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EFNS GUIDELINES

Neurophysiological tests and neuroimaging procedures in non-acute headache (2nd edition)

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Background and purpose: A large number of instrumental investigations are used in patients with non-acute headache in both research and clinical fields. Although the literature has shown that most of these tools contributed greatly to increasing understanding of the pathogenesis of primary headache, they are of little or no value in the clinical setting.

Methods: This paper provides an update of the 2004 EFNS guidelines and recommendations for the use of neurophysiological tools and neuroimaging procedures in non-acute headache (first edition). Even though the period since the publication of the first edition has seen an increase in the number of published papers dealing with this topic, the updated guidelines contain only minimal changes in the levels of evidence and grades of recommendation.

Results: (i) Interictal *EEG* is not routinely indicated in the diagnostic evaluation of patients with headache. 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 or basilar migraine. (ii) Recording *evoked potentials* is not recommended for the diagnosis of headache disorders. (iii) There is no evidence warranting recommendation of *reflex responses or autonomic tests* for the routine clinical examination of patients with headache. (iv) *Manual palpation* of pericranial muscles, with standardized palpation pressure, can be recommended for subdividing patient groups but not for diagnosis. Pain threshold measurements and EMG are not recommended as clinical diagnostic tests. (v) In adult and pediatric patients with migraine, with no recent change in attack pattern, no history of seizures, and no other focal neurological symptoms or signs, the routine use of *neuroimaging* is not warranted. In patients with trigeminal autonomic cephalalgia, *neuroimaging* should be carefully considered and may necessitate additional scanning of intracranial/cervical vasculature and/or the sellar/orbital/(para)nasal region. In patients with atypical headache patterns, a history of seizures and/or focal neurological symptoms or signs, MRI may be indicated. (vi) If attacks can be fully accounted for by the standard headache classification (IHS), a PET or SPECT scan will normally be of no further diagnostic value. Nuclear medical examinations of the cerebral circulation and metabolism can be carried out in subgroups of patients with headache for the diagnosis and evaluation of complications, when patients experience unusually severe attacks or when the quality or severity of attacks has changed. (vii) *Transcranial Doppler* examination is not helpful in headache diagnosis.

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Conclusion: Although many of the examinations described in the present guidelines are of little or no value in the clinical setting, most of the tools, including thermal pain thresholds and transcranial magnetic stimulation, have considerable potential for differential diagnostic evaluation as well as for the further exploration of headache pathophysiology and the effects of pharmacological treatment.

Introduction

The most important tools in the diagnosis and treatment of headache disorders are, without doubt, careful clinical neurological examinations and detailed reports on the patient's history and symptoms. Application of the diagnostic criteria of the International Headache Society (IHS Classification 2nd edition, 2004 [1]) can lead to a probable diagnosis that 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 an update of the first edition of the EFNS guidelines and recommendations for the use of neurophysiological tools and neuroimaging procedures in non-acute headache [2], based on a critical review of the literature and an evaluation of the clinical usefulness of these tests and procedures in the diagnostic setting. Guidelines on this same topic have been published by various authors [3–5]. Of all the available techniques, neuroimaging, particularly magnetic resonance imaging (MRI), is still the most suitable and cost-effective paraclinical testing method used in patients with headache, with the highest rate of diagnosis. Finally, we consider the potential use of these methods in headache research.

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 patients with non-acute headache. An extensive review of the main references in the literature (1988–2003), together with an update on the most important contributions made by neurophysiological studies to our understanding of the pathogenesis of primary headache, was published in connection with the release of the first edition of these guidelines [2,6]. Key literature references pre-dating the first edition of the IHS Classification [7] were particularly carefully examined as these studies applied different diagnostic criteria for headache. Additional reviews of published clinical evidence (from 2004 to July 2009) were performed for the present update (based on PubMed searches for each method combined with headache, cephalalgia, or migraine).

Table 1 Summary of recommendations and levels

Method	Routine evaluation	Level of recommendation[a]	Change from the 2004-guideline[b]
EEG	Indicated for basilar/hemiplegic migraine and epilepsy-related headache	IIB	Unchanged
EP	Not recommended	IIB	Unchanged
Reflex responses	Not recommended	IV (flexion reflex), IIIC (ES2, corneal and blink reflex)	Unchanged
Autonomic tests	Not recommended	IIIC	Level increased from IVC in 2004, recommendation unchanged
Clinical tenderness test and surface EMG	Not recommended for diagnosis, manual palpation useful in classification	IIB	Level increased from IVC in 2004, recommendation unchanged
Neuroimaging	MRI recommended in patients with TAC, atypical headache, seizures or focal signs	IIIB	Level increased from IVC in 2004, TAC is a new indication
SPECT and PET	Recommended when selected patients experience unusual and/or severe attacks,	IV	Unchanged
Transcranial Doppler	Not recommended	IV	Unchanged

[a]Brainin *et al.* [8]; [b]Sandrini *et al.* [2]; TAC trigeminal autonomic cephalalgia.

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The guidelines were prepared according to the EFNS criteria [8,9], and the levels of evidence and grades of recommendation are expressed in accordance with this reference (Table 1).

Main findings for the different techniques

Electroencephalography (EEG)

The usefulness of EEG in the diagnosis of headache is debated. Early EEG studies of migraine emphasized the frequent abnormal recordings found; however, contemporary reviewers have criticized most of these studies for various methodological omissions and flaws [10,11]. The American Academy of Neurology concluded that '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 [12].

EEG is the best laboratory investigation to support the clinical diagnosis of epilepsy, showing good sensitivity (80–90% in serial recordings) and specificity (false-positive findings in 0.2–3.5% of healthy subjects) [13]. It also plays an important role in the evaluation of other focal and diffuse 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 [14].

Spectral bandpower abnormalities have recently been reported before and during headache in migraineurs [15]. The utility of advanced methods based on coherence and neural networks [16] has not yet been independently confirmed. Current QEEG methods are still not routinely indicated in the diagnostic evaluation of patients with headache.

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

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 [17].

Reflex responses

Several electrophysiological techniques have been used to explore polysynaptic reflexes in patients with headache. The blink reflex (BR) and corneal reflex (CR) are reflected in the bilateral closure of the eyelids in response to a stimulus, which is usually, in laboratory settings, an 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 BR R1 component reflects the integrity of the efferent pathway (the facial nerve), the R2 the activity of the trigeminal complex at the brainstem, while the R3 seems to be part of the startle reaction. 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 [18–21] 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 interneurons 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 headaches (TTHs) [22].

Recent evidence suggests that nociceptive blink reflex (nBR) testing could provide an indicator for sensitization phenomena induced by nitroglycerin [23]. Using the nBR and pain-related evoked potentials (PREPs), Obermann *et al*. [24] highlighted an impairment of the trigeminal nociceptive system due to demyelination and/or axonal dysfunction on the symptomatic side and located this defect close to the root entry zone in the brainstem in trigeminal neuralgia.

Nociceptive flexion reflexes (NFRs), evoked at the biceps femoral muscle by electrical stimulation of the

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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 patients with headache [19]. NFRs made it possible to document sensitization phenomena and impairment of diffuse noxious inhibitory controls in migraine and chronic TTH [25,26].

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 neurons. 'Sympathetic' and 'parasympathetic' neurons are actually defined on the basis of anatomical rather than functional criteria; thus, afferent neurons innervating visceral organs are not denoted as sympathetic or parasympathetic, but as visceral [27,28]. When considering the role of the ANS in the different types of headache, there are three questions that should be borne in mind [29,30]:

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 [30–32].
2 Are the 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 that 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 pathophysiological conditions [30].
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 that may underlie both headache and autonomic disturbances.

The diagnosis and management of autonomic disorders are highly dependent on the testing procedures used [33]. Neurophysiological techniques have revealed several autonomic disturbances in primary headache, cluster headache, and trigeminal autonomic cephalalgia in particular [34], but the clinical importance of these findings is doubtful.

Clinical tests in headache

Central sensitization is thought to play an important role in the maintenance and exacerbation of the acute migraine headache attack and in the development of the chronic form of migraine, as well as in TTH [35–38]. Clinically, central sensitization may result in allodynia of the face and scalp [35,37,38] during the headache attack, whereas pain sensitivity seems to be normal between attacks [37,38]. Central sensitization is also associated with cortical plastic changes in the chronic subforms [36]. However, clinical tests to demonstrate central sensitization are still unspecific and cannot yet be used to discriminate between different coexisting primary or secondary headaches. The ICHD-I and II divided TTH arbitrarily into two subgroups to study the pathophysiological relevance of pericranial muscles in this disorder. This subdivision was motivated by the clinical observation that many patients with TTH have increased tension, tenderness, and stiffness in their neck and shoulder muscles, whereas some, a smaller group and much more difficult to treat, lack muscle tenderness. The first IHS Classification did not lay down specific diagnostic methods, and although several studies have been carried out since then [20,35,39–41], 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, but methodological studies now show manual palpation to be an easy and reliable method of studying myofascial pain sensitivity in a clinical setting, providing the intensity of the applied pressure is controlled [39]. Most but not all systematic studies of the pressure pain threshold (PPT) demonstrate that patients with chronic TTH have increased pain sensitivity because of central sensitization [20,35,36,39,42]. Nevertheless, neither PPT nor surface EMG recordings from the pericranial muscles provide additional, diagnostic information in the clinical setting. Therefore, although the evidence is limited, only manual palpation, preferably pressure-controlled palpation, can be recommended to discriminate between the three subtypes of TTH (infrequent episodic, episodic, or chronic TTH), and as yet, no clinical test can be recommended for migraine.

Neuroimaging

Radiological examinations are often sought in patients with headache. Most headache sufferers seeking medical attention fear they may have a serious illness and will often request a radiological investigation. As radiological examinations are not particularly invasive or uncomfortable and as they detect any intracranial

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diseases present, the threshold for requesting them is low. However, when deciding whether to use radiological techniques in patients with headache, one should consider the likelihood of detecting underlying diseases [43]. In the medical literature, studies that use radiological techniques in populations of patients with headache can be divided into three categories. First, studies investigating the etiology and pathophysiological mechanisms of headache; second, studies focusing on the pathological sequelae of headache; and third, studies on the role of radiological techniques in the work up of patients with headache. As one of the aims of this paper was to provide guidelines on the usefulness of radiological techniques in the evaluation of patients with headache with normal neurological examinations, we reviewed a subset of the third category.

A previous literature review, too, was conducted to establish guidelines for the future use of radiological methods in patients with headache [44], and the authors found these methods to present certain limitations. Although there is a need for further systematic studies on this topic, some conclusions can, nevertheless, be drawn [44].

There is no role for conventional Roentgen techniques (skull films) in the work up of patients with headache, 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 arteriovenous malformations (AVMs) and fistulas. However, it is relatively rare for any of these conditions to underlie the headache, and furthermore, most 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 patients with headache 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. In the presence of a normal MRI (without Gd) and in the absence of other disease and suspicion on metastasis/vasculitis/etc., there is no need for additional scans with Gd.

A large prospective consecutive study by Sempere *et al*. [45] included 1876 patients with non-acute headache. Neuroimaging was performed with MRI or CT. Significant intracranial lesions were found in 22 patients (1.2%). The rate of significant intracranial abnormalities in patients with headache and normal neurological examination was 0.9%. However, the only clinical variable associated with a higher probability of intracranial abnormalities was neurological examination. The authors concluded that the proportion of patients with headache and intracranial lesions was relatively small and that neither neurological examination nor features in the clinical history provide a basis on which to rule out such abnormalities.

Very recently, a population-based MRI study demonstrated that migraine is associated with an increased risk of deep white matter lesions in women and migraine with aura with an increased risk of subclinical cerebellar infarcts. However, further investigations are needed to define the long-term functional correlates [46]. The identified lesions are not thought to be the cause of headache attacks.

Prospective studies on the prevalence of causal lesions for trigeminal autonomic cephalalgias (TACs) are not available. Wilbrink *et al*. [47] recently reviewed the relevance of neuroimaging in TACs. The review included data from 56 case reports of patients who clinically had a typical or atypical TAC and who all improved after treatment or resolution of an underlying lesion. This supports the concept that – at least in some cases – TACs are secondary to a treatable lesion. Cases had tumors ($n = 27$; e.g., pituitary tumor, orbital tumor, intracranial meningioma, primary brain tumor), vascular lesions ($n = 22$; e.g., carotid or vertebral artery dissection, intracavernous, intracranial or cervical artery aneurysm, and arteriovenous malformation), and other disease ($n = 7$; including demyelinating disease, sinusitis and foreign body). The authors concluded that even clinically typical TACs can be attributed to structural lesions and that no 'typical' warning signs or symptoms help in selecting patients for imaging. Therefore, it was recommended to carefully consider neuroimaging (preferably brain MRI scanning) in all patients with TAC(-like) syndromes. Depending on the degree of suspicion, additional imaging should also be considered to assess intracranial and cervical vasculature, and the sellar and paranasal region.

SPECT and PET

Single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) are nuclear medicine imaging methods [48], 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.

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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 [49]. Tc^{99m}-labeled rCBF tracers are the ones most frequently used because Tc^{99m} is readily available in all nuclear medicine departments. SPECT rCBF investigations can provide information about acute changes in regional perfusion that often arise in relation to the neurological symptoms associated with the aura phase of migraine [6,50]. SPECT combined with transcranial Doppler (TCD) can, furthermore, provide information about changes in the diameters of the larger intracranial arteries [51].

Positron emission tomography is a cumbersome and more expensive technique than SPECT. With the exception of F^{18}-labeled tracers ($t_{1/2}$ = 10 min), most PET isotopes decay very quickly. Therefore, PET requires an in-house cyclotron and online radiochemistry production unit [52]. 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-labeled tracers for PET, for example, 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 centers, located in university hospitals. Both techniques are currently used in the investigation of vascular changes in migraine.

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 patients with headache, as each cerebral vessel supplies a defined volume of cerebral tissue [53]. TCD is mainly used to evaluate vascular reactivity in migraine [6].

Recommendations and guidelines

EEG

Interictal EEG is 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; (v) other risk factors for epilepsy.

Ictal EEG is indicated when headache is suspected to be a symptom of epileptic seizures or an encephalopathy. Ictal EEG is indicated during episodes suggesting complicated aura and during auras associated with decreased consciousness or confusion.

Neither interictal routine EEG with standard visual interpretation nor quantitative EEG spectral analysis is routinely indicated in the diagnostic evaluation of patients with headache. This is a class II level of evidence, and the grade of recommendation is B.

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 patients with headache or between primary headache patients and headache-free subjects (Class II, Grade B).

Evoked potentials

The literature data, often conflicting, fail 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 reflex response investigations have only limited usefulness in the diagnosis of headache. Further research in large populations is needed to establish which electrophysiological markers could be relevant in clinical practice.

This is a class IV level of evidence for the nociceptive flexion reflex (non-blinded studies) and a class III level for the corneal reflex and the blink reflex. The grade of

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recommendation is C for the corneal and blink reflex. 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 patients with headache (class III, grade C).

Clinical tests in headache

Tenderness recorded by manual palpation is the most specific and sensitive test in patients with tension-type headache and can therefore be recommended as a routine clinical test in contrast to EMG and pressure pain thresholds. Manual palpation is, however, non-specific and cannot be used to discriminate between different coexisting primary or secondary headaches. No clinical test can be recommended in migraine.

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

Neuroimaging

1 In adult and pediatric 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 new symptoms suggesting a trigeminal autonomic cephalalgia, neuroimaging is recommended to be carefully considered. Depending on the degree of suspicion, additional imaging should also be considered to assess intracranial and cervical vasculature, and the sellar and paranasal region.
3 In patients with atypical headache patterns, a history of seizures, or neurological signs or symptoms, or symptomatic illness such as tumors, acquired immunodeficiency syndrome (AIDS) and neurofibromatosis, MRI may be indicated (to be carefully evaluated in each case).

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

This is a class III recommendation 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 (the grade of recommendation is B).

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 patients with headache for diagnosis and evaluation of complications. rCBF recordings 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. In such situations, rCBF recordings should 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, that is, most studies are case reports or case series. 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 an excellent temporal resolution that is useful for studying the vascular aspects of the headache pathophysiology and the vascular effects of antiheadache 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.

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