Clinical presentation and diagnosis of neuropathic pain
Quadro clínico e diagnóstico da dor neuropática
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ABSTRACT

BACKGROUND AND OBJECTIVES: Neuropathic pain is reason for distress and incapacity of several patients, being that symptoms, mechanisms and management distinguish it from nociceptive pain. This study aimed at discussing the clinical presentation and diagnosis of neuropathic pain.

CONTENTS: Neuropathic pain is manifested by several symptoms, being continuous burning pain, shock sensation and mechanical allodynia the most common ones. Neurophysiologic studies and skin biopsy suggest that burning pain is reflex of spontaneous activity of affrent nociceptive fibers, while shock sensation is originated from high frequency ectopic stimuli, generated in demyelinated Aβ fibers. Clinical exam, made up of history and elementary physical neurological evaluation, is critical for the adequate diagnosis of the type of pain, as well as more detailed exams, such as quantitative sensory tests and confocal optic microscopy, may bring further subsidies to the diagnosis of the type of pain.

CONCLUSION: Clinical presentation of neuropathic pain has characteristics which help the accurate diagnosis of the syndrome or disease responsible for the onset of the complaint. Adequate clinical evaluation, including directed physical neurologic exam, sensory quantitative tests and cornea confocal microscopy cooperate for a more accurate diagnosis.

Keywords: Clinical presentation, Diagnosis, Neuropathic pain.

INTRODUCTION

Neuropathic pain (NP) is reason for distress and incapacity for many patients, being a public health problem. So, all physicians should know how to diagnose it. Its symptoms, mechanisms and management make it different from nociceptive pain, reason why its accurate diagnosis is important for the institution of adequate management. This study aimed at discussing NP clinical presentation as well as clinical exams. Sensory quantitative test and corneal confocal optic microscopy will be briefly addressed. The discussion of other diagnostic methods, including electrophysiologic studies and the use of standardized questionnaires are covered by other sections of this publication.

CONCEPT OF NEUROPATHIC PAIN

Pain induced by injury or disease affecting afferent somatosensory pathways, manifested through different symptoms, being the most common continuous burning pain, pain in electric shock and mechanical allodynia.

ELEMENTARY NEUROPATHIC PAIN NEUROANATOMY

Poorly myelinated Aδ fibers and unmyelinated C fibers, which are commonly called small fibers, make up a heterogeneous population with different functions and subtypes. Some of these fibers have autonomic functions, such as sweating and blood pressure regulation and, additionally, they transport sensations such as temperature, pain, itching or touch. Small fibers cell bodies are located in dorsal root ganglia and their fibers end as nociceptors in the epidermis.

Small fibers neuropathy, which courses with burning pain affecting toes and soles of the feet, is normally very severe and is followed by paresthesias and dysesthesias. The reason for small fibers pain is still not completely understood and the most probable hypothesis is a decrease in the number of peripheral nociceptors and also the fact that remaining small fibers are more susceptible to the influence of their medium, such as increased painful and pro-inflammatory cytokines.

Nociceptive peripheral afferences carried by first order neurons enter spinal cord dorsal horn. Gelatinous substance, consisting of laminae I and II, receive messages from myelinated Aδ fibers and unmyelinated C fibers (especially the latter). Lamina II interneurons and deeper laminae (III to V) receive impulses carried by larger Aβ-type myelinated fibers, which in normal situations do not transmit painful impulses. Primary afferent neuron terminals relieve excitatory neurotransmitters, such as glutamate and P substance and the calcitonin genetically related peptide (CGRP), to activate second order neurons in spinal cord dorsal horn.

Laminae I and V neurons are projected along spinothalamic and segmental thalamic reticulum pathways and are sent to supraspinal structures, such as brainstem, thalamus, somatonsensory cortex, insular cortex and anterior superior cortex. Integrative studies show strong evidences that NP is largely a consequence of persistent plastic changes along somatosensory pathways.

After traveling through the spinal cord, nociceptive information reaches suprasegmental nervous structures in bulb, midbrain and diencephalon with which they may synapse or end there. Among such structures there are thalamus reticular formation, hypothalamus, limbic system and brain cortex. The role of these supraspinal systems in pain pathophysiology is not clearly known. Probably different regions are involved in sensory and affective understanding of the painful phenomenon.

Encephalic responses to nociception may be more easily understood than allodynia, for example. Allodynia is a severe pain induced by normally painless stimuli, such as touch or thermal stimuli experienced by NP.

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REVIEW ARTICLE
NP is manifested by several symptoms, being the most common burning sensation, generated in unmyelinated Aβ fibers. Shock sensation is presumably originated from ectopic high frequency of the spontaneous activity of afferent nociceptive fibers, while electric afferent fibers known that harmless stimuli may induce pain by stimulating sensitized fibers. NP may be classified as spontaneous (burning and pressing) or provoked (tugging and shock) by means of skin brushing, by pressure and by thermal stimuli, such as cold. Hyperalgesia, increased response to a normally painful stimulus, may be frequently observed. NP patients also complain of paresthesia and dysesthesia such as tingling, tugging and pricking. A simple questionnaire filled by patients or by the examiner may be used to call the attention of the physician to the need for a careful evaluation of NP patients. This subject, as already described, will be deeply addressed in another text of this same publication.

Table 1. Sensory changes found in neuropathic pain patients

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<thead>
<tr>
<th>Quantitative</th>
<th>Qualitative</th>
<th>Spatial</th>
<th>Temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoesthesia</td>
<td>Alldynia</td>
<td>Poor location</td>
<td>Abnormal latency</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>Paresthesia</td>
<td>Abnormal irradiation</td>
<td>After stimulation</td>
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<tr>
<td>Hypoalgesia</td>
<td>Dysesthesia</td>
<td>Summation</td>
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<tr>
<td>Hyperalgesia</td>
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OBJECTIVE AND GENERAL PRINCIPLES OF THE EVALUATION OF PAINFUL PATIENTS

Objectives of painful patients evaluation are: to identify pain pathophysiologic type, whether nociceptive, neuropathic or mixed, or none of them; to diagnose the disease or the event inducing pain; and to recognize functional limitation, possible associated comorbidities and other relevant aspects. The final objective of the evaluation is to better plan patients’ care and management.

Clinical exam

It is important that patients describe their painful experience they way they understand it and self-report should be encouraged. History should gather data on location, temporal profile, intensity, improvement or worsening factors and simultaneous symptoms. One should ask about previous medical history, identify the presence of past and current diseases, previous surgeries, previous treatments for pain control and the results of such interventions. It is interesting to document the functional history, such as interference of symptoms on mobility, daily activities, interpersonal relations, as well as on sleep and mood.

Anamnesis

One should first listen to patients’ history, avoiding interferences and encouraging them to describe their complaints and their understanding about causal factors of their pain.

After this first approach, one should specifically ask about signs and symptoms indicative of NP, taking into consideration that patients may not value or may over-value factors which are more or less important, depending on their point of view. Professionals should ask objective questions, according to their knowledge, to get answers for the diagnosis of pain pathophysiology, anatomy, classification and etiology, always considering that NP most of the times has late onset with regard to its cause. So, the difficulty in evidencing a physical-organic justification for the presence of pain does not mean that pain does not exist.

Physical evaluation

Sometimes there might be discrepancy between patients’ complaint and physical evaluation findings being necessary in some cases to repeat the tests. For a general evaluation, painful area is inspected and palpated. A thorough evaluation of cranial nerves, of motor function, of tendon reflexes, of muscle tone, of walking pattern and balance is carried out in sequence.

Sensory evaluation is the most important part of physical evaluation in case of suspicion of NP. As part of minimum recommended neurological exams, one should smoothly apply a cotton ball on the skin (tactile sensitivity), apply stimuli with sharp materials such as needles (painful sensitivity), thermal sensation by means of warm or cold objects (thermal sensitivity) and 128Hz vibrations sensation by means of diapason. It is important to compare the side affected by pain to the same contralateral area when pain is unilateral and when pain is bilateral, comparison evaluation should be proximal and distal to pain.

The relationship between stimulus and perception may change quantitatively (hypo or hyper-phenomenon), qualitatively, spatially and temporally. Sensory losses should be specified with regard to involved sensory submodalities, such as tactile, painful and thermal. As example, allodynia evaluated with light pressure movements in a single point, harmless warm and cold to stimulate the injured area. The extension of body area affected by sensory changes should be always documented.

Sensory quantitative tests

Added to other ways to evaluate pain, sensory quantitative tests (SQT) may be extremely useful. These are noninvasive psychophysiologic tests to evaluate responses to a series of painful and painless stimuli. Differently from what happens with skin biopsy tests and with corneal confocal microscopy studies, their results express functional changes rather than possible anatomic injuries associated to them. SQTs go beyond neurological physical evaluation which traditionally evaluates somatosensory function. They provide a more precise evaluation of somatosensory changes in areas with changes determined by the sensory test. An expressive number of studies evaluating procedures which allow the evaluation of any aspect of a certain sensory function has been already published, all of them directly based on patient’s sensory experience report.

Although potentially useful for NP diagnosis, the method has several limitations, being two of them of major practical importance. The first is the fact that there is no consensus or standardization of procedures, so any aspect of the sensory function may be evaluated by different ways. So, two measures of the same sensory function using the same tool in the same patient may result in different values due to variations on used parameters. The second limitation is the time needed for the application of the methods, which in general goes beyond the time reserved by the physician for a routine consultation. In general, the test demands at least one hour to be applied, reason why there are proposals of standardized protocols with a limited number of tests. Limitations are described in table 2.

Methods

In the last decades, the method made up of increasing and decreasing intensity stimuli has been enhanced. Patients respond to stimuli by pressing a button or informing verbally the physician when the stimulus is perceived or when it disappears. So, with serial application of stimuli, patients’ threshold for a certain stimulus is determined. Stimuli may be continuously applied, which is called limit methods, or by means of a se-
Table 3. Limitations of the quantitative sensory test (QST)\(^{11}\)

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Implications</th>
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<tr>
<td>Psychological approach; requires active participation of patients (with risks of false-positives).</td>
<td>Special relevance in cases of limited verbal communication, impaired cognition, severe psychiatric diseases, sleepiness states due to tiredness or use of drugs (e.g., benzodiazepines), simulation of diseases.</td>
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<td>The test can only be performed in a single body area and just once.</td>
<td>Choice of test area should be done after clinical evaluation; if necessary, test several areas.</td>
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<td>Limited sensitivity to detect function loss in neuropathies (risk of false-negatives)</td>
<td>Examples: children with diabetes or increased limbo-cortical representation; sensitivity may be increased by bilateral evaluation in systemic neuropathies (comparison with contralateral area) and when using face and upper limbs as control areas.</td>
</tr>
<tr>
<td>Only the evaluation of the complete pathway is possible.</td>
<td>There is no differentiation between the origin of loss, or of hyperalgesia, between peripheral and central (e.g., evaluate face as control area in case of polyneuropathy and lateral radioulnopathy).</td>
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<tr>
<td>Limiting values are needed to prevent skin injuries</td>
<td>In some cases it is not possible to detect minor changes due to the confidence interval of 95% of healthy individuals be close to limiting values used in the test.</td>
</tr>
<tr>
<td>Time needed for the application (approximately one hour for two areas)</td>
<td>Possible problems with tiredness and loss of concentration.</td>
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<tr>
<td>Contralateral area inadequate as control</td>
<td>In patients with systemic or bilateral diseases, choose face or hand as control to improve sensitivity and specificity.</td>
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There are 13 different tests, including smaller and larger neurological fibers evaluation. In general, painful sensitivity is evaluated by mechanical stimuli (such as needle prick) or thermal stimuli with intensity above or below individual threshold. These stimuli are especially useful to evaluate positive signals, such as allodynia and hyperalgesia. Although there is correlation in some somatosensory aspects with specific QST tests, the evaluation of total sensory profile with the complete test is useful for better understanding possible mechanisms involved. As example, an abnormal threshold to cold may mean changes in Aδ fibers, but if it is simultaneous with abnormal warmth sensation, it may be result of descending inhibitory system impairment.

To evaluate deep tissues, such as muscles and fascia, just pressure pain threshold (PPT) is used as parameter and is decreased in regional complex pain syndrome (RCPS), neurological injuries and peripheral neuropathy. The so-called wind up rate may be evaluated with the application of a single stimulus, followed by a series of stimuli to measure painful response to temporal summation, which would be indirectly correlated to posterior horn neurons phenomenon\(^{11}\).

Validation and adaptation
The application protocol of QST established by DFNS is already broadly used in European countries. Since recommended protocols were developed based on reference databases, there are already parameters according to gender, age group and affected body areas for a certain patient. It is also possible to compare in the same individual two different sides, which is particularly useful in unilateral affection situation. The use of specific software helps data interpretation, also allowing the comparison of the exam performed in different moments by different examiners\(^{11}\).

Clinical use
QST may be used to detect small fibers impairment, such as unmyelinated C fibers and poorly myelinated Aδ fibers. These clinical situations in general are followed by dysesthesias or paresthesias with normal nervous conduction studies, such as electroneuromyography. These changes may be early signs of neuropathy different from peripheral neuropathy, identified by changes in thermal threshold which is increased and has sensitivity of 36-85% as compared to skin biopsies\(^{14}\).

It is known that the same disease, or the same type of NP, have different sensory profiles in different patients. So, a classification based on QST findings was proposed, to differentiate normal sensory aspects (L0G0) from hypesthesia to thermal stimuli (L1), to mechanical stimuli (L2) or to both (L3); or hyperalgesia to thermal stimuli (G1), to mechanical stimuli (G2) or to both (G3)\(^{11}\). QST has been of diagnostic value in several situations, among them diabetes, even in asymptomatic patients to differentiate types of CRPS, peripheral nervous injury, Fabry disease, spinal cord trauma, and fibromy-
algia, among others. Other indication that will be useful in the future is monitoring the response to topic treatment with lidocaine or capsaicin, as well as the indication of treatment according to pain phenotypic profile15.

NEUROPHYSIOLOGY

Neurophysiological techniques, such as studies of nervous conduction, trigeminal reflexes and somatosensory evoked potential are mediated by non-nociceptive large afferent Aβ fibers and are widely used to evaluate central and peripheral nervous system diseases16. Such techniques are useful to show the location and to quantify peripheral and central somatosensory pathway changes. Most clinical and experimental studies show that NP is induced by nociceptive conduction injury and so the results of non-nociceptive fibers do not contribute to the diagnosis17.

Recent studies, however, have suggested that some specific NP types are specifically associated to Aβ fibers injury. Patients with peripheral and central nervous system diseases with sensations of electric shock in paroxysm are associated to abnormal neurophysiologic responses mediated by non-nociceptive Aβ fibers18.

CORNEAL CONFOCAL MICROSCOPY

The eye is the only human organ allowing the inspection of central and peripheral nerves at one time. Cornea is densely innervated by the ophthalmic branch of the trigeminal nerve. Corneal innervations may be divided in three structures: subepithelial plexus, stromal nerves and subbasal plexus, which is located between the basal epithelium and Bowman membrane, being parallel to eye surface and made up of small nervous fibers with thickness of 0.2 to 10μm19,20. Corneal nerves are Aβ fibers or C fibers with polymodal receptors with low threshold to nociception and mechanical and cold stimuli.

Methods

To perform corneal confocal microscopy (CCM) the eye is prepared with local anesthetics and hypropromellose. The microscope is placed on central cornea and connected to a tomograph, allowing high resolution pictures of the sub-basal nerve plexus. The analysis of the images with the best representation of corneal nervous fibers may be done manually or by means of a software21.

Analyzed parameters are: (a) corneal nervous fibers length (NFL), defined as the absolute length of branches and nerves in mm2; (b) nervous fiber density (NFD), defined as the total number of larger nerves by mm2 (being considered normal the number of 42 [31-54]; and (c) nervous fibers branches (NFB), defined as the number of branches per mm2 (normal 35 [25-55]). NFL is the most practical parameter, but NFD is the best parameter to diagnose NP by CCM22,23.

Clinical application

CCM has been primarily used to diagnose diabetic polyneuropathy and sarcoidosis, being that data of its application for other diseases are scarce. A recent metanalysis of 13 studies with 1680 participants has confirmed its value to early detect nervous changes in patients with diabetic neuropathy. Curiously, patients with intolerance to glucose already show evidences of neuropathy detectable by CCM. In addition, patients with intolerance to glucose, who later developed diabetes type 2, had significantly lower NFD, NFL and NFB as compared to the control group. SB has been used to investigate the density of intradermal fibers in peripheral nerve diseases, such as diabetic neuropathy, infectious and inflammatory neuropathies associated to systemic diseases24,25. In all studies, IENF density was significantly lower in patients with neuropathies as compared to control individuals26. Distal leg SB with quantification of intradermal small fibers density using established rules is considered an effective technique for the diagnosis of small fibers neuropathy27,28. With SB it was possible to detect evidences of small fibers neuropathy in a variety of conditions29, including fibromyalgia patients30,31. So, SB has been recommended as important part of diagnostic tests for small fibers neuropathy in fibromyalgia patients32.

CONCLUSION

NP has clinical presentation and result of simple physic neurologic evaluation at bedside, which helps its diagnosis. However, additional methods, such as QST, CCM and SB are significant contributors to the accuracy of the diagnosis. NP treatment is different from that of nociceptive pain and for this reason its accurate diagnosis is important to establish the treatment. It is worth reminding that, as with any other symptom, NP is present in a significant number of diseases and so specific treatments for the underlying cause should be available.

REFERENCES

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