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EFNS GUIDELINES

EFNS guidelines on neuropathic pain assessment: revised 2009

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Background and purpose: We have revised the previous EFNS guidelines on neuropathic pain (NP) assessment, which aimed to provide recommendations for the diagnostic process, screening tools and questionnaires, quantitative sensory testing (QST), microneurography, pain-related reflexes and evoked potentials, functional neuroimaging and skin biopsy.

Methods: We have checked and rated the literature published in the period 2004–2009, according to the EFNS method of classification for diagnostic procedures.

Results: Most of the previous recommendations were reinforced by the new studies. The main revisions relate to: (i) the new definition of NP and a diagnostic grading system; (ii) several new validated clinical screening tools that identify NP components, and questionnaires which assess the different types of NP; (iii) recent high-quality studies on laser-evoked potentials (LEPs) and skin biopsy.

Conclusions: History and bedside examination are still fundamental to a correct diagnosis, whilst screening tools and questionnaires are useful in indicating probable NP; QST is also useful for indicating the latter, and to assess provoked pains and treatment response. Amongst laboratory tests, LEPs are the best tool for assessing Aδ pathway dysfunction, and skin biopsy for assessing neuropathies with distal loss of unmyelinated nerve fibres.

Background and objectives

Neuropathic pain (NP) is a major symptom which may be intractable in common neurological disorders such as neuropathy, spinal cord injury, multiple sclerosis and stroke. Pain is a complex sensation strongly modulated by cognitive influences, and understanding the underlying pathophysiological mechanisms in patients remains a challenge for pain specialists. The EFNS launched a task force that published guidelines for the assessment of NP to address an unmet clinical need [1]. The aim of this new task force was to revise the previous guidelines, in accord with evidence-based studies published thereafter. We have now performed so, drawing in part on similar work in this field by the NP special interest group (NeuPSIG) of the International Association for the Study of Pain (IASP).

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Search methods

Search methods adhered to those used in previous guidelines [1] and complied with EFNS recommendations [2]. Briefly, after an initial search through the central database in the Cochrane Library, Medline, and other electronic databases (2004–to date), two task force participants were assigned to check the sorted material per method of assessment, i.e. screening tools and questionnaires, quantitative sensory testing (QST), microneurography, reflexes and evoked potentials, functional neuroimaging and skin biopsy. Pertinent studies were rated for evidence level according to EFNS rules [2] whenever applicable; in some instances, such as

for statements generally accepted or demonstrated by basic neuroscience, we did not give an evidence level; adequately powered systematic reviews (SR) were considered Class I.

Considerations on the methods of assessment in light of the new definition and grading system

According to a new proposal, NP is 'Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system' [3]. This proposal represents a strengthening of the old IASP definition [4], by eliminating 'dysfunction' of the nervous system as a possible cause and by requiring a specific lesion of the somatosensory system. It is clear that NP is not a single disease but represents a syndrome, i.e. a constellation of specific symptoms and signs with multiple potential underlying aetiologies. Hence, an accurate neurological history and neurological examination, including sensory testing, is most important to reach a diagnosis and to postulate the presence of a NP syndrome. The elucidation of underlying disease aetiology and the dissection of pain will in practice often occur simultaneously. However, for clarification, the following is a brief description of steps in assessing a NP syndrome:
A. The history will indicate whether the character and distribution of the pain is in accord with neuropathic criteria, and whether a relevant lesion or disease in the nervous system is probably responsible for the pain.
B. The clinical examination will determine the presence of negative (loss of function) and positive (hyperalgesia and/or allodynia) sensory signs, for one or more sensory modalities affecting the somatosensory system, and their relevance to the underlying disease or lesion.
C. Further diagnostic tests can be conducted to either document the presence of a specific underlying neurological disease (e.g. imaging of the brain to document a stroke in a patient with suspected post-stroke pain) or confirm a sensory lesion within the pain distribution (e.g. skin biopsy to document presence of small fibre loss in cases with small fibre neuropathy).
Based on this stepwise assessment, it has been suggested that patients can be categorized into possible NP (fulfilling step A above), probable NP (fulfilling A with supporting evidence for *either* lesion/disease *or* pain distribution according to B or C) and definite NP (fulfilling A with supporting evidence for *both* lesion/disease *and* pain distribution according to B and C) [3].

So far, there are no studies to document the effectiveness of this diagnostic grading system.

Recently, simple questionnaires and/or combinations with sensory examinations have been introduced, e.g. [Class I: 5], for these to partially substitute or contribute to diagnosing NP. In a new proposal, using standardized questions and testing a few somatosensory functions, a high degree of specificity and sensitivity has been obtained for certain types of NP: the diagnostic sensitivity of the interview and sensory examination exceeded that obtained with a relevant imaging technique [Class I: 6].

Recommendations

History and clinical examination are a requirement to confirm the presence of a NP syndrome, and also an important step in reaching an aetiological diagnosis for NP (Good Practice Point).

Screening and assessment tools

Several tools essentially based on pain descriptors have been proposed for the purpose of distinguishing NP from non-NP (screening tools) or characterizing multiple neuropathic phenotypes (assessment tools).

Screening tools

The development of the McGill Pain Questionnaire (MPQ) revealed that pain quality descriptors vary across different pain conditions [7]. The lack of specificity of the MPQ for NP has led to development of screening tools for the recognition of NP. Interestingly, these tools generally share similar clinical characteristics.

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) contains five symptom items and two clinical examination items [Class I: 8]. It has also been validated as a self-report tool, the S-LANSS [Class I: 9]. Compared to clinical diagnosis, its sensitivity and specificity range 82–91% and 80–94%, respectively. The S-LANSS has also been used in epidemiological studies in the general population.

The Neuropathic Pain Questionnaire (NPQ) contains 12 items (of them 10 sensory and two affective) [Class I: 10]. It demonstrated 66% sensitivity and 74% specificity compared to clinical diagnosis in the validation sample, but the aetiologies of pain were not reported. The short form of the NPQ (three items) has similar discriminative properties [Class II: 11]. It has been found able to discriminate between NP and non-NP in patients referred to a specialist pain clinic.

The Douleur Neuropathique en 4 questions (DN4) contains seven items related to symptoms and three related to clinical examination [Class I: 5]. A total score ≥4 out of 10 suggests NP. The DN4 showed 83% sensitivity and 90% specificity when compared to clinical diagnosis in the development study. The seven sensory

descriptors can be used as a self-report questionnaire with similar results. The tool was developed and validated in French and translated into 15 languages. The DN4 has been used in epidemiological studies in general population and diabetics.

PainDETECT was developed and validated in German [Class I: 12] and is available in several other languages. It is a self-report questionnaire with nine items. It correctly classifies 83% of patients to their diagnostic group with 85% sensitivity and 80% specificity.

ID Pain consists of five sensory descriptor items and one item relating to whether pain is located in the joints [Class II: 13]. In the validation study, 22% of the nociceptive group, 39% of the mixed group and 58% of the neuropathic group scored above three points, the recommended cut-off score; the exact sensitivity and specificity of the tool using this cut-off compared to clinical diagnosis was not reported.

The standardized evaluation of pain (StEP) was recently validated to identify NP in patients with chronic low back pain categorized into 'axial' (non-neuropathic) or 'radicular' (neuropathic) low back pain [Class I: 6]. It contains 10 physical tests and six questions, thus emphasizing clinical examination. Several ymptoms (e.g. burning pain), are scored negatively, suggesting that they are less likely in NP, which is in contrast with the other screening tools. This may reflect specificities related to low back pain or difficulties inherent to the classification of low back pain patients [14].

Assessment questionnaires

Although the MPQ [7] and the short-form MPQ (SF-MPQ) [15] have not been validated for NP assessment, the SFMPQ has been the most commonly used quality assessment tool. However, it is not more sensitive to change than unidimensional intensity scales. To overcome this limitation, the SF-MPQ 2 [16] has been recently developed as a measure of neuropathic and non-neuropathic symptoms, but it is not fully validated.

The Neuropathic Pain Scale (NPS) [Class I: 17], the first pain quality assessment tool devoted to NP assessment, has been translated into 24 languages and used in several NP trials. However, it lacks several pain qualities commonly seen in NP and is fully validated only in multiple sclerosis. To overcome these limitations, the Pain Quality Assessment Scale (PQAS) has been derived from the NPS [18]. To date, no data exist regarding its use in blinded NP trials.

The Neuropathic Pain Symptom Inventory (NPSI) was originally validated in French [Class I: 19] and has been submitted to linguistic validation in 50 other languages. One study found that several NP dimensions of the NPSI were particularly sensitive to treatment effect. The factorial structure of the NPSI makes it suitable to capture different aspects of NP with presumably distinct mechanisms.

Recommendations

The main advantage of screening tools is to identify potential patients with NP, particularly by non-specialists (grade A). However, these tools fail to identify 10–20% of patients with clinician diagnosed NP, showing that they cannot replace careful clinical judgment. They have also been used in epidemiological studies, but validation studies for this purpose are necessary. More research is also needed to clarify whether they can predict response to therapy.

Pain quality assessment measures are useful to discriminate amongst various pain mechanisms associated with distinct dimensions of NP experience (grade B). The NPS or NPSI are recommended to evaluate treatment effects on neuropathic symptoms or their combination (grade A), but should also be used in future trials to try to predict treatment outcome and better define responder profiles. Assessment of the sensory and affective dimensions of pain can be performed with the SF-MPQ scale, but whether such assessment is more sensitive than the pain intensity measures remains to be confirmed. The SFMPQ-2 and the PQAS have not yet been fully evaluated in NP.

Quantitative sensory testing

Quantitative sensory testing is a psychophysiological measure of perception in response to external stimuli of controlled intensity. Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is measured using von Frey hairs or Semmes-Weinstein monofilaments, pinprick sensation with weighted needles and vibration sensitivity with a tuning fork or an electronic vibrameter; thermal perception and thermal pain are measured using a probe that operates on the Peltier principle (for references see previous guidelines [1]).

The main problem with studies using QST as a diagnostic tool remains that of blinding, with only four studies (out of some 50 new studies) being prospective, in a broad spectrum of patients and controls, and having blinded examiners [Class I/II: 20–23]. The variability of methods, results and patient population (diabetic neuropathy, spinal cord injury, radiculopathy) prevents any conclusion. We must also emphasize that QST changes were also found in non-NP states, such as rheumatoid

arthritis, inflammatory arthromyalgias and fibromyalgia (although all these studies are Class IV, e.g. [24,25]).

Most QST studies are still dedicated to the assessment of sensory small fibre function only, assuming that large fibre function was probably documented by standard clinical neurophysiology. This bias precludes any analysis on the relative importance of small vs. large sensory fibre function deficits in NP syndromes. However, extensive validation data for all somatosensory submodalities have now been published by the German Research Network on Neuropathic Pain [26,27]. QST is used for diagnosis and follow-up of small fibre neuropathy (all Class IV; e.g. [28,29]), and its usefulness is agreed in the early diagnosis of diabetic neuropathy [SR Class I: 1].

Quantitative sensory testing is particularly appropriate to quantify positive sensory phenomena, like mechanical and thermal allodynia and hyperalgesia, which may help characterize painful neuropathic syndromes, and predict or monitor treatment effects. In particular, pharmacological and non-pharmacological treatment trials using QST found effects on dynamic mechanical allodynia, pinprick hyperalgesia and sensory loss, whereas treatment efficacy was predicted by thermal detection thresholds, vibration detection thresholds, heat hyperalgesia and dynamic mechanical allodynia [Class I/II: 30–37].

Recommendations

Quantitative sensory testing can be used in the clinic along with bedside testing to document the sensory profile. Because abnormalities have often been reported in non-NPs as well, QST cannot be considered sufficient to separate differential diagnoses (Good Practice Point). QST is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components (grade A). To evaluate mechanical allodynia/hyperalgesia, we recommend the use of simple tools such as a brush and at least one high-intensity weighted pinprick or von Frey filament (e.g. 128 mN). The evaluation of pain in response to thermal stimuli is best performed using the computerized thermotest, but we do not recommend the systematic measure of thermal stimuli except for pathophysiological research or treatment trials. A simple and sensitive tool to quantify pain induced by thermal stimuli in clinical practice is still lacking.

Neurophysiology

We wish to remind that our previous guidelines recommended the standard nerve conduction study, although it does not provide information on small fibre function, as a most useful tool for documenting and assessing peripheral neuropathies.

Microneurography

Microneurography is a minimally invasive technique in which single-axon recordings from peripheral nerves are made in awake subjects and provides valuable information on the physiology and pathophysiology of all nerve fibre groups. Because it can discriminate individual action potentials in single, identified peripheral fibres, microneurography is nowadays the only technique able to record and quantify positive sensory phenomena mediated by large-myelinated fibres (tactile paresthesias and dysesthesias) or small-myelinated and unmyelinated fibres (spontaneous pains). The possibility of performing intraneural microstimulation may provide a direct link between activity in peripheral nerve fibres and pain perception [38]. Because prospective studies monitoring sides effects of the technique did not find overt or persistent nerve damage [39,40], microneurography is considered a relatively safe technique if performed by experienced examiners [41].

Microneurography is time consuming and requires both an expert investigator and a collaborative patient. Furthermore, microneurography is currently performed only in a few centres around the world. For these reasons, it has only been used on very few occasions to study NP patients. There are no published normative data for healthy subjects, and published reports are unblinded group comparisons only (Class IV).

New developments in analysis software now allow multiple simultaneous recordings of C-fibres, thus enhancing the possibility of studying ongoing abnormal activity arising from peripheral nociceptors, which is considered a possible cause for spontaneous pain in patients with peripheral neuropathies [42–45].

Pain-related reflexes

Pain-related reflexes appear to be diagnostically useful only for facial pains. Two Class I studies [46,47] and the recent AAN-EFNS guidelines on trigeminal neuralgia management [SR Class I: 48,49] confirmed that the Aβ-mediated trigeminal reflexes (early R1 blink reflex and early SP1 masseter inhibitory reflex) are efficient tools to reveal symptomatic forms of trigeminal neuralgia, yielding an overall specificity of 94% and sensitivity of 87% in over 600 patients. Six other studies used blink reflexes in facial pains. Although four studies were Class IV, one Class I study in patients with ophthalmic postherpetic neuralgia (PHN) yielded a specificity of 100% and sensitivity of 73% for the early

R1 blink reflex [50] and one Class III study found that the nociceptive blink reflex (elicited by the concentric electrode) was delayed in patients with atypical odontalgia, thus supporting the view that this condition is neuropathic [51].

For the upper limb, the Cutaneous Silent Period (CSP, an inhibitory reflex recorded from the small hand muscles after noxious stimulation of the fingers) was assessed in two studies, one in distal symmetric polyneuropathy [Class III: 52] and the other in carpal tunnel syndrome [Class I: 53]. In neither study did CSP differentiate patients with and without pain, and this measure did not correlate with pain. This confirms the conclusions of the previous guidelines [1] that the CSP is not an adequate tool for assessing nociception. Regarding the lower limb, the nociceptive flexion reflex (RIII) is still being used in physiological and pharmacological studies of modulation of nociception, but not in patients with NP.

Pain-related evoked potentials

According to the previous EFNS guidelines on NP assessment [SR Class I: 1], and the Recommendations from the International Federation of Clinical Neurophysiology [SR Class I: 54], laser-evoked potentials (LEPs) are the easiest and most reliable of the neurophysiological methods for assessing function of nociceptive pathways.

Many new studies investigated Aδ fibre pathways in a total of over 300 patients with NP: five studies used LEPs, three the contact heat-evoked potentials [55], and three evoked potentials elicited by a surface concentric electrode that provides a preferential activation of superficial terminals (i.e. small-diameter afferents) [56]. Although all techniques revealed significant sensory abnormalities when compared to controls or contralateral side, and several showed significant correlations with pain, only three studies – all using LEPs – were Class I, those using other techniques were all Class III/IV. The LEP studies investigated patients with sensory neuropathy [57], PHN [50] and carpal tunnel syndrome [53]. A cumulated analysis of these three Class I studies revealed a highly significant difference to controls, with high specificity but low sensitivity (considering the responses to be certainly abnormal only when absent; sensitivity would increase considerably if the recently recommended normal limits of amplitude were used [SR Class I: 54]).

One study only dealt with C-fibre-related LEPs (elicited from the trigeminal territory) [Class I: 50]. The recording of C-LEPs after limb stimulation is probably still technically too difficult for reliable clinical applications.

Recommendations

Thus far, microneurography cannot be suggested as a routine procedure for the assessment of patients with peripheral NP (Good Practice Point). However, we encourage new studies in selected groups of patients with NP, to understand the frequency and pathophysiological role of spontaneous ectopic activity, and the potential efficacy of drugs in reducing ectopic impulse generation in peripheral nociceptors.

The trigeminal reflexes mediated by Aβ fibres are useful in the diagnosis of trigeminal pain disorders, as they are abnormal in patients with structural damage, in conditions such as trigeminal neuropathy and PHN, and normal in patients with classic trigeminal neuralgia (grade A). The CSP is probably inadequate for NP assessment (grade B).

Laser-evoked potentials are useful for assessing function of the Aδ fibre pathways in patients with NP (grade A). Other EP techniques which do not use laser stimulators are not supported by evidence-based studies that demonstrate their diagnostic value.

The available evidence regarding EPs for assessing the C-fibre pathways (with any method of stimulation) is so far insufficient to make recommendations.

Functional neuroimaging

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure with different methods cerebral blood flow (rCBF) or metabolic activity in defined brain regions. Activation studies investigate local synaptic changes specifically associated with a given task or a particular stimulus by comparing statistically activated and control conditions. Functional neuroimaging has disclosed a network of brain regions jointly activated by noxious stimuli (labelled 'pain matrix'). Activation of the lateral thalamus, SI-SII and posterior insula are thought to be related to the sensory-discriminative aspects of pain processing, whilst mid-anterior cingulate, posterior parietal and prefrontal cortices participate in the affective and attentional concomitants of pain sensation [58,59]. In unilateral *spontaneous neuropathic pain*, moderate but converging evidence from independent groups indicates decreased resting rCBF in contralateral thalamus, and reversal of this abnormality by analgesic procedures (but only case reports or small series with < 20 patients: [60–63]). Should this be confirmed in larger series, thalamic hypoperfusion might be used in the future as a marker of NP and restoration of thalamic blood flow for treatment monitoring. In patients with *provoked neuropathic pain*, allodynia and hyperalgesia have been associated with amplification of the thalamic, insular,

SI, SII and prefrontal–orbitofrontal responses, but not anterior–perigenual cingulate [59,63–66]. Neuropathic allodynia has been shown to enhance insular activity ipsilateral to pain [65,67,68] suggesting that a shift in hemispheric balance might contribute to the allodynic experience. Again, the total number of reported patients ($n = 80$) is still too small to support any diagnostic application; however, neuropathic allodynia has shown a different activation pattern than non-neuropathic allodynia (e.g. CRPS-I [69]) which may open diagnostic perspectives. Opioid-receptor imaging has demonstrated different abnormalities in central and peripheral NP [70–72], but the predictive value of these findings remains unknown. Assessing the effect of analgesic drugs on pain-related brain activity will provide a better understanding of pain and analgesia and hence the development of novel therapeutic strategies.

However, data in patients are still scarce, and in most studies, examiners were unblinded. Hence, no graded recommendation could be drawn in the frame of the EFNS classification for diagnostic procedures. The comments below represent our expert opinion.

Recommendations

Studies in NP patients have lagged far behind equivalent studies in acute pain. There is converging evidence that chronic spontaneous NP is associated with decreased activity in contralateral thalamus, whereas provoked NP is associated with increased activity in the thalamic, insular and somatosensory regions. In view of the potential relevance of these data, we encourage functional neuroimaging studies in patients with NP.

Skin biopsy

A punch biopsy of the skin in the painful area allows immunostaining and visualization of the intraepidermal terminals of Aδ and C nerve fibres, and thus measurement of the Intraepidermal Nerve Fibre Density (IENFD). Standardized counting rules for IENFD are required to obtain reproducible results [SR Class I: 73,74]. In experienced centres, the sensitivity and specificity of IENFD are 88% [SR Class I: 73; Class II: 28].

In patients with painful feet and a normal nerve conduction study, a small fibre neuropathy can be demonstrated by IENFD [Class II/III: 28,75–77]. Several studies have investigated the correlation between skin biopsy findings and other tests of small fibre function. Contact heat-evoked potentials correlated significantly with IENFD [Class III: 78]. In small fibre neuropathy, the sensitivity of IENFD may be higher than that of QST [Class II/III: 28,76,79] and LEPs [Class II: 28].

Although in patients with diabetic or HIV neuropathy, IENFD was inversely correlated with pain [Class III: 76,80], whereas in other conditions, it was not [Class II: 28].

Old and recent studies in PHN patients showed that IENFD in the area of pain is lower than in contralateral mirror-image skin [Class II: 81,82] and that the relative sparing of cutaneous innervation was associated with allodynia, thus suggesting that allodynia was related to the surviving 'irritable' nociceptors [Class II: 82,83].

Quantitative and qualitative changes in skin innervation have been reported in complex regional pain syndrome (CRPS) [Class III/IV: 84,85].

Recommendations

Skin biopsy should be performed in patients with painful/burning feet of unknown origin and clinical impression of small fibre dysfunction (grade B). In PHN, skin innervation is reduced (grade B) and higher numbers of preserved fibres are associated with allodynia (grade B). IENFD shows only a weak negative correlation with the severity of pain and cannot be used to measure pain in individual patients (grade C).

Table 1 Summary of choice methods of assessing nerve function per sensation

		Testing		
Fibre	Sensation	Clinical	Quantitative sensory testing	Laboratory
Aβ	Touch Vibration	Piece of cotton wool Tuning fork (128 Hz)	von Frey filaments Vibrameter[a]	Nerve conduction studies, SEPs[b]
Aδ	Pinprick Cold	Cocktail stick Thermoroller	Weighted needles Thermotest[d]	LEPs[c] None
C	Warmth Burning	Thermoroller None	Thermotest[d] Thermotest[d]	Skin biopsy

[a]Or other device providing graded vibratory stimuli; [b]Somatosensory-evoked potentials; [c]Laser-evoked potentials; [d]Or other device providing graded thermal stimuli. Note the lack of suitable methods of assessing burning in a clinical setting and cold with a laboratory tool.

Conclusions

The majority of previous recommendations were reinforced by recent studies. The new definition of NP and the diagnostic grading system will probably lead to more accurate diagnosis in clinical practice and research studies. History and bedside examination are still fundamental to a correct diagnosis. The previous lack of questionnaires and screening tools explicitly dedicated to NP has been resolved by a number of new validated tools. Laboratory techniques that were restricted to research, such as QST, LEPs, and IENFD, are being used more widely in clinical practice and trials. Amongst these methods of assessment, QST is the best for provoked pains and response to treatment, LEPs are the best for Aδ pathways, and IENFD for C-fibre loss in distal axonal neuropathies (Table 1).

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