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PECULIAR CLINICAL ASPECTS OF MIGRAINE

Chronification of migraine: what clinical strategies to combat it?

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Abstract Once migraine becomes chronic and has transformed into a form of headache that occurs daily or almost, the treatment options available are few and complex. This makes it important to take action before this point is reached, using all the measures that can be obtained from our current knowledge of chronic migraine (or transformed migraine) on the one hand, and on the potential factors of chronification (or transformation) on the other. Therefore, in order to reduce the risk of migraine chronification, it would appear important to: (a) administer suitable preventive treatments for subjects who have been suffering from migraines ≥4 days a month for ≥3 months; (b) take special care not to overuse symptomatic medications, particularly when they contain substances with a sedative effect; and (c) investigate the concomitant presence of depression, hypertension and excess weight and administer appropriate treatment when present.

Keywords Migraine · Migraine without aura · Chronic migraine · Transformed migraine · Chronification factors

Introduction

In most cases, the natural history of migraine without aura (MO) follows a favourable trend, with a reduction in the frequency and severity of attacks until, in some cases, they disappear completely, often many years after onset and usually after the age of 50–55 years [1].

Conversely, over the years, a minority of subjects suffering from MO experiences a gradual worsening, particularly as regards the frequency of the attacks, which eventually leads to the regular presence of headaches more than 15 days every month, if not every day or almost. In these cases, we talk about chronic migraine (CM) or transformed migraine (TM).

From the very first reports of this possible worsening evolution of MO, the attention of researcher was, quite rightly, focussed on identifying the factors for the transformation of MO into CM or TM. In other words, it was immediately clear how important it was in order to understand why some subjects, unlike the majority, experience chronification rather than a remission of their MO, to investigate the existence of potentially negative prognostic elements, by performing comparative analyses on large case series. This type of research constitutes the essential bases for being able to organise adequate strategies to treat or, better still, prevent CM or TM.

In order to be able to debate this issue in a complete manner and succeed in identifying the ways in which MO chronification can be avoided, we first need to consider, on a one-by-one basis, the protagonists of the case—MO, CM or TM—and the potential factors of transformation, evaluating what we know for sure and what we can suggest for a better and clinically more tangible definition of them.

Migraine without aura

Since the International Headache Society (HIS) published its classification in 1988 [2], at least as regards the

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characterisation of the individual attacks, MO has had a universally accepted position and set of diagnostic criteria. As further evidence of this, it did not undergo any variation in the subsequent edition, issued in 2004 (ICHD-II) [3]. In these classifications, MO is included as a migraine subtype (code 1) with a second diagnostic level (code 1.1), with no further subdivision.

A third diagnostic level for MO was recently proposed [4, 5] based on the frequency of attacks, more specifically according to the number of migraine days per month, According to which the code 1.1.1 refers to MO that occurs less than 4 days a month (infrequent MO), code 1.1.2 indicates MO that involves between 4 and 9 migraine days per month (frequent MO), and code 1.1.3 MO that presents 10–20 days a month (CM or very frequent MO).

This subdivision has a corresponding treatment plan to be followed: subjects with infrequent MO can be treated with symptomatic therapy alone, those with frequent MO must have preventive therapy, whilst continuing to take their current symptomatic therapy, provided it is efficacious and well tolerated and patients with CM (or very frequent MO) must follow preventive therapy and should change their symptomatic treatment, even when it is efficacious, to avoid running the risk of worsening their MO due to overuse.

The utility of a classification that considers the frequency with which MO presents, making a distinction between the various levels of progressive “severity”, is further iterated by the fact that high attack frequency constitutes a prognostic element that is predictive of MO chronification [6, 7].

Chronic migraine and/or transformed migraine

Although with MO we are well aware of what we are talking about, the same consensus does not exist for CM and TM. The current edition of the International Classification of Headache Disorders (ICHD-IIR del 2006) [8] resolves the issue by adopting the term CM with corresponding diagnostic criteria that are significantly different from those formulated in the ICHD-II published in 2004. Neither classification makes any reference to the term TM introduced by Mathew et al. [9] in the 1980s and subsequently widely adopted thanks to its practical classification and simple definition by Silberstein et al. [10].

In our recent proposal for a review of the migraine classification, mentioned in the previous paragraph, in which MO is split into three subtypes according to the number of migraine days per month, TM is considered a complication of migraine [4, 5, 11]. In this way, CM is a very frequent MO that maintains all the clinical characteristics typical of migraine, whereas TM is a form of MO that is modified (i.e. complicated) with respect to the past not merely because the number of headache days per month is higher than that of CM, but also because the headache does not present the aspects typical of migraine. This makes TM a more severe form and one that is more difficult to treat than CM, the latter being more likely to revert to frequent or infrequent MO than TM [7, 12].

The terms “chronic” and “chronification” are ambiguous and misleading. We believe that they should be disregarded and the terms “very frequent MO” (code 1.1.3) and “TM” (code 1.5.1) used instead, with the corresponding diagnostic criteria listed in Table 1. If we really want to keep the term CM, which it would appear that certain

Table 1 Proposed revision of migraine classification, and proposed diagnostic criteria for the three migraine without aura subtypes, and for transformed migraine

1.1 Migraine without aura
1.1.1 Infrequent migraine without aura
1.1.2 Frequent migraine without aura
1.1.3 Very frequent migraine without aura
1.1.3.1 With medication overuse
1.1.3.2 Without medication overuse
1.5 Complications of migraine
1.5.1 Transformed migraine
1.5.1.1 With medication overuse
1.5.1.2 Without medication overuse
1.1.1 Infrequent migraine without aura
Diagnostic criteria
A. headache fulfilling criteria C and D for 1.1 migraine without aura on ≤ 3 days/month for ≥ 3 months
B. Not attributed to another disorder
1.1.2 Frequent migraine without aura
Diagnostic criteria
A. headache fulfilling criteria C and D for 1.1 migraine without aura on >3 but <10 days/month for ≥ 3 months
B. Not attributed to another disorder
1.1.3 Very frequent migraine without aura
Diagnostic criteria
A. Headache fulfilling criteria C and D for 1.1 migraine without aura on ≥ 10 but ≤ 20 days/month for ≥ 3 months
B. Not attributed to another disorder
1.5.1 Transformed migraine
Diagnostic criteria
A. Headache (tension-type and/or migraine) on >20 days/month for ≥ 1 year and never with more than 5 consecutive headache-free days
B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 migraine without aura
C. On ≥ 10 days/month for ≥ 1 year, headache has fulfilled criteria for pain and associated symptoms of migraine without aura or patient has been successfully treated with an ergot or triptan
D. Not attributed to another disorder

authors are reluctant to give up, it could be used to define very frequent MO, but not TM, which can no longer be considered a simple migraine, rather a fully blown complicated migraine. In any case, what does not seem clinically acceptable is to contemplate including under the current single denomination of CM as defined by the ICHD-IIR [8], patients with such a difference in gravity as to warrant a subdivision into two well-defined groups: very frequent MO (or CM, if we wish) on the one hand, and TM on the other.

Potential factors of chronification/transformation

Regardless of whether we want to call it chronification or transformation, the important thing is to try and identify those factors, situations and any concomitant conditions that could favour a progression from MO towards CM or even TM.

Mathew et al. [9] identified overuse of symptomatic medications, depression, hypertension and surgical menopause as elements that are often present when MO transforms into TM.

Since then, several studies have dealt with the subject and further elements have been added [13–16], although some of them may appear dubious and need to be confirmed or refuted by further specific research, and to date the factors originally suggested by Mathew et al. [9] remain those most widely accepted.

Of the factors identified more recently, the potential role of obesity [17, 18] and cerebral venous sinus alterations [19] are undoubtedly of particular interest.

A comparative analysis [7] that we recently conducted between (a) a group of patients who at first observation presented with MO that either remained such, improved or completely disappeared over time and (b) a group of patients, similar to the first, originally affected by MO but that, over the years, evolved towards CM or TM, shows that a high frequency of attacks in both men and women and depression in men at first observation, i.e. when the diagnosis was still one of "simple" MO, constitute factors predictive of chronification/transformation. In addition, there is statistically significant evidence that depression in women and hypertension in both sexes, even when not present at first observation, tends to present in MO patients evolving towards CM/TM more frequently than in MO patients who either remain stable or improve over time.

Strategies for combatting the chronification/transformation of MO

Despite all the limits due to (a) a clinical classification of CM/TM that is not yet unanimously accepted and (b) an as yet incomplete and uncertain identification of the potential negative prognostic factors in the natural history of MO, at the current state of knowledge, it would appear possible and useful to adopt measures aimed at preventing the chronification of MO. The great importance of this operation derives also from the considerable difficulties of treating CM/TM once it is established [20, 21].

The first action to be taken is to treat MO while there is still time—"before the horse has bolted" [22], so to speak. For this to be plausible, we should take into consideration the data produced by an epidemiological study conducted in the USA [23], according to which unfortunately, just 6–7 % of subjects with MO in the general population consults a doctor and receives a correct diagnosis, suitable treatment and regular follow-up. This highlights the importance of transmitting adequate and correct information on migraine to both general practitioners and patients [24]. Treating MO whilst there is still time means making use, in those subjects who regularly suffer more than 3 migraine days a month, not merely of the necessary symptomatic medications, but above all, all the possible preventive treatments available, which, fortunately, are now fairly numerous.

Correct use of prophylactic treatments can also contribute to a better approach to the second important step in preventing MO chronification: avoiding overuse of symptomatic medications which, as has been extensively proven, can create a vicious circle of dependency and addiction, with a progressive worsening in the migraine situation [25]. Since the highest risk symptomatic medications in this sense are products containing a combination that also includes substances with a sedative action [26], it would appear appropriate for very frequent MO patients, until such time as they benefit from the preventive treatments prescribed, to avoid or at least limit the use of this type of symptomatic medication and also seek psychological support.

The third, fundamental measure for reducing the risk of chronification consists in dedicating the greatest possible care to the existence of potential comorbidities. Although it has been known for some time that certain conditions present more frequently in MO subjects [27, 28] and others have been identified more recently, not all the potential comorbidities of MO favour chronification. As far as we know at the current time, the highest-risk conditions are depression [9, 29], hypertension [9] and excess weight [17, 18]. As far as possible, these should be prevented in MO subjects and where they are already present, they require particularly careful treatment. In this sense, the fact that the medications that provide efficacious prophylaxis for MO also include antihypertensives and antidepressants may constitute an advantage.

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

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