms may operate in concert.[10]

The introduction of number-needed-to-treat values has made it possible to compare the effects of a particular drug with a specified set of actions on different pain conditions.[29] This would indirectly allow one to determine the possible pain mechanisms involved in certain types of neuropathic pains. The same principle can also be applied to the use of different drugs on the same pathologic condition to determine whether distinct or identical mechanisms may be in operation. However, this principle has not yet been systematically applied, partly because rather crude measures are often used for quantification of efficacy in chronic pain, eg, global pain intensity or global pain relief. Studies using pharmacologic trials to assess the effect of various drugs on neuropathic trigeminal pain should be encouraged in order to obtain more information on pain mechanisms and to establish guidelines for pain management.

Conclusions

Assessment of neuropathic trigeminal pain involves a series of systematic steps, including cataloguing the patient's past and present history of pain; a detailed description of the intensity, quality, and spatial and temporal characteristics of the pain; and a neurologic examination with emphasis on sensory testing. The sensory examination may need to be supplemented by QST and eventually neurophysiologic tests. It has now become clear that neuroplastic changes in the nervous system play a significant role in development and maintenance of chronic neuropathic pain, with interaction between peripheral and central mechanisms. There is still a big gap between our preclinical

knowledge about pain mechanisms and the clinical translation of such mechanisms into daily clinical practice.[16,30] Lack of standardized criteria for pain assessment and lack of internationally accepted guidelines for examination of patients with neuropathic trigeminal pain contribute to the difficulties in closing this gap. A better understanding of neuropathic pain mechanisms and their clinical manifestations in the trigeminal region is a prerequisite for designing a rationally based treatment. An important step would be to establish a task force to set up such guidelines for classification, assessment, and management of neuropathic trigeminal pain. One suggestion is that the IASP Special Interest Group on Orofacial Pain could play an active role in this obviously difficult but necessary process.

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