

## REVIEW

# The complications of migraine classified under the International Classification of Headache Disorders: a review

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## ABSTRACT

Literature on the complications of migraine is scarce, and precise epidemiologic and pathophysiologic information is lacking, resulting in under-diagnosis and management challenges.

This article reviews the available information and underlines the importance of migraine complications classified under the International Classification of Headache Disorders, 2nd edition (ICHD-2).

The prevalence of migraine peaks between the ages of 25 and 55 years and accounts for the majority of serious headaches in this age group. The complications of migraine registered

in the ICHD-2 (International Headache Society [IHS] Classification), are chronic migraine (CM), status migrainosus (SM), persistent aura without infarction and migraine infarction (MI).

Published literature confirms the functional impact of CM and SM, which is characterized by increased frequency and/or intensity of headache. Aura without infarction is possibly a risk factor for migrainous stroke. MI accounts for 1% of the causes of ischemic cerebral infarct in the young, with a mortality rate of 10% and a recurrence rate of 8% within 5 years, with a regain in autonomy of 68–94%, and an impact on productivity of 42–91%.

## Introduction

Migraine is a common disabling disorder that is costly for the patient and a management challenge for the physician. The prevalence of migraine peaks between the ages of 25 and 55 years and accounts for the majority of serious headaches in this age group<sup>1</sup>. Recent studies suggest that severe headaches account for a large number of lost workdays and that people with severe migraine headache cost the American employers \$13 billion per year, and \$3.2 billion dollars to the Canadians<sup>2</sup>. The complications of migraine registered in the International Classifications of

Headache Disorders, 2nd edition (ICHD-2) (IHS Classification)<sup>3</sup>, are chronic migraine (CM) (IHS 1.5.1), status migrainosus (SM) (IHS 1.5.2), persistent aura without infarction (IHS 1.5.3) and migraine infarction (MI) (IHS 1.5.4). Migraine affects approximately 13% of the adult population and is approximately three times more common among women than men<sup>4</sup>. Population based studies have shown that headache is under diagnosed; specific medications may be underutilized, and over the counter analgesics may be overused. Diagnosis and management of CM needs a careful and detailed interview. Time limitations in a busy clinic often make this a challenge. SM is often

addressed in the emergency ward, with no adequate long-term follow-up. Persistent aura and MI are rare and difficult to diagnose. Patients that suffer from complications of migraine may have problems with headache management, disability, pain, worry and dissatisfaction with care. They may perceive themselves to be in worse general health, and have a significantly greater use of medical services than those with lower headache severity or without complications<sup>5</sup>.

## Complications classified in the ICHD-2

### Chronic migraine

#### *Generalities*

Chronic daily headache is defined by the IHS as more than 15 days of headache per month and regroups a heterogeneous group of primary and secondary conditions<sup>6</sup>. The IHS has not accepted a uniform classification for chronic daily headache but CM is the most prevalent. The underlying mechanisms of CM are not well known, but medication overuse is often associated.

#### *Description*

CM is described as migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse. Most cases of CM start as episodic migraine without aura<sup>7</sup>. As attack frequency increases, the number of migraine features diminish<sup>8,9</sup>. Loss of typical migrainous features sometimes lowers the number of headaches meeting the criteria for migraine, making the diagnosis of CM impossible. Some authors have described this phenomenon by the term 'transformed migraine' (TM), which is not included in the ICHD-2. It has been stated that CM is an earlier stage of TM<sup>8</sup>. The vicious circle of frequent headache causing frequent medication use often forces the clinician to diagnose CM and probable medication overuse headache (MOH). More recent criteria have accepted the diagnosis of MOH before improvement following discontinuation of the drug<sup>10</sup>. The role of medication overuse in promoting chronic headache is still controversial. In conclusion, the concept of CM itself is still a subject of debate.

#### *Prevalence*

The overall prevalence of chronic daily headache is 4.1%. In females and males respectively, in this group,

30% and 25% met the criteria for IHS migraine, 52% and 56% for chronic tension type headache, and 33% and 25% for TM<sup>11</sup>. Among adolescents and adults, there are substantial differences in the distribution of chronic daily headache subtypes<sup>12</sup>. Medication overuse is less common in adolescents (28.2% vs. 62.5%). TM without medication overuse is also more common in adolescents (40.5% vs. 24.9%). Adolescents tend to keep typical migrainous features, making the diagnosis of CM possible (74.5% vs. 25.8%)<sup>13</sup>. The frequency of TM is lower in adolescents (68.8% vs. 87.4%). The frequency of TM increases until the age of 50 years<sup>12</sup>.

### *Pathophysiology*

Identifiable trigger factors, such as hormonal changes, dietary items and stress were found in a significantly larger number in CM patients. Triggers may induce an increased rate of attacks. Repeated attacks of migraine induce central sensitization, defined as lowered firing threshold of nociceptive neurons in the trigeminal nucleus caudalis<sup>14</sup>. It can be clinically appreciated by the presence of allodynia (painful perception of non-painful stimuli)<sup>15</sup>. Magnetic resonance imaging (MRI) studies of CM patients have shown irreversible iron deposits in the periaqueductal gray matter<sup>16</sup>, and positron emission tomography (PET) studies showed changes of blood flow in the dorsal rostral pons, suggesting a role of these structures in pain modulation and, maybe, in the chronification process<sup>17</sup>.

### *Risk factors*

CM is predicted by recent onset of chronic daily headache, recent onset of migraine (< 36 months), and younger ages (< 15 years), but not gender or use of migraine-preventive drugs or medication overuse<sup>18-20</sup>. Obesity is a risk factor for TM<sup>21</sup>.

### *Prevention*

Identification and avoidance of triggers are essential. Avoidance of excessive use of symptomatic medications, and recognition of a development of tolerance to symptomatic medication, are important. Improvement of sleep abnormalities, reduction of stress and traumatic life events, improvement of depressive symptoms, if present, could be helpful<sup>22</sup>. Weight control is likely to prevent evolution to chronic headache. It is important to institute effective management of headaches to avoid progression of migraine to the more disabling TM. Headache diaries help to identify an increasing frequency.

## *Severe headaches in adults: psychological distress and co morbidities*

Approximately 15.1% of adults aged 18 years or older have reported a severe headache in the previous 3 months, migraine being the most frequent incapacitating headache. Those reporting such headaches were more likely to report insomnia, recurrent pain, and depressive or anxiety symptoms during the preceding 12 months. The level of functioning of persons with chronic headaches is worse than that associated with major chronic medical conditions such as arthritis and diabetes, and comparable to that reported by persons who have experienced recent myocardial infarction or congestive heart failure. Between episodes, those suffering from headache reported greater emotional distress, as well as less vitality, and more sleep disturbance than those without headache<sup>23</sup>.

## **Status migrainosus**

### *Generalities*

SM is an episodic migraine attack that is prolonged and refractory to standard therapy. For some patients the headache eventually continues unabated and indefinitely<sup>24</sup>. SM may require hospitalization or precipitate numerous visits to the emergency room for symptomatic relief.

### *Description*

SM is a debilitating migraine attack that lasts more than 72 hours. This time limit, distinguishing migraine from SM, has no physiological or rational basis. Interruption during sleep, and short lasting relief due to medication, do not exclude the diagnosis<sup>24</sup>. Debilitating and persistent are the key words of this condition. It can be difficult to differentiate SM from chronic daily headache with severe exacerbations.

### *Prevalence*

The prevalence and incidence of SM are unknown, but it is not a rare condition in specialized clinics and in the emergency room.

### *Evolution*

Most episodes start as a severe attack of migraine with or without aura. Initially, the attack resembles the subject's usual migraine, but the persistence and refractory nature of the attack are characteristic.

Patients are nauseated and vomit, sometimes to the point of dehydration. Patients become allodynic and hyperalgesic, exhausted, desperate, fatigued, and very worried. The severity and recurrence rate of attacks may vary. Some patients may have recurrent episodes, especially when acute episodes of migraine are not promptly and adequately treated.

### *Risk factors*

The first study on SM identified the following risk factors: emotional stress (67.5%), depression (30.2%) medication overuse and rebound (29.4%), anxiety (27.0%), dietary (19%), menstrual association (7.1%), estrogen therapy (2.4%), sleep loss (4.0%), heredity (4.0%), and discontinuance of prophylactic medication (4.0%)<sup>24</sup>. Perimenstrual migraine occurs in 50–60% of female migraineurs. Menstrual migraines are usually more resistant to treatment, generally not associated with aura, of longer duration (> 72 hours) and associated with more functional disability compared with attacks at other times of the month<sup>25</sup>. Rebound-withdrawal headache has been described in 61% and 78% of patients with SM<sup>26</sup>. Identification of triggers and evaluation of hormonal status help in management and avoidance of future episodes.

### *Prevention*

By the time patients are seen in SM, they have tried several remedies, over-the-counter and prescription drugs, migraine specific drugs such as triptans and ergots, with minimal or no benefit at all. As a result of severe and repeated vomiting, patients may become dehydrated. The mainstay of prevention is the recognition of risk factors, and providing the patient with appropriate rescue medication adjusted to the severity and complexity of the attacks, and providing punctual or continuous preventive migraine therapy<sup>27</sup>. In the emergency ward, patients with SM may improve with a dihydroergotamine protocol<sup>28</sup>.

## **Persistent aura without infarction**

### *Generalities*

A variety of positive and negative phenomena characterize a migraine aura. Positive visual phenomena may occur in patients with visual loss due to disruption at any level in the afferent visual pathway. The IHS defines a typical aura as one that develops over more than 4 minutes, lasts less than 1 hour, and precedes, accompanies, or follows a headache. A prolonged aura

lasts more than 60 minutes but less than or up to 7 days. Persistent aura without infarction is defined as more than 7 days of aura symptoms, without evidence of infarction<sup>29</sup>. Once again, this time definition is arbitrary. The migraine aura is predominantly visual (99%)<sup>30</sup>. Persisting aura symptoms are rare but are documented. They are often bilateral and may last for months or years. Prevalence is unknown and pathophysiological information about persisting aura is very limited.

### **Description**

A few reports are available. Liu *et al.*<sup>29</sup>, have reported three groups of patients, classified as persistent auras definitely, probably, or possibly secondary to a migrainous phenomenon. The first group had visual aura with headache, followed by persistent visual phenomena. The second group had a history of migraine with aura, but the temporal relationship between the onset of the persistent positive visual phenomena and migraine events was not typical. The third group had histories suggestive of migraine, but the persistent visual phenomena developed without any associated migraine events. The visual phenomena were commonly described as diffuse small particles, such as TV static, snow, lines of ants, dots, and rain that lasted for months to years. Previous reports have described hemi-field symptoms, but no full-field persistent visual phenomena have been described<sup>29</sup>.

### **Evolution**

Patients may be between the ages of 9 to 67. Most of the patients have typical migraine with aura before the constant phenomena develops. Visual symptoms and headaches do not seem to crescendo prior to the onset of the persistent phenomena, and no unifying prodromal event is apparent<sup>29</sup>. The persistent aura generally resolves spontaneously, but during the episodes patients are bothered by it and worried and may have difficulties in performing daily activities. Brain single photon emission computed tomography (SPECT) and brain perfusion MRI have revealed decreased occipital cortical blood perfusion<sup>31</sup>. In the cortical spreading model of Leao, which has been shown to be the mechanism underlying the typical aura<sup>32</sup>, the hypo-perfusion of the occipital cortex is secondary to lowered neuronal activity. Whether the persistence of the aura is due to persistence of this hypo perfusion despite return of normal neuronal activity or to prolonged neuronal depression by itself is unknown. This kind of sustained brain hypo-perfusion may represent a risk factor for the development of a

definitive ischemic structural lesion<sup>33</sup>. Patients with prolonged aura seem to have dysfunctions of P/Q Ca<sup>2+</sup>-channels, with subtle impairment of neuromuscular transmission (single endplate abnormalities) measured by single fiber electromyography<sup>34</sup>. The treatment of persistent aura is unknown, but successful treatment with divalproex sodium has been reported<sup>35</sup>.

### **Prevalence**

Aura symptoms are frequently visual disturbances, but the actual prevalence of persistent aura without infarction is unknown.

### **Prevention**

Until the pathophysiological mechanisms are better understood, prevention will be difficult.

## **Migraine infarction**

### **Generalities**

The prevalence of ischemic stroke in the young adult (< 45 years) is 8–23 per 100 000<sup>36,37</sup>. Migraine, particularly with aura, is a risk factor for ischemic stroke with a relative risk of 3, increased by tobacco smoking and oral hormonal contraceptives.

Epidemiological studies suggest the existence of close but complex relationships between estrogens, migraine and stroke in women before menopause<sup>38</sup>. Incidence of stroke in young women with migraine is rising, essentially as a result of the increase in tobacco smoking and obesity<sup>39</sup>.

### **Description**

MI is defined by one or more migrainous aura symptoms lasting more than 1 hour and/or associated with an ischemic brain lesion in the appropriate territory, demonstrated by neuroimaging. Ischemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura. Only the last fulfills the criteria for MI.

### **Prevalence and incidence**

In a population-based epidemiological survey in young Swedish adults aged 18 to 44 years<sup>40</sup>, cardio-embolism was the leading probable etiology (25–34%)

for ischemic stroke, followed by patent foramen oval or atrial-septal aneurysm (28%), spontaneous cervical arterial dissection (15–24%), anticardiolipin antibodies (4.7%), atherothrombotic vasculopathy (3.7%), oral contraceptives (7%), and migraine (1%).

The strict definition of migraine-induced stroke applied in studies conducted up to now have been inconsistent and probably explains why cerebral infarctions in the young, attributed to MI, have varied between 1.2% and 25%, with a mean value of 7%<sup>41</sup>.

### *Risk factors*

When cerebral ischemic infarction in the young adult is in the context of migraine as a syndrome (MELAS, CADASIL, Von Willebrandt, and autosomal dominant vascular retinopathy/migraine/Raynaud's phenomenon) there are no sex differences in prevalence, and estrogens are unlikely to play a major role<sup>39,42</sup>.

When migraine is considered a risk factor for cerebral ischemic infarction, in the context of migraine as a disease, although numerous potential biases exist when one reviews the large cohort studies, the case control studies, the computerized tomography (CT) and MRI studies, these biases are unlikely to explain this consistent increase (relative risk  $\times$  3) in the ischemic stroke risk observed in young women with migraine<sup>39,40,42–44</sup>. The increase is more marked for migraine with aura than in migraine without aura. The risk is more than tripled by smoking, and quadrupled with the use of oral hormonal contraceptives (OC). The triple combination of migraine, OC, and tobacco smoking increases the risk with an odds ratio of 34 to 35<sup>39</sup>. The mechanism of the increased risk of ischemic stroke in migraine, and in young migrainous women remains unknown and does not seem to be due to an increase in conventional risk factors such as diabetes, hypertension, and dyslipidemia.

### *Prevention*

Findings in young women aged less than 50 years are that 30% are affected by migraine mostly without aura, which is strongly influenced by estrogens. The absolute risk of ischemic stroke is very low, therefore there is no systematic contraindication to hormonal oral contraceptive use in migraineurs but a firm recommendation to stop smoking and to use low estrogen-content or progestogen only pills, particularly in cases of migraine with aura<sup>39</sup>.

For women after menopause, migraine improves in 50–60% of cases but may worsen with hormonal replacement therapy. In this age group, stroke is more frequent, affecting one of five women, and the risk

is significantly increased by hormonal replacement therapy<sup>39</sup>. There are no specific data on the association between migraine and hormonal replacement therapy and stroke risk. Migraine is not a contraindication to the use of hormonal replacement therapy which should be decided on a case-by-case basis.

## **Conclusion**

The complications of migraine are classified in the ICHD-2. CM is frequent, and has significant repercussions for quality of life. The exact definition and pathophysiological determinants of this condition are still imprecisely understood. SM, though commonly seen in the emergency ward and a very severe condition, has seldom been studied as an entity. There may be an overlap between exacerbations of CM and SM refractory headaches. Both conditions are associated with common triggers, including medication overuse. Persistent aura without infarction is rare. It may be a key to a better understanding of migraine, and patients presenting with it should be studied and the results published. Migraine and stroke may coexist for different reasons. True migraine-induced stroke may be difficult to diagnose, and the management of this condition is still to be determined.

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