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# Migraine - symptomatology, diagnostics, non-pharmacological and pharmacological procedures

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## ABSTRACT

Surprisingly, migraine is in the 3rd place of all diseases occurring in the world and affects 12% of the population, between the ages of 25 and 55. Migraine headaches significantly affect the quality of human life, while limiting proper bio-psycho-social functioning. This explains the vigorous

efforts of researchers to establish the still enigmatic pathomechanism of the disease. The dichotomy of migraine is based on its division into with aura or without aura, and its semiology is extremely diverse. Pharmacological and non-pharmacological treatment of migraines should include 2 strategies: immediate, aimed at combating the seizure, and prophylactic, the goal of which is to reduce the onset of the disease.

**Keywords:** headache, migraine, aura, triptans

## Introduction

Migraine is a chronic neurological disease with the cardinal feature being paroxysmal headache with significant intensity, which is accompanied by other, reversible neurological and systemic symptoms. The latest version of the classification of migraine headaches with or without aura, developed by *International Headache Society (IHS)*, shown in Table 1.

| *Table 1. Classification of migraines* |
|---|
| 1.1. Migraine without aura |
| 1.2. Migraine with aura |
| 1.2.1. A typical aura with migraine headache |
| 1.2.1. A typical aura with headache other than migraine |
| 1.2.3. A typical aura without headaches |
| 1.2.4. Half-head migraine family |
| 1.2.5. Occasional half-life migraine |
| 1.2.6. Basal-type migraine |
| 1.3. Children periodic syndromes that often precede migraine |
| 1.3.1. Cyclic vomiting |
| 1.3.2. Abdominal migraine |
| 1.3.3. Mild dizziness in children |
| 1.4. Retinal migraine |
| 1.5. Complicated migraine |
| 1.5.1. Chronic migraine |
| 1.5.2. Migraine state |
| 1.5.3. Aura without infarction |
| 1.5.4. Migraine cerebral infarction |
| 1.5.5. Convulsions caused by migraine |
| 1.6. Probable migraine |
| 1.6.1. Probable migraine without aura |
| 1.6.2. Probable migraine with aura |
| 1.6.3. Probable chronic migraine |

## Migraine epidemiology

The 1-year morbidity for migraine in the general population fluctuates at the level of 12% [1], which puts it in third place among all diseases occurring in the world. This means that migraine is significantly more common than diabetes or bronchial asthma [2]. 18% of women will have migraine during the year, and 33% in their lifetime, while the annual and lifetime prevalence for the male sex is 10% and 13% respectively [3]. Although the peak of migraine incidence is projected on the age range between 25 and 55, 10% of school-age children are given the diagnosis [4]. The most common

subtype of migraines is the form without aura [5]. The incidence of chronic migraine in the general population ranges between 0.9% and 5.1% [6]. Risk factors such as the high frequency of migraine attacks and their inadequate medication, female gender, low socioeconomic status, consumption of caffeine, snoring, head trauma, obesity, depression, anxiety, allodynia and associated pain syndromes risk escalating episodic migraine to chronic [3]. Despite widely available evidence-based guidelines for the management of migraine patients, its therapy is still suboptimal. The correct diagnosis is made only in 25% of patients, and half of them have been prescribed the appropriate emergency and prophylactic drugs [3,7]. The cardinal problem in the pharmacotherapy of migraines, which is an extremely difficult challenge for clinicians, is the abuse of painkillers by people with frequent headaches, which is seen in over 50% of cases [3].

Migraine ranks second among the most important causes of disability, thus contributing to sickness absence at work and the destruction of personal and family life. Approximately, more than half of respondents diagnosed with migraine participating in a longitudinal, web-based study *(The Chronic Migraine Epidemiology and Outcomes, CaMEO)* suffered a reduction of time dedicated to family life at least 1 or more times in the last month (48.2% -57.4% depending on the daily/monthly frequency of headaches), and many of them felt that they would be better parents if they did not have migraine headaches (subgroup with episodic migraine - 29.9% -58.0%, subgroup with chronic migraine 71.7%). Concerning the relationships of patients and their spouses, migraines, also during the interictal period, significantly increased stress in the relationship. In addition, 1/3 of respondents and 21.2% of their partners expressed concern about the family's financial security due to headaches [8].

**Migraine etiopathogenesis**

From *post hoc* analysis, an impressive number of scientific reports indicate that the etiopathogenesis of migraine headaches has not been fully elucidated.

The vast majority of scientific research on migraines focuses on the seizure phase. Nevertheless, no exact pathomechanism has been known so far to imply its origin in the prodromal period. A characteristic circadian rhythm of headaches (morning onset) and the specific nature of the prodromal symptoms suggest brainstem involvement in the early stages of the seizure. This is supported by positron emission tomography results *(PET),* by the means of which the first place in the central nervous system activated in the heraldic phase is the posterior and lateral part of the hypothalamus, the adjoining part of the abdominal cap [9], grey matter, the dorsal part of the bridge near the noradrenergic lupus and serotonergic Raphe nuclei [10]. In addition, from the histopathological point of view, it appears that the prodromal phase is based on phenomena occurring

globally in the neuroglia - cerebral tissue responsible for central energy metabolism, extracellular ion homeostasis, neural signalling, neuroprotection and fluid regulation [5].

*Pietrobon* [11] believes that migraine aura should be associated with the occurrence of cortical depression *(cortical spreading depression, CSD)*. This is an excessive membrane depolarisation of nerve and glial cells propagating at a velocity of 2-6 mm/min, the implication of which is the dysfunction of ion transport through the central nervous system membrane, increased concentration of extracellular potassium ions, release of neurotransmitters such as glutamate and transient intensity with subsequent decrease of cerebral blood flow. The *CSD* relationship with migraine visual aura is supported by changes in the *Blood-Oxygen-Level Dependent* signal in functional magnetic resonance imaging *(fMRI)* [12]. In addition, transgenic mice expressing mutations typical of familial hemiplegic migraine *(FHM)* characterised by an increased glutamatergic route, while proposing *CSD* [13]. There is also evidence that the experimental medicine - tonaberest [14], as well as single pulse transcranial magnetic stimulation *(sTMS)* [15] block *CSD*, thus showing preventive and curative effects in relation to migraine attacks with aura. In *induced and event-related potential studies* in patients with migraine, greater *CSD* excitement was demonstrated using visual, auditory, olfactory, self-sensory and nociceptive stimuli compared to healthy people. The above studies have consistently proved that in healthy people, repetitive stimulus weakens the feedback response (habituation), whereas in patients with migraine this response remains unchanged and even increased. Habituation is absent in the interictal period, but appears just before or during the onset of headache [16,17].

The triggering of the sensory nerve root fibres providing the pain-sensitive intracranial structures, i.e. the eye, the dura mater, the large cerebral vessels and the pia mater, and the sinus of the dura mater, is considered the source of headache in the onset phase. These non-myelinated fibres converge impulses to secondary neurons, and these in turn to the brainstem, thalamus, hypothalamus, cortical and subcortical regions. The discussed central convergence of the signal implies the characteristic distribution of migraine headache, from the eye and orbital area, through the frontal and temporal regions, to the occiput and the nape. The tripartite activation of individual structures of the central nervous system also explains the basis of the migraine-associated symptoms [18,19]. Projection of nociceptive stimuli from tripartite peripheral sensory fibres to secondary neurons is also associated with the release of calcitonin gene-related peptide *(CGRP)*, pituitary adenylate cyclase-activating polypeptide *(PACAP-38)* glutamate and nitric oxide [20]. *CGRP* and *PACAP-38* secretion induces dilatation of blood vessels and mast cell degranulation, which in turn activates vascular and meningeal nociceptors, thus arousing migraine headache [3].

**Migraine symptomatology**

Based on the available scientific reports, the classic course of a migraine attack was divided into 5 phases, that is the phase of heralds, aura, headache, regression of pain and post-lethal phase. However, not every episode is characterised by the presence of all phases, and some of them, except the aura, are not clearly delimited, and even overlap [5].

The onset of migraines is usually heralded by precursor symptoms, recorded a few hours or days before the onset of a headache. The prodromal phase usually includes concentration disorders, fatigue or stiff neck. Sometimes patients experience agitation, psychiatric disorders (i.e. depression, irritability, anxiety), neurological disorders (i.e. photophobia, phonophobia, hyperosmosis, allodynia), symptoms from the parasympathetic autonomic system (i.e. lacrimation) or general symptoms (i.e. pathological yawning), polyuria, specific cravings for selected foods, nausea and diarrhoea) [3].

The dichotomy of a migraine is based on its division into being with or without aura. 1/3 of patients, just before or together with headache, suffer from migraine aura, defined as fully reversible focal symptoms, developing gradually over 5-20 minutes and lasting less than 60 minutes [21]. The semiology accompanying the aura is extremely diverse and consists of, among others, visual, sensory, motor, speech and brainstem symptoms. In more than 90% of cases, clinicians are faced with a visual aura that manifests in the form of photophobia, image scintillation (shaking), light headedness, photopsins (flashes of light) and teichopsins (bright zigzag lines, reminiscent of fortifications, often shifting in the field of vision). Patients are less likely to report visual hallucinations (e.g., seeing "waving hot air"), metamorphosis (deformation of the visible image) to which, among others, macropsias (seeing objects that are excessively large) or micropipses (seeing objects that are excessively small). The second, most common symptom associated with the aura are paresthesia, which usually include the perioral region and distal parts of the limbs. These ailments, analogous to visual symptoms, are characterised by a migratory location and a tendency to transform their perception from positive (paresthesia) to negative (numbness). Occasionally, the aura manifests itself as a dysfunction in language expressiveness and aphasia. The aura manifestation is dizziness, dysarthria, bilateral paraesthesia, diplopia and ataxia. [3]. In turn, in migraine without aura, there are isolated headaches, without additional ailments. Importantly, in many cases, one patient has migraine with aura and without aura [5].

The axial phase of the disease includes headaches. While they may appear at any time of the day or night, their most common origin is in the period of sleep, just before waking up or immediately after getting up [22]. Pain can cover every part of the head. As a rule, it begins in the occipital region, but also in the cervical spine, and then spreads in the fronto-temporal direction [3]. Bilateral in children, during adolescence, transforms into a typical adult one-sided headache [5]. During a

seizure, the pain may change its location. Its pulsating nature was documented in 90.9% of patients [23]. During the natural course of the attack, pain gradually increases, reaching the peak of intensity - from moderate to severe, usually within 1 hour (48.1%) [23]. The average duration of migraine headache in adults varies between 4 and 72 hours, while in children it varies between 2 and 48 hours [3]. The dominant escalator of pain is routine physical activity (90%), and head movements [2,23]. Heterogeneous semiology that may accompany migraine headaches undeniably confirms their complex pathophysiology and the involvement of innumerable neural networks and various anatomical regions of the brain. Gastrointestinal disorders such as nausea (over 90% of patients), vomiting (70%), diarrhea (16%) and abdominal cramps are common complaints reported during a migraine attack. The intensity of nausea usually correlates with the headache severity profile [5]. Patients often experience sensory hyperstitia, in the form of photophobia (94%), phonophobia (91%), hyperosmia, osmophobia or allodynia [24,25]. It is believed that allodynia may be both a predictor of the sub-spectrum of therapeutic response to triptans, but also a risk factor for the progression of the disease to its chronic form [26]. Other symptoms may include nasal obstruction, dizziness, blurred vision, polyuria, urgent stool pressure, pale skin and excessive sweating [27].

A migraine headache usually diminishes within a few hours, often while sleeping. In this postdromal phase, the patient suffers from asthenia, somnolence, attention deficit, irritability, nausea and photophobia. In addition, there was an increased predilection for the induction of short-term headaches with its movements or the Valsalva test [3]. After a definitive resolution of the attack, headaches can be converted. If they appear in less than 24 hours, then according to the scholars' position they are a continuation of the same migraine attack - an attack of extreme fluctuation of pain intensity [28].

On the one hand, migraine was considered a disease of a paroxysmal nature - individual seizures are interspersed with asymptomatic intervals. On the other hand, a group of patients presenting a high frequency of seizures experienced interictal discomfort without accompanying headaches. These symptoms occur significantly more often in people with chronic migraine, compared to its episodic form. However, chronic migraine is diagnosed when headaches occur for more than 15 days a month, and at least 8 episodes meet the diagnostic criteria of migraine with or without aura [3].

**Recognising migraines**

Diagnostic criteria for migraines are based on the *International Clasification of Headache Disorders* classification (table 2 and 3). Nevertheless, the first-time seizure of migraine headache should be differentiated primarily with subarachnoid or intracerebral haemorrhage, as well as with meningitis and brain inflammation, and less frequently with other types of headache [29].

| ***Table 2. Diagnostic criteria for migraine without aura according to the International Clasification of Headache Disorders (ICDH, 2nd edition) [5]*** |
|---|
| A. At least 5 seizures meeting the B-D criteria. |
| B. Duration of pain 4-72 h (untreated or untreated unsuccessfully). |
| C. Pain is characterised by at least 2 of the following features: |
| 1. One-sided location |
| 2. A pulsating character |
| 3. Moderate or significant intensity |
| 4. Increases during normal physical activity or forces you to avoid it |
| D. Seizures are accompanied by at least 1 of the following ailments |
| 1. Nausea and/or vomiting |
| 2. Photophobia and phonophobia |
| 1.3.3. Mild dizziness in children |
| E. No relation to another disease |

| *Table 3. Criteria for the diagnosis of migraine with aura according to the International Classification of Headache Disorders (ICHD, 2nd edition) [5]* |
|---|
| A. At least 2 seizures fulfilling criterion B |
| B. Aura in migraine subtypes 1.2.1-1.2.6 meeting criteria B and C below |
| C. No relation to another disease |
| 1.2.1. A typical aura with migraine headache |
| A. At least 2 seizures meeting the B-D criteria |
| B. The aura proceeds from at least 1 of the following symptoms, but without paresis: |
| 1. Fully reversible visual disturbances consisting of additional symptoms (e.g. flickering lights, spots or lines) and/or symptoms of vision loss (e.g., impaired) |
| 2. Fully reversible sensory disturbances consisting of additional symptoms (e.g. stinging or tingling sensation) and/or symptoms of sensation loss (e.g. numbness) |
| 3. Fully reversible speech disorders |
| C. At least 2 of the following characteristics: |
| 1. Single tensive visual disturbances or one-sided sensory disturbances |
| 2. At least 1 of the aura symptoms develops gradually over ≥ 5 min and/or various consecutive aura symptoms within ≥ 5 min |
| 3. Each of the symptoms of the aura lasts ≥ 5 min and ≤ 60 min |
| D. Headache meeting the B-D criteria for 1.1 commencing at the time of the aura or within 60 minutes of its resignation |
| E. No relation to another disease |

**Migraine therapy**

Migraine treatment should include 2 strategies: immediate, targeted to combat the attack, and prophylactic, the goal of which is to reduce the onset of the disease.

**Interim therapy**

The first-line medications for mild or moderate headache are individually matched painkillers given as soon as possible after the onset of an attack in the right dosage and form. In at least one placebo-controlled trial, the efficacy of drugs such as acetylsalicylic acid (*(ASA)*; up to 1000 mg), diclofenac (50-100 mg), ibuprofen (200-800 mg) and paracetamol (1000 mg) [5,30,31] was proven. Increased nausea and vomiting impose the need to add antiemetics such as metoclopramide (at a dose of 10-20 mg), domperidone (at a dose of 20-60 mg) or prochlorperazine (10-25 mg) [5]

The priority analgesics in patients with moderate and severe headache are triptans, in the absence of contraindications to their use. They are highly selective 5-HT receptor agonists1B, 5-HT1Dand some of them also have affinity for the 5-HT receptor1F [3]. Individual relations vary in strength and duration of action, biological availability, and the frequency of adverse events. The first discovered triptan was sumatrymptane, which was the most-published clinical trial in relation to other drugs used in the treatment of migraine [5]. In comparative analyses of sumatrypan and zolmitriptan with *ASA* and metoclopramide has been shown to have comparable or slightly higher efficacy in favour of triptans [32,33]. Certainly, the advantage of tryptans is the heterogeneity of pharmaceutical forms of these drugs (tablets, tongue-soluble tablets, intra and subcutaneous injections, suppositories and nasal sprays), which allows their administration not only by oral, but also by nasal, rectal or subcutaneous delivery. It definitely helps the doctor and the patient to individualise the route of administration based on the dynamics and nature of the current seizure of migraine and the accompanying ailments. Treatment with triptans, like NSAIDs, should be started immediately after the onset of seizure, optimally in the prodromal phase. These medications, when given during the aura, are ineffective. Subcutaneous administration of sumatriptan, characterised by the lowest NNT number *(number needed to treat),* allows you to reach a painless period within 2 hours [34]. The analgesic effect of the group of drugs is determined by their repetitive doses, which means that the triptans do not eradicate a migraine attack *per se* but they alleviate its symptoms as long as they remain in high blood levels [28]. Resistance to the above drugs are prescribed at the point when 3 different triptans do not interrupt the migraine attack. The main side effects of triptans include excessive drowsiness, dizziness, chest discomfort, hot flushes, redness, tingling of arms and legs [35].

**Pharmacological prophylaxis**

The fundamental goal of the broader prophylactic treatment of migraine is to reduce the frequency, severity and duration of seizures in people with high frequencies of migraines. Pharmacological intervention is primarily indicated in patients with migraine attacks occurring more often than four times a month, and in people whose disease seriously disturbs proper functioning, reflecting on vital areas of life. In addition, it seems reasonable to implement prophylaxis in patients who are not subject to emergency treatment for seizures, as well as intolerance or contraindications to such pharmacotherapy. Prophylaxis is also recommended in people with hemiplegic migraine, base, in attacks with prolonged migraine aura and after migraine brain infarction [3]. According to scientifically-based guidelines of the Canadian Headache Society, the first-line drugs particularly recommended in the prevention of migraines are: topiramate, propranolol, nadolol, metoprolol, amitriptyline, gabapentin, candesartan, riboflavin, coenzyme Q10 and magnesium [36]. Patients with depression, sleep disorders and accompanying tension headaches benefit from amitriptyline [37]. In

turn, oestrogen preparations administered in the perimenal period [38] turn out to be effective in menstrual migraine. It is assumed that prophylactic treatment should last 3 months, on average half a year. Therapy ends when the stabilisation of seizure intensity is achieved by gradually reducing the dose of the drug. An important element in assessing the effectiveness of prophylaxis is a symptom diary recorded by the patient themselves. Deterioration of the general condition and recurrence of seizures during the withdrawal of the drug, imposes the need to increase its dose again and continue treatment for the next 6-9 months. Experience has shown that the abuse of analgesics, poor tolerance of the drug or side effects of these therapies, increase the risk of its failure [35].

**Non-pharmacological prophylaxis treatment**

It is extremely important to note, that not only pharmacological but also non-pharmacological procedures are effective in dealing with people with migraines. In particularly complicated and refractory cases, the implementation of combination therapy is suggested.

An extremely important element of non-pharmacological procedures is the avoidance of factors inducing seizure, as well as an adequate amount of sleep. In conservative procedures, the beneficial effects of relaxation techniques (i.e. progressive muscle relaxation, autogenic relaxation, meditation), behavioural-cognitive therapy and biofeedback were also confirmed. As clinical practice indicates, the next, quite frequent methods used in prevention are regular and often practiced aerobics, acupuncture, massages, posture and neck exercises, chiropractic and other manual procedures related to the spine [5]. A multidisciplinary strategy of action developed jointly by neurologists and physiotherapists, in a randomised clinical trial, has been assessed by patients with migraine as a major and significantly more effective treatment, compared to patients with whom the family doctor has implemented conventional therapy [39].

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