

## Migraine diagnosis

### Introduction

Numerous epidemiological studies have demonstrated that migraine affects approximately 15%–18% of women and 6% of men in the course of their lives, with a peak prevalence between the ages of 25 and 55 years, in the period of maximum productivity [1–3]. Its disabling nature makes it a social disease with elevated direct and indirect economic costs [4–7]. Therefore, it is necessary to make an early diagnosis and to provide a correct treatment.

Migraine diagnosis has been up to now based on diagnostic criteria in the international classification deriving from clinical and epidemiological data, because of the incomplete knowledge of pathophysiological mechanisms and lack of specific “markers” [8]. The great merits of the International Headache Society (IHS) classification consist in having identified a set of diagnostic criteria specific for each headache form, in having edited the previous terminology, introducing, when necessary, a new terminology and creating a uniform interna-

tional dictionary in the matter of head pain. Twelve years from its publication, the classification of headache proposed by the IHS [8] is in many aspects still current even if its use has brought to light, which always happens when passing from theory to practice, some defective aspects. As an example, all the criteria have a high level of specificity or a high level of sensitivity, but never both; moreover, specific criteria were not provided for menstrual headache or chronic headache.

The lacking aspects of headache classification are being re-evaluated by an appropriate international committee for the purpose of publishing a revised version.

### Clinical history

Case history data are necessary for diagnosis and questions should be oriented to:

1. Determine if headache fulfills the set of diagnostic criteria for migraine. Tables 1 and 2 summarize the IHS

**Table 1** International Headache Society diagnostic criteria for migraine without aura. (From [8] with permission)

- A. At least 5 attacks fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours\* (untreated or unsuccessfully treated)<sup>a</sup>
- C. Headache has at least two of the following characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe intensity (inhibits or prohibits daily activities)
  4. Aggravation by walking stairs or similar routine physical activity
- D. During headache at least one of the following:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia
- E. At least one of the following:
  1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5–11 of the IHS classification
  2. History and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
  3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

\*In children below age 15, attacks may last 2–48 hours. If the patient falls asleep and wakes up without migraine, duration of attack is until time of awakening

<sup>a</sup> In the classification, at points 5–11, secondary headaches are listed

**Table 2** International Headache Society diagnostic criteria for migraine with aura. (From [8] with permission)

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- A. At least 2 attacks fulfilling B.
- B. At least 3 of the following 4 characteristics:
1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction.
  2. At least one aura symptom developing gradually over more than 4 minutes, or 2 or more symptoms occurring in succession.
  3. No aura symptom lasting more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
  4. Headache following aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura.)
- C. At least one of the following:
1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5–11
  2. History and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
  3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.
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criteria for migraine without aura and migraine with aura, respectively. To improve the reliability of the diagnosis, the use of semistructured interviews is recommended [9, 10].

2. Formulate additional questions to improve specificity and sensitivity of IHS diagnostic criteria. Additional information can be:
  - (i) Favorable to migraine diagnosis,
  - (ii) Unfavorable to migraine diagnosis.

When not otherwise specified, all statements have Level of evidence D; strength of evidence grade +. For the clinical history, level of recommendation is I.

(i) Additional information favorable to migraine diagnosis

1. *Alternating side in the case of unilateral pain.* Migrainous pain is unilateral in more than 50% of cases, and generally alternating [11–16]. A side-locked unilaterality of pain suggests another type of headache.
2. *Severe intensity of nausea, phonophobia and photophobia.* As these symptoms can also be present in tension-type headache, although with milder intensity, the use of a graded scale is recommended to distinguish the two forms (0, absent; 1, mild; 2, moderate; 3, severe) [13, 17, 18].
3. *Family history.* First-degree relatives of migraine patients show a 1.9-times higher risk than the general population to develop migraine without aura and a 1.4-times higher risk to develop migraine with aura [19].
4. *Prodromal symptoms* (irritability, mood changes, difficulty in concentrating, etc.). The incidence of prodromal symptoms varies from 7% to 88% in different studies on this topic [20].
5. *Triggers or aggravating factors.* These include food (not enough or too much), sleep, stress factors, relaxation after stress as in week-end migraine, etc. In particular, a positive likelihood ratio of 3.6 was calculated for food triggers (CI, 2.8–4.6) [21].

6. *Osmophobia and hyperosmia.* Both are sensitive and specific markers of migraine attack [18, 22, 24], even if they are not included in the present IHS classification.
7. *Recurrence of crises in the perimenstrual period.* Most women affected by migraine complain of crises in the menstrual period [24].
8. *Motion sickness.* Several studies have demonstrated that migraineurs are more susceptible to motion sickness than non-migraineurs [25].
9. *History of recurrent abdominal pain, cyclic vomiting, and benign paroxysmal vertigo in juvenile age.* These situations are common in this period of life but are more frequent in families of migraineurs [26].

(ii) Additional information unfavorable to migraine diagnosis

1. *Changes in attack severity.* Particular attention should be given when the crisis is referred to as “the worst headache of one’s life”. In these cases, a secondary headache must always be suspected. In a study carried out on adult patients visited in the emergency room in a 16-month period, 17% of those reporting “the worst headache of my life” revealed the signs of a subarachnoid hemorrhage on computed tomography (CT) [18, 27, 28].
2. *Changes of pain features.* One has to suspect a secondary headache [18, 28].
3. *Changes in frequency, in particular when frequency rapidly increases.* Also in this case, a secondary headache must be suspected [28, 29]. A rapidly increasing attack frequency significantly increases the odds of detecting significant lesions by neuroimaging [29]. Level of evidence A; strength of evidence grade ++.
4. *Progressively worsening course.* In this case a secondary headache should always be suspected [18, 28].
5. *History of headache causing awakening from sleep.* Although both migraine and cluster headache can occur

during sleep, it is important not to underestimate the possibility of a secondary headache [30–32].

6. *Headache worsening after Valsalva maneuver.* The precipitation of headache by coughing, sneezing or bending down can hide a secondary headache disorder [18].
7. *Association with systemic symptoms.* The presence of systemic symptoms such as myalgia, fever and weight loss indicates that a more serious underlying cause may be present [18].
8. *Association with further neurological symptoms.* The complaint of any impairment in the level of consciousness, seizures, somnolence or confusional state suggests the need for further investigations [18].
9. *Headache not responding to adequate pharmacological treatments (symptomatic or prophylactic).* After excluding the possibilities of poor therapeutic compliance and of symptomatic abuse, it is necessary to consider an alternative diagnosis.
10. *New onset after 40 years of age.* Only 8% of migraineurs report a new-onset headache after 40 years of age, so in this case, further investigations are needed [33]. Mean age at onset positively correlates with both significant (e.g. brain tumors, arteriovenous malformations, hydrocephalus) and insignificant (e.g. white matter lesions, brain atrophy) lesions detectable by neuroimaging techniques [29].
11. *Recent onset.* Two studies demonstrated the relevance of this factor. The former, by Duarte et al. [34], showed a shorter mean duration of disease (2.9 months) in patients with significant intracranial lesions than in patients without (8.2 months). When reviewing papers published after 1998, the Italian Ad Hoc Committee found one study which confirmed the shorter headache duration as a risk factor for intracranial lesions [35]. Although in Spanish, the study had been carried out in agreement with the criteria stated by the American guidelines [29]. In fact, that study was prospective, was carried out on a series of 299 consecutive patients and compared the clinical evaluation with CT, demonstrating that in subjects with headache onset over one month the prevalence of intracranial lesions was 1%, while in those cases with headache onset of less than or up to 1 month prevalence was 36% [35]. Level of evidence A; strength of evidence grade ++.

severe, prohibiting daily activities and compelling bed rest). The exact assessment of pain is important in choosing the right treatment and in evaluating the effects of therapy.

2. *It is strongly recommended to use a headache diary* to better define diagnosis, to follow the course of disease and to evaluate the effects of therapy.
3. *Menstrual headache* is not recognized as a nosographic entity in the current international classification [29]. This underscores the need for an exact definition of true forms and their characteristics. This should be one of the goals of the future revised classification.
4. *History of syncope.* A study investigating the occurrence of syncope in comorbidity with other diseases, in a sample of 16 809 inpatients from 3 Florence hospitals in 1998, demonstrated a significant association between migraine and syncope; these results support the hypothesis of the non-predictive value of syncope toward the detection of intracranial abnormalities in migraineurs [36].
5. *Vertigo.* Among papers published from 1996 through 2001, a study carried out on 400 patients (200 referring to a vertigo center and 200 to a headache center) showed an epidemiological association between vertigo and migraine (the prevalence of migraine was 38% in patients from the vertigo center while in the general population it was 24%) [37].

After the clinical history, the physician must perform general and neurological examinations, and request appropriate laboratory and radiological tests to exclude all the possible forms of secondary headache as stated by IHS criteria.

1. *General physical examination.* A complete general physical examination is mandatory. In particular, blood pressure, heart rate and body temperature should be measured. Paranasal sinuses, cervical and paraspinal muscles, as well as temporomandibular joints should be evaluated. Level of recommendation I.
2. *Neurological examination.* A complete neurological examination is mandatory. Particular attention must be given to exclude any impairment in the level of consciousness, the presence of meningeal irritation, abnormalities of the optic fundi and focal signs. Level of recommendation I.
3. *Neuroimaging tests* (CT, MRI, angio-MRI) are not warranted as routine diagnostic procedures, but must always be performed in patients with neurological signs. The presence of focal signs increases the likelihood of finding significant intracranial lesions such as brain tumors, arteriovenous malformations and hydrocephalus, while the absence of abnormalities revealed by the neurological examination decreases the odds of finding significant intracranial lesions with neuroimaging [29, 38]. Level of evidence C; strength of evidence grade ++; level of recommendation I.

### Additional recommendations

1. *It is recommended to grade pain severity through a scale* ranging from 0 to 3 (0, absent; 1, mild without any limitation of routine activities; 2, moderate and restraining daily activities but not requiring bed rest; 3,

Neuroimaging tests (CT, MRI, angio-MRI) should be considered in the following cases:

- *Patients with neurological symptoms.* In a 1996 review, Evans [39] confirmed the poor diagnostic contribution of neuroimaging in patients with recurrent headache and normal neurological examination which had already been stated in the American guidelines [29]. In a series of 3026 MRI scans performed since 1977, the overall prevalence of intracranial lesions was 0.8% for brain tumors, 0.2% for arteriovenous malformations, 0.3% for hydrocephalus, 0.1% for aneurysm, 0.2% for subdural hematoma and 1.2% for stroke [39]. Level of evidence D; strength of evidence grade ++, level of recommendation II.
- *Patients complaining of headache or with other risk factors* (see section entitled Additional information unfavorable toward the diagnosis of migraine). Level of recommendation II.

Brain MRI has a higher sensitivity than brain CT in detecting white matter abnormalities, arteriovenous malformations and posterior cranial fossa lesions, so the choice between these two techniques should be made according to the clinical suspicion [29, 39]. According to Evan's review, white matter abnormalities can be observed by MRI in 12%–46% of cases [39]. The results concerning a presumed higher frequency of white matter abnormalities in migraineurs than in controls are still contradictory [39]. As both white matter abnormalities and cortical atrophy are non-specific lesions, their detection does not furnish a consistent contribution to migraine diagnosis [39].

4. *Electroencephalography (EEG)* is not useful in the routine diagnosis of headache patients. EEG continues to be recommended in headache patients whose symptoms suggest a seizure (e.g. atypical migraine aura, loss of consciousness), but is not warranted to exclude intracranial lesions. These recommendations were already formulated in the American guidelines [29] and remain the same in the present guidelines. A report on EEG practice parameters for headache evaluation was published in 1995 [40]. The American guidelines [29] were based upon that document, which was realized after reviewing the scientific literature published from 1966 through 1994.

As for the possible increased prevalence of EEG abnormalities in migraineurs, published results are contradictory. Although no higher prevalence has been demonstrated in migraineurs than in controls, in the former there is a prominent photic driving for high frequencies of stimulus (H-response) that differentiated them from controls. This reported sensitivity of H-response varies from 26% to 100% and its specificity varies from 80% to 91%; in spite of this one cannot affirm that this

test is useful for diagnosis [40]. A recent study concerning H-response confirmed the presence of a more prominent photic driving in migraineurs than in controls [41]. Few studies have been carried out on the identification of a subgroup of headache sufferers by EEG features, and evidence is not sufficient to confirm that EEG can differentiate headaches [40]. Similarly, H-response seems not to be useful for differentiating migraine and tension-type headache [41]. Data regarding the possible role of EEG in identifying patients with secondary headache suggest that EEG is not useful to exclude intracranial disorders in patients with headache [42].

No scientific evidence exists to affirm that further laboratory and instrumental examinations (on blood, cerebrospinal fluid or other biological fluids) or electrophysiological, ultrasound, radiological and histological tests can detect sensitive and specific abnormalities in migraine from a diagnostic point of view. Each test should be used every time that the clinical suspicion suggests its utility.

Some abnormalities reported by scientific papers do not have a diagnostic value but a research aim

As for visual evoked potentials, an abnormal visual reactivity by steady state stimulus in the frequency range of 15–21 Hz was confirmed in the interictal phase of migraine patients compared to controls [42]. The linear discriminant analysis and, even more, the neural network method stated the absolute similarity of migraine and tension-type headache concerning that abnormal neurophysiological pattern, thus explaining both the difficulties in differential diagnosis and the pathophysiological affinity [43]. During the attack of migraine without aura, the visual potential steady state was suppressed, then increased in amplitude during the interictal phase: such pattern can be explained by an interictal abnormality, probably genetically defined and predisposing to migraine attacks. The potential suppression during the ictal phase is in agreement with a phenomenon similar to the spreading depression described in migraine with aura [43].

By studying the trigeminal pathways by using the blink reflex, a specific hyperexcitability of such circuits was found in both adult and juvenile migraineurs without aura during the interictal phase. That hyperexcitability may predispose to trigeminal activation and to the consequent precipitation of migraine attack [44]. Ictally, the delayed component of the blink reflex has been shown to be suppressed by the administration of triptans with activity also on the central nervous system, thus suggesting that the abnormalities of the blink reflex in migraine may be due to a specific serotonergic modulation [45].

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