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EFNS TASK FORCE/CME ARTICLE

Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations

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The use of instrumental examinations in headache patients varies widely. In order to evaluate their usefulness, the most common instrumental procedures were evaluated, on the basis of evidence from the literature, by an EFNS Task Force (TF) on neurophysiological tests and imaging procedures in non-acute headache patients. The conclusions of the TF regarding each technique are expressed in the following guidelines for clinical use.

1. Interictal electroencephalography (EEG) is not routinely indicated in the diagnostic evaluation of headache patients. Interictal EEG is, however, indicated if the clinical history suggests a possible diagnosis of epilepsy (differential diagnosis). Ictal EEG could be useful in certain patients suffering from hemiplegic and basilar migraine.
2. Recording of *evoked potentials* is not recommended for the diagnosis of headache disorders.
3. There is no evidence to justify the recommendation of *autonomic tests* for the routine clinical examination of headache patients.
4. *Manual palpation* of pericranial muscles, with standardized palpation pressure, can be recommended for subdividing patient groups but not for diagnosis. Pressure algometry and electromyography (EMG) cannot be recommended as clinical diagnostic tests.
5. In adult and paediatric patients with migraine, with no recent change in attack pattern, no history of seizures, and no other focal neurological signs or symptoms, the routine use of *neuroimaging* is not warranted. In patients with atypical headache patterns, a history of seizures and/or focal neurological signs or symptoms, magnetic resonance imaging (MRI) may be indicated.
6. If attacks can be fully accounted for by the standard headache classification [International Headache Society (IHS)], a positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) and scan will generally be of no further diagnostic value.
7. Nuclear medicine examinations of the cerebral circulation and metabolism can be carried out in subgroups of headache patients for diagnosis and evaluation of complications, when patients experience unusually severe attacks, or when the quality or severity of attacks has changed.
8. *Transcranial Doppler* examination is not helpful in headache diagnosis.

Although many of the examinations described are of little or no value in the clinical setting, most of the tools have a vast potential for further exploring the pathophysiology of headaches and the effects of pharmacological treatment.

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Introduction

The most important tools in the diagnosis and treatment of headache disorders are, without doubt, careful clinical neurological examinations and the compilation of detailed reports on the patient's history and symptoms. By applying the diagnostic criteria of the International Headache Society (IHS Classification, 1988), there can be a probable diagnosis which allows adequate treatment. However, in many cases, particularly when the headache presents as atypical with changing clinical features or as a symptom of another primary illness, neurologists find it necessary to supplement the clinical work up of the patient with paraclinical tests. The differential diagnosis of acute headache (e.g. primary thunderclap headache) versus symptomatic headache presents several difficulties and neuroimaging investigations are mandatory. This report is a critical review of the literature on the application of neurophysiological tests and imaging procedures in non-acute headache patients. In addition to evaluating the clinical usefulness of these tests and procedures in the diagnostic setting, we have also attempted to outline the guidelines for their use, as attempted by various authors (Silberstein, 2000; Lewis *et al.*, 2002). Of all the available techniques, neuroimaging, particularly magnetic resonance imaging (MRI), is the most suitable and cost-effective paraclinical testing method used in headache patients, with the highest rate of diagnosis. Finally, we consider the potential use of these methods in headache research. An extensive review of the main references in the literature, together with an update on the most important contributions made by neurophysiological studies to our understanding of the pathogenesis of primary headache, is being published elsewhere (Friberg *et al.*, 2003).

Aims and methods

The intention in compiling the information in this document was to develop guidelines to help physicians make appropriate choices regarding the use of instrumental tests in non-acute headache patients. Reviews of published clinical evidence (from 1988 to 2002) were evaluated. Key literature references pre-dating the IHS Classification (1988) were particularly carefully examined as these studies applied different diagnostic criteria for headache.

The guidelines were prepared according to the EFNS criteria (Hughes *et al.*, 2001) and the level of evidence and grade of recommendation were expressed in accordance with this reference.

Main findings for the different techniques

Electroencephalography

The usefulness of electroencephalography (EEG) in the diagnosis of headache is debated. Although early EEG studies of migraine emphasized the frequent abnormal recordings, contemporary reviewers have criticized most of them for various methodological omissions and flaws (Sand, 1991). The American Academy of Neurology concludes, 'EEG is not useful in the routine evaluation of patients with headache (guideline)', admitting, however, that EEG may be used in headache patients with associated symptoms suggesting a seizure disorder (Rosenberg *et al.*, 1995).

Electroencephalography is the best laboratory technique to support the clinical diagnosis of epilepsy, showing good sensitivity (80–90% in serial recordings) and specificity (false positive rates in 0.2–3.5% of healthy subjects) (Walczak and Jayakar, 1998). It also plays an important role in the evaluation of other focal and diffuse central nervous system (CNS) disorders.

Quantitative frequency analysis of EEG (QEEG), with or without topographic mapping, is a more objective method than conventional EEG interpretation, although there are a number of possible methodological pitfalls that should be avoided. The use of QEEG is generally recommended only in conjunction with visual EEG interpretation performed by a skilled observer (Nuwer, 1997).

Evoked potentials

Evoked potentials (EPs) are cortical EEG potentials temporally linked to a specific sensory input. Although all sensory stimuli contribute to the overall EEG activity, EPs cannot be identified in the normal EEG because they are not separable from ongoing EEG activity. However, when clear temporal definition of the stimulus is possible (i.e. in the case of a sudden onset), short stretches of post-stimulus EEG can be averaged. Any activity that is not time-locked to the stimulus disappears from the average, while the EEG response to the stimulus remains. In this way, the cortical response to very specific stimuli can be investigated in spatial and temporal detail. In migraine, much attention has been paid to visual stimuli, which is not surprising given the presence of visual auras and photophobia in this disorder. EPs have made it possible to document cortical excitability, as well as habituation and gating phenomena in migraine (Ambrosini *et al.*, 2003).

Reflex responses

Several electrophysiological techniques have been used to explore polysynaptic reflexes in headache patients. The blink reflex (BR) and corneal reflex (CR) are reflected in the bilateral closure of the eyelids in response to a stimulus, usually, in laboratory settings, electrical stimulation of the supraorbital nerve. The BR consists of three components: an ipsilateral early component (R1), a bilateral late component (R2), and a bilateral ultralate component (R3). The precise nature of R1 and R2 is still debated, while R3 is considered to be a nociceptive component. The CR is composed of two late bilateral symmetrical components, probably equivalent to the R2 component.

Several BR and CR abnormalities have been described in primary headaches, but data documenting the specificity and sensitivity of these tests (Sandrini *et al.*, 1991, 2002, 2003; Proietti Cecchini *et al.*, 2003) are scarce. The exteroceptive suppression (ES) of masticatory muscle activity is a trigemino-trigeminal reflex consisting of biphasic (ES1 and ES2) inhibition of voluntary contraction (of variable duration) that occurs bilaterally in response to various exteroceptive stimuli. The inhibitory effect is mediated by interneurones located in the propriobulbar and pontine reticular formation, close to the trigeminal motor nucleus on each side. The literature contains conflicting data on ES abnormalities in tension-type headache (Schoenen and Bendtsen, 2000).

Nociceptive flexion reflexes (NFRs), evoked at the biceps femoral muscle by electrical stimulation of the sural nerve, are thought to constitute a useful tool for exploring the pain control system in human beings, but only a few NFR studies have been conducted in headache patients (Sandrini *et al.*, 1993).

Autonomic tests

The autonomic nervous system (ANS) consists of three parts, the sympathetic, parasympathetic and enteric nervous systems. Each of these is divided into subsystems according to the effector organs innervated by the terminal neurones. 'Sympathetic' and 'parasympathetic' neurones are actually defined on the basis of anatomical rather than functional criteria; thus, afferent neurones innervating visceral organs are not denoted as sympathetic or parasympathetic, but visceral (Jänig and McLachlan, 1999; Jänig, 2003a). When considering the role of the ANS in the different types of headache, there are three different questions that should be borne in mind (Jänig, 2003b):

1 Is the ANS involved in the generation and maintenance of pain? Hypotheses regarding the mechanisms of possible sympathetic nervous system involvement in the generation and maintenance of pain have been formulated and tested in animal and human experimental models (Jänig, 1999; Jänig and Baron, 2001, 2002).

2 Are functional autonomic abnormalities associated with different types of headache, the consequence of and therefore secondary to headache? This question addresses the observation that all pain is accompanied by autonomic reactions which are based on central reflex pathways in the neuraxis, and on the central integration of nociceptive with autonomic systems. In normal biological conditions, these autonomic reactions are primarily protective for the organism, but this may not necessarily continue to be the case in pathobiological conditions.

3 Are headache and functional autonomic abnormalities parallel events and therefore the consequence of possible central abnormalities? If they are, it could be useful to investigate these autonomic abnormalities in an attempt to elucidate the central pathophysiological changes which may underlie both headache and autonomic disturbances.

The diagnosis and management of autonomic disorders are highly dependent on the testing procedures used (Mathias and Bannister, 1999). Neurophysiological techniques have revealed several autonomic disturbances in primary headache, in cluster headache in particular (Saunte *et al.*, 1983; Salvesen *et al.*, 1988), but the clinical relevance of these findings remains to be verified (Schoenen and Thomsen, 2000).

Pericranial muscle tenderness evaluation

The tension-type headache (TTH) was divided into two subgroups in the IHS classification, in order to study the pathophysiological relevance of pericranial muscles in this disorder. This subdivision was necessitated by the clinical observation that many TTH patients have increased tension, tenderness and stiffness in their neck and shoulder muscles, and that some, a smaller group and much more difficult to treat, lack muscle tenderness. The IHS classification did not lay down specific diagnostic methods and, at the time, no scientific basis for this subdivision had been established. Although several studies have been carried out since then (Schoenen *et al.*, 1991; Jensen *et al.*, 1993, 1994; Jensen and Rasmussen, 1996), it is still not clear whether different pathophysiological mechanisms subtend the headache in these two subgroups. The recording of tenderness has been a widely debated subject as it has been difficult to compare the results of different observers. A fairly recent methodological study showed manual palpation to be an easy and reliable method of studying myofascial pain sensitivity in a clinical setting, provided the intensity of the applied pressure is controlled (Bendtsen *et al.*, 1995).

Pressure pain threshold (PPT) recording is also recommended in the IHS Classification (1988), although the methodology to be used and the locations to be examined are not specified. Pressure algometry, not requiring specific skills and having no particular technical requirements, is easy and safe for clinical use. The PPT, as a quantitative measure of pain, can be recorded either from a localized tender spot, or from a fixed spot in all subjects, regardless of findings on palpation. Previous studies have demonstrated that the latter method gives highly reliable and reproducible results within the same subject, but considerably varying results between subjects (Jensen *et al.*, 1993).

Neuroimaging

Radiological examinations are often sought in patients with headache. Most headache sufferers seeking medical attention fear they may have a serious illness and often request a radiological investigation. As radiological examinations are not particularly invasive or uncomfortable, and as they detect any intracranial diseases present, the threshold for requesting them is low. However, when deciding whether or not to use radiological techniques, one should consider the likelihood of the detection of underlying diseases in headache patients (Mitchell *et al.*, 1993). In the medical literature, studies that use radiological techniques in populations of headache patients can be divided into three categories. First, studies investigating the aetiology and pathophysiological mechanisms of headache; secondly, studies focusing on the pathological sequelae of headache; and thirdly, studies on the role of radiological techniques in the work up of headache patients. As the aim of this paper was to provide guidelines on the usefulness of radiological techniques in the evaluation of headache patients with normal neurological examinations, we reviewed a subset of the third category.

The current literature has been reviewed with a view to establishing guidelines for the future use of radiological methods in headache patients (Frishberg, 1994), and were found to present certain limitations. Although there is a need for further systematic studies on this topic, some conclusions can, nevertheless, be drawn (Frishberg, 1994).

There is no role for conventional roentgen techniques (skull films) in the work up of headache patients, as the conditions underlying headache in these subjects are generally located inside the skull and therefore not detectable using these methods. Digital subtraction angiography (DSA) is an invasive procedure associated with a significant morbidity and mortality rate. DSA still seems to be superior to other radiological techniques in detecting intracranial arterio-venous malformations (AVMs) and fistulas. However, it is relatively rare for any of these conditions to underlie the headache, and, furthermore, some lesions of this kind are also visible using non-invasive techniques [computerized tomography (CT) and MRI)]. Therefore, it is not appropriate to use DSA in the screening of headache patients for intracranial disease.

Both CT and MRI can be performed with and without the application of intravenous contrast agents. MRI is more sensitive to the presence of intracranial disease than CT, and the sensitivity of both techniques is increased when they are used in conjunction with intravenous contrast agents.

Detection of the presence of a recent intracranial haemorrhage is straightforward on CT. However, it has been demonstrated that MRI is at least as sensitive as CT in detecting bleeding in the subarachnoid space, if adequate sequences such as fluid attended inversion recovery (FLAIR) are used (Noguchi *et al.*, 1997). Recently, functional MRI (fMRI) of the brain also allowed very interesting studies of brain time perfusion, water molecular diffusion and cerebral cortical activation. However, these techniques and applications are still in a state of evolution. The extent to which they can be applied in the examination of headache is not yet clear, although they may prove to be helpful in differentiating between ischaemic insult and prolonged migraine aura in select patients during migraine attacks (Ay *et al.*, 1999).

SPECT and PET

Single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) are nuclear medicine imaging methods (De Deyn *et al.*, 1997), both of which require the administration of radioactive tracers to the patient. SPECT involves the sampling of emitted radiation, by means of a gamma camera with the camera heads or their collimators moving around the subject's head during data acquisition. Because SPECT cameras are versatile, less expensive and less costly to run than PET cameras, SPECT brain scans are carried out at most large hospitals.

The most commonly performed type of brain SPECT reveals regional cerebral blood flow (rCBF) changes. Following inhalation or i.v. injection of Xe^{133}, it is possible to quantify the rCBF, although at the expense of spatial resolution (Croft, 1990). Tc^{99m}-labelled rCBF tracers are the ones most frequently used because Tc^{99m} is readily available in all nuclear medical departments.

SPECT rCBF investigations can provide information about acute changes in regional perfusion which often arise in relation to the neurological symptoms associated with the aura phase of migraine (Friberg, 1999; Friberg *et al*., 2003). SPECT combined with transcranial Doppler (TCD) can, further, provide information about changes in diameter of the larger intracranial arteries (Friberg *et al*., 1991).

Positron emission tomography is a cumbersome and more expensive technique than SPECT. With the exception of F^{18}-labelled tracers ($t_{\frac{1}{2}} = 110$ min), most isotopes for PET decay very quickly. Therefore PET requires an inhouse cyclotron and online radiochemistry production unit (Saha *et al*., 1992). The positron emitting isotopes, such as C^{11}, O^{15} and F^{18}, are naturally incorporated into biologically active molecules. This has facilitated the synthesis of a large number of radioactive labelled tracers for PET, e.g. receptor-specific ligands and metabolism markers. However, only a fraction of these are used in clinical scans. As a result of the high cost of establishing and running a PET unit, the availability of PET scans is limited. Most countries in Europe have only a few PET centres, located in university hospitals.

Transcranial Doppler

The Doppler principle is utilized in medicine in the following way: an ultrasound signal is transmitted into the body and the changes in sound frequency that occur when it is reflected or scattered from the moving blood cells are observed. The accuracy of TCD velocity recordings is influenced by the angle of insonation, which, in turn, is determined by the technique adopted and the local vessel anatomy. Assuming the angle of insonation is constant, velocity (V) is dependent on volume flow (F) through the vessel and on the vessel cross-sectional area (A), according to the formula $F = V \times A$. It will, therefore, be influenced by factors that cause changes in CBF, vessel diameter, or both. Simultaneous TCD and rCBF measurements may contribute to determining vascular changes in headache patients, as each cerebral vessel supplies a defined volume of cerebral tissue (Dahl *et al*., 1990). TCD is mainly used to evaluate vascular reactivity in migraine (Friberg *et al*., 2003).

Recommendations and guidelines

Electroencephalogram

Routine EEG with standard visual interpretation

Interictal EEG is not routinely indicated in the diagnostic evaluation of headache patients. Interictal EEG is only indicated if the clinical history suggests a possible diagnosis of epilepsy, e.g. in the case of: (i) unusually brief headache episodes; (ii) unusual aura symptoms (e.g. gastric/olfactory sensations, circular visual symptoms); (iii) headache associated with unusually brief auras or aura-like phenomena; (iv) headache associated with severe neurological deficits; and (v) other risk factors for epilepsy. Ictal EEG is indicated during episodes suggesting complicated aura and during auras associated with decreased consciousness or confusion.

Quantitative EEG methods (frequency analysis with or without topographic mapping)

Current QEEG methods are not routinely indicated in the diagnostic evaluation of headache patients.

Quantitative frequency analysis of EEG must always be recorded with raw EEG data and interpreted by a skilled physician in order to avoid misinterpretation of technical artifacts, normal state fluctuations and various physiological rhythms.

Analysis of photic driving

Photic driving may be increased in migraine and tension-type headache patient groups as compared with headache-free subjects. The specificity of the method is not yet sufficiently documented.

There is not enough evidence to suggest that the photic driving methods that are currently in use can reliably discriminate either between migraine and non-migraine primary headache patients or between primary headache patients and headache-free subjects.

This is a class II level of evidence and the grade of recommendation is B.

Evoked potentials

The literature data, often conflicting, failed to demonstrate the usefulness of EPs as a diagnostic tool in migraine. Findings should therefore be replicated before visually evoked potentials (VEPs) can be recommended in the diagnosis of migraine (not enough data are available for other types of headache). In conclusion, we do not recommend the use of EPs in the diagnosis of headache disorders.

This is a class II level of evidence, but the literature contains contrasting data and the clinical significance of abnormalities is poorly understood. The grade of recommendation is B.

Reflex responses

Most of the neurophysiological investigation techniques have only limited usefulness in the diagnosis of headache. Further research in large populations is needed in order to establish which electrophysiological markers could be relevant in clinical practice.

This is a class IV level of evidence for nociceptive flexion reflex (not blinded studies), and class III for corneal reflex and blink reflex. The grade of recommendation is C and B respectively. As for exteroceptive suppression of masticatory muscle activity, only few blinded studies (class III) fail to confirm previous investigations: the grade of recommendation is C.

Autonomic tests

Studies of autonomic functions in migraine and cluster headache were mostly focused on autonomic systems innervating specific target organs which, anatomically and functionally, are not necessarily related to the supposed autonomic origin of the pain. Autonomic parameters are confounded by effector organ response characteristics. Therefore, there is no clear evidence justifying the recommendation of autonomic tests for the routine clinical examination of headache patients.

This is a class IV level of evidence and the grade of recommendation is C.

Clinical tests, PPTs and EMG (with special reference to TTH)

Tenderness recorded by manual palpation is the most specific and sensitive test in patients with TTH, and can therefore be recommended as a routine clinical test in contrast to EMG and PPTs. However, this manual palpation is non-specific and cannot be used to discriminate between different coexisting primary or secondary headaches.

This is a class IV level of evidence and the grade of recommendation is C (few blinded studies mainly concerning methodology in healthy volunteers).

Neuroimaging

When neuroimaging is warranted, the most sensitive method should be used, and we recommend MRI and not CT in these cases.

The grade of recommendation is C, as most studies are non-analytical and although there exist a few randomized clinical trials, some of them are not directly relevant to these recommendations (class IV).

Our specific recommendations are:

1. In adult and paediatric patients with migraine, with no recent change in pattern, no history of seizures, and no other focal neurological signs or symptoms, the routine use of neuroimaging is not warranted.
2. In patients with atypical headache patterns, a history of seizures, and/or neurological signs or symptoms, or symptomatic illness such as tumours, acquired immunodeficiency syndrome (AIDS) and neurofibromatosis, MRI may be indicated (to be carefully evaluated in each case).

SPECT and PET

If attacks can be fully accounted for by the standard headache classification (IHS), a PET or SPECT scan will generally be of no further diagnostic value.

Nuclear medicine examinations of cerebral circulation and metabolism can be carried out in subgroups of headache patients for diagnosis and evaluation of complications. rCBF can be of particular value in patients in whom the standard classification (IHS) cannot be fully applied, when patients experience unusually severe attacks, or the quality or severity of attacks has changed. rCBF recordings should then be carried out both during an attack (if possible several repeated scans) and interictally (at a time interval of >5 days after an attack). Quantifiable rCBF measurements are preferable to distribution images.

This is a class IV level of evidence, i.e. most studies are case reports or case series, and therefore the grade of recommendation is C. There is insufficient evidence to make specific recommendations.

Transcranial Doppler

Transcranial Doppler examination is not helpful in headache diagnosis. It is, however, a non-invasive examination with excellent temporal resolution which is useful for studying the vascular aspects of the headache pathophysiology and the vascular effects of anti-headache medication. The information obtained using this method is easier to interpret if side-to-side comparisons are made or if it is combined with rCBF measurements.

This is a class IV level of evidence and the grade of recommendation is C.

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Note

As this paper was going to press, the new International Headache Society Classification of Headache Disorders was published (Cephalalgia 2004, vol. 24, Suppl. 1). This key reference includes clinical and instrumental diagnostic criteria for differentiating between primary and secondary headaches and its consultation is strongly recommended.

The present guidelines and recommendations are intended to furnish the reader with information, based on the evidence in the literature, concerning the usefulness of instrumental investigations in non-acute headache; clearly, however, each clinical judgment is the responsibility of the physician(s) concerned.

This review is based on a vast number of publications, even though only the key references could be included. The following papers provide more exhaustive lists:

- Friberg L, Sandrini G, Jänig W *et al.* (2003). Instrumental investigations in primary headache. An updated review and new perspectives. Funct Neurol 8:27–44
- Sandrini G, Friberg L, Schoenen J, Nappi G (2003). Exploring pathophysiology of headache. Cephalalgia 23(suppl 1):1–52