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Clinical and Pathogenetic Characteristics and Diagnostic Criteria of Migraine in Patients with Nonspecific Connective Tissue Dysplasia

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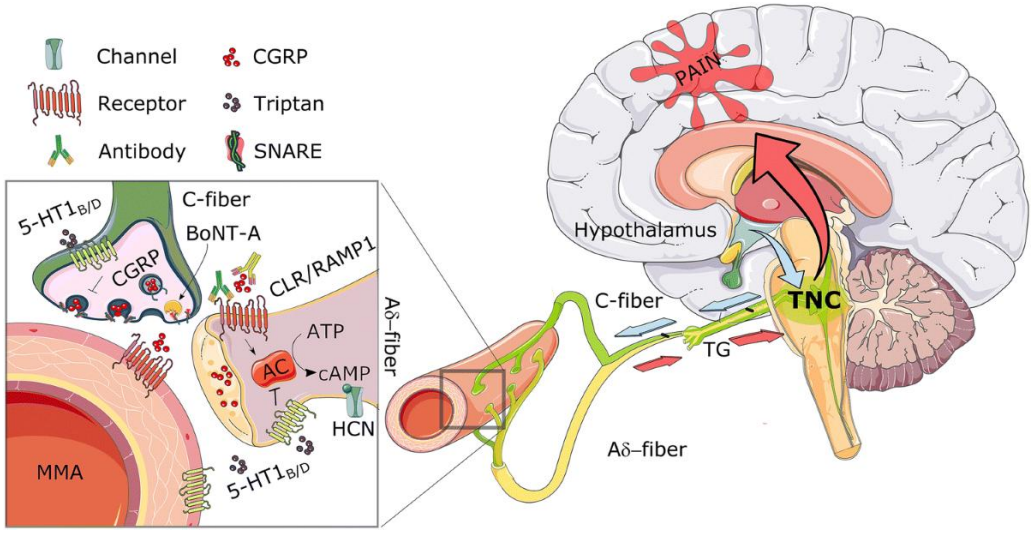
Abstract: Preliminary studies have shown that migraine is more common in patients with joint hypermobility syndrome (JHS). The aim of this study was to determine whether the prevalence, frequency, and disability of migraine differed between women with JHS and a control population. Twenty-eight patients with JHS and 232 controls participated in a cohort study. Participants underwent a structured interview and were diagnosed with migraine based on the criteria of the International Classification of Headache Disorders, 2nd edition. The primary outcome measures were migraine prevalence, frequency, and headache-related disability. Logistic regression was used for prevalence analysis, and Poisson regression was used for frequency and disability analyses. The results showed that the prevalence of migraine was 75% in JHS patients and 43% in controls. The adjusted odds ratio for migraine prevalence in patients with JHS was 3.19 (95% CI 1.24, 8.21).

Key points: Migraine diagnostic criteria, prevalence, diagnosis, treatment of migraine patients, pathogenesis, migraine genetics.

Introduction: The odds ratio for migraine frequency and headache-related disability was 1.67 (95% CI 1.01, 2.76) and 2.99 (95% CI 1.66, 5.38) for JHS patients, respectively. Our study shows that JHS is a clinical disorder strongly associated with the prevalence, frequency, and disability of migraine in women. Migraine is a common neurological disorder that affects women more than men, has a clear genetic basis, is often associated with connective tissue dysplasia and other genetic disorders, and is mainly reported in urban women. The diagnosis is based on the clinical criteria established in the International Classification of Headache Disorders, 3rd revision. Common symptoms of migraine are recurrent attacks of moderate to severe headache lasting 4-72 hours, unilateral, throbbing, aggravated by physical activity. Associated symptoms include nausea, vomiting, photophobia, and phonophobia. In some cases, migraine is preceded by an aura, which is characterized by reversible focal neurological symptoms that include visual or semisensory disturbances. The trigeminovascular system is involved in the pathogenesis of migraine. Nociceptive signals from the trigeminovascular system are transmitted to the brain centers responsible for the perception of pain. Migraine treatment is based on the identification of molecules involved in the genesis of its attack. The main treatment methods are presented based on domestic and foreign recommendations.

Materials and methods of research. The study sample included 260 women aged 18–65 years, including 28 JHS cases and 232 non-cases (controls). Men were not included in the regression analyses due to the small number of cases (n = 3) that prevented us from examining the effect of gender on the effect of Age was modeled as a binary variable (<45, ≥45 years) in all regression models (21 , 22). Age cutoff points were determined by generalized additive models (GAMs) of migraine and tension-type headache prevalence and were optimized for other models determined to fit the model.



GAMs showed a non-linear effect of continuous age, consistent with visual plots, indicating that age slopes changed at approximately 45 years for both headache types. Two separate models were run for each outcome measure to determine whether the observed associations were accounted for by the presence of comorbid psychiatric disorders. Model 1 used JHS (yes/no), age (<45, ≥45 years), and preventive medication (yes/no) as covariates, while Model 2 included JHS (yes/no), age (<45, ≥45 years), preventive medication (yes/no), and anxiety (yes/no). Comorbid depression was not included as a covariate in Model 2 because depression and anxiety were highly correlated and did not reach statistical significance in any of the models that included anxiety and depression. Analyses were performed using SAS for Windows v9.3 (SAS Institute, Cary, NC, USA); the R statistical software package was used to generate data plots (R Design Package 2008). Unless otherwise stated, a P value <0.05 was considered statistically significant.

Results: Twenty-eight cases and 232 controls were included in the study. The mean age was significantly different between the cases and controls (35.6 and 46.8 years; P value <0.01). The mean GAD-7 and PHQ-9 scores, which measure general anxiety and depression, were higher in those with JHS compared with controls, respectively (P values <0.01); general anxiety and depression in those with JHS were rated as moderate compared with mild in controls. The GAD-7 is a 7-item questionnaire designed to assess generalized anxiety disorder. Several domains of functional impairment are assessed based on days of disability. Each item is scored 0–3, and on a 21-point scale, generalized anxiety is rated as follows: 0–5, mild; 6–10, moderate; 11–15, moderately severe; and 16-21, severe.

The PHQ-9 is a 9-item questionnaire designed to assess depression. Several areas of functional impairment are assessed based on days of disability. Each item is scored 0–3, and depression is rated on a 27-point scale: 0–5, mild; 6–10, moderate; 11–15, moderately severe; and 16–27, severe.

The characteristics of the JHS patients showed a mean Beighton score of 6.54. All neurological examinations were normal in the JHS group. In addition, no intracranial lesions were detected by imaging in the three JHS patients who had brain MRIs.

Comorbid medical conditions were common in patients with JHS. The most common were arthritis in 54% (15/28), fibromyalgia in 39% (11/28), and POTS in 18% (5/28), followed by restless legs syndrome (18%, 5/28), sleep apnea (14%, 4/28), and periodic limb movements (11%, 3/28). Most

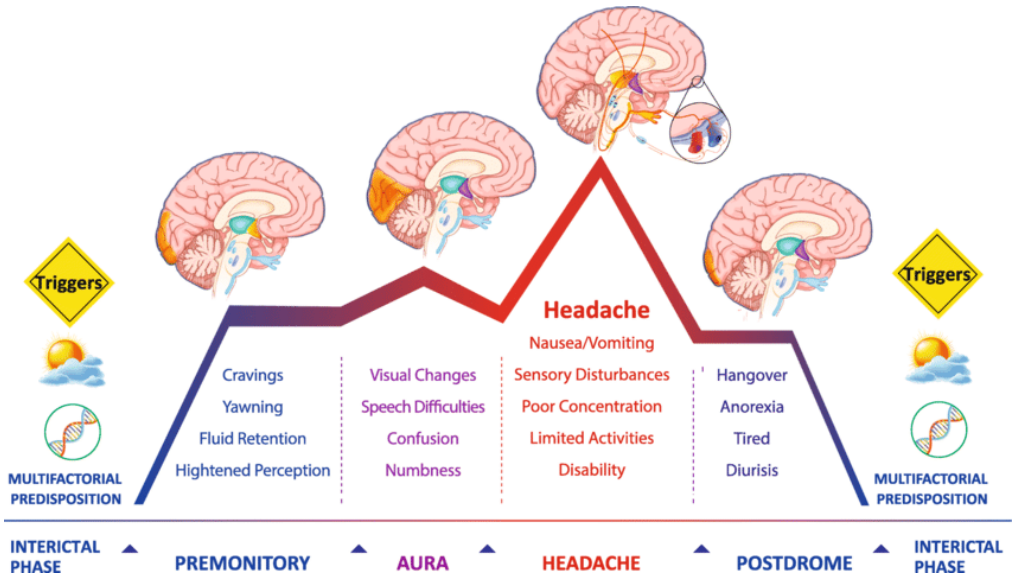
cases presented with TMD symptoms at screening (74%, 20/27). Echocardiogram reports from 18 cases showed three cases with trivial to mild tricuspid regurgitation without other valvular disease. Three cases had cervical disc disease based on available MRI reports, but NDI questionnaire results suggest that neck pain is very common. As indicated by the NDI questionnaire, functional disability due to neck pain in patients with JHS was rated as moderate in 22% (6/27), moderate in 59% (16/27), severe in 15% (4/27), and complete in 4% (1/27).

The overall prevalence of migraine was 75% in the JHS group and 43% in the control group (Tables 3 and 4). Migraine without aura and migraine with typical aura were diagnosed in 68% and 32% of the JHS group, respectively, and in 39% and 10% of the control group, respectively. The use of migraine abortives was almost the same between the two groups (P = 0.97), and cases were more likely to use migraine preventives (P < 0.01). The adjusted odds ratio (OR) of model 1 for the prevalence of migraine in the JHS group compared with the control group was 3.19 (95% CI 1.24, 8.21) after adjusting for the effects of age (<45 and ≥45 years). and migraine preventives (yes/no) were modeled as dichotomous variables. When anxiety was included as a covariate in Model 2, the adjusted OR for migraine prevalence was 2.91 (95% CI 1.02, 8.30) in the JHS group. Anxiety was significantly associated with migraine prevalence with an OR of 3.72 (95% CI 1.67, 8.25; Table 4).

Migraine (G43 according to the International Classification of Headache Disorders, 3rd revision, ICHD-3) is a complex of neurovascular disorders characterized by recurrent episodes of headache, often unilateral, often associated with visual or sensory disturbances, characterized by an aura and usually preceding the headache, although sometimes occurring after an attack of cephalalgia. Based on this, migraine is classified as migraine with aura (G43.1) or migraine without aura (G43.0).

Migraine has a clear genetic predisposition and is most often observed in women with onset at a young age. A characteristic feature of migraine is the sensitivity of nociceptive neurons of the central nervous system to pain. As a result, the slightest external irritation can cause severe headaches, even neurological disorders. The process becomes chronic, resulting in a sharp decrease in quality of life [1]. Migraine is often associated with systemic processes and the risk of cardiovascular diseases.

The problems of timely diagnosis and differential diagnosis of headache syndrome, treatment and prevention of migraine complications lead patients to neuropathologists, family doctors, therapists, and specialists in functional and visual diagnostics.



Distribution

According to our data, out of 485 urban women aged 20-39 years, 72 (14.85%) reported migraine during a clinical examination. According to the results of objective diagnostics, migraine was noted in 24 (4.95%) women. According to the results of a survey of 350 women of the same age in rural

areas and small regional centers, 28 (8%) of the respondents reported migraine. According to objective diagnostics, migraine was detected in seven (2%) cases. In developed countries, migraine is noted in 7% of school-age children and 15% of the adult population, 2/3 of whom are women. The highest prevalence is between 35 and 40 years of age, in 75% of cases, migraine begins before the age of 35. With age, the frequency of attacks, their intensity, and the overall prevalence of migraine decrease. The onset of migraine after the age of 50 requires the exclusion of secondary headaches.

Diagnostics

Diagnosis is based on the ICHD-3 criteria: migraine without aura, migraine with aura, and chronic migraine [2] (table). A more detailed classification is given in the International Classification of Diseases, 10th edition [3]. Migraine aura is usually described as a flickering or scotoma, less often as a semi-sensory symptom or speech disorder. Recurrent focal neurological symptoms develop gradually over 5–60 minutes. Headache occurs within the first hour after the onset of the aura. However, aura can occur both during and after the onset of pain.

The physiological basis of the aura in migraine is a self-propagating wave of depolarization of the cerebral cortex, which disrupts ion gradients and leads to cerebral hypoperfusion. Headache occurs. Hemodynamic disturbances are recorded on neuroimaging only in migraine patients with aura, but not in patients without aura. The wave of depolarization of the cerebral cortex temporarily opens the pannexin-1 neuronal channel. As a result, inflammatory mediators are released: nitric oxide and prostanoids. Intracranial vessels, according to the laws of inflammation (rubor, tumor, dolor, color, functia lesae), expand, edema and pain appear.

The workup should include a general physical examination and neurological examination, but abnormal findings are usually absent. Epileptiform activity may be noted on the EEG at the height of the attack. Migraine is a clinical diagnosis. Diagnostic studies are performed only to exclude structural, metabolic, inflammatory, and other causes of headache that mimic or accompany migraine. The choice of laboratory and/or imaging studies is determined by the clinical presentation in each individual case. Measurement of erythrocyte sedimentation rate and C-reactive protein may be useful to exclude temporal/giant cell arteritis, especially in older individuals with similar symptoms (eg, scalp tenderness). Visual field testing should be performed in the presence of persistent visual symptoms. The development of an objective, quantitative biological measure of cephalalgia severity has the potential to improve the diagnosis of migraine and accurately assess the effectiveness of treatment. Quantitative sensory tests can detect significant differences in the perception of vibratory stimulation in migraineurs compared with non-migraine patients, including stimulus amplitude discrimination, temporal order assessment, and duration discrimination [4]. Elevated peripheral blood concentrations of calcitonin gene-related peptide (CGRP), a neurotransmitter that causes vasodilation, may serve as a biomarker of persistent trigeminovascular activation and may aid in the diagnosis of chronic migraine.

In the study, migraine patients had CGRP levels of 74.90 pg/mL, significantly higher than controls. In the study, blood samples were taken between migraine attacks, not during them. Furthermore, chronic migraine patients with a history of aura had significantly higher CGRP levels than chronic migraine patients who had never had an aura [5].

The differential diagnosis of migraine includes other primary headaches, mainly tension-type headaches, and some secondary headaches, especially post-traumatic headaches. To rule out non-migraine pain, you need to:

a. with the patient's first or most severe headache in his life, especially one that began quickly;

b. change in attack frequency, severity, and/or clinical symptoms;

c. a new progressive headache lasting several days;

d. Intensification or occurrence of headache during Valsalva maneuvers (strain, cough, sneezing);

e. the presence of concomitant neurological signs or symptoms (diplopia, sensory loss, weakness, ataxia);

f. Headache onset over the age of 55;

g. Headaches that develop after a traumatic brain injury or other serious injury;

h. persistent one-sided throbbing headache;

i. headache accompanied by a stiff neck and/or fever;

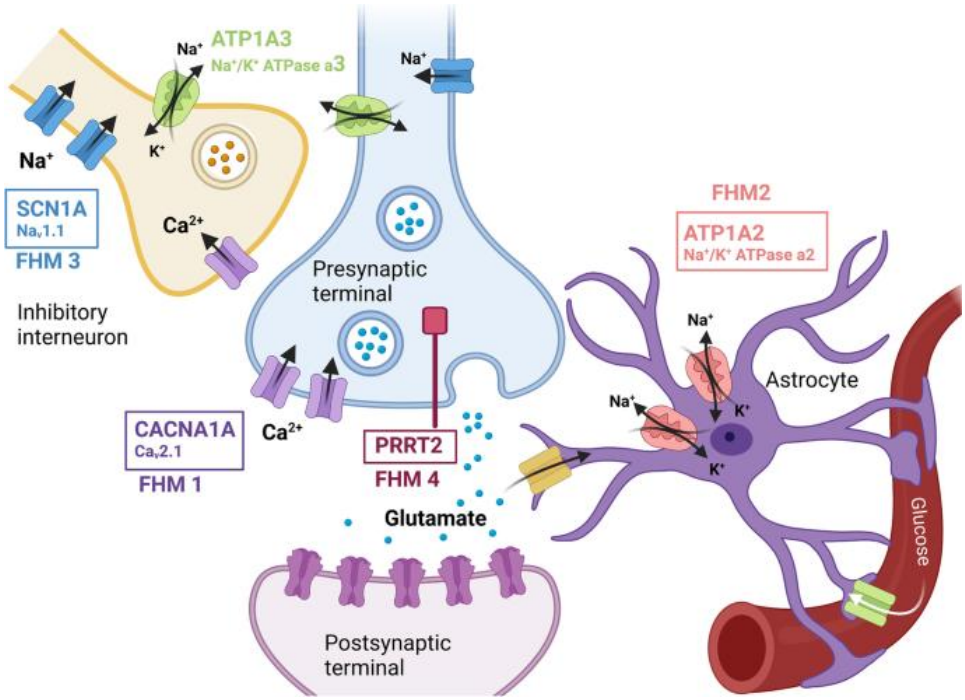
j. a typical history or unusual pattern that does not meet criteria for migraine;

k. inadequate response to optimal therapy.

Non-migraine headaches include intracranial aneurysms and hemorrhages, chronic paroxysmal hemicrania, cluster headache, viral and bacterial meningitis and encephalitis, Toloza-Hunt syndrome (painful recurrent ophthalmoplegia: severe periorbital headache and usually aching headache, eye pain, decreased eye movement, usually symptoms decrease; one eye), temporal giant cell arteritis, etc. [6].

Migraine genetics

Studies have identified at least 123 loci that assess the common and distinct genetic components of the two major subtypes of migraine: migraine with aura and migraine without aura. Stratification of the risk loci has identified three risk variants that are specific to migraine with aura (in HMOX2, CACNA1A, and MPPED2), two that appear to be specific to migraine without aura (close to SPINK2 and FECH), and nine that appear to be specific to migraine without aura (close to SPINK2 and FECH, which increase susceptibility to migraine regardless of subtype). The risk loci include genes encoding targets for its treatment, namely calcitonin gene-related peptide (CALCA/CALCB) and serotonin receptor 1F (HTR1F). In general, genomic loci associated with migraine are primarily associated with blood vessels, central nervous system tissues/cells, and visceral smooth muscle, confirming the primacy of neurovascular mechanisms in migraine pathophysiology [7 , 8].



Genes involved in ion transport and glutamatergic transmission in synapses are noteworthy. Studies of familial migraine with aura have also identified other causative genes for monogenic forms of migraine. Given the female predominance of migraine (3:1), it can be assumed that hormonal or X-linked components contribute to migraine. Genetic variants of mitochondrial DNA are not in doubt (mitochondria are transmitted to offspring only from the mother!). Epigenetic variants have shown a

link between hormonal changes and changes in DNA methylation and gene expression. Thus, migraine is a polygenic disease, with the exception of a few monogenic syndromes (for example, familial hemiplegic migraine).

Twin and family studies show that migraine is 49% hereditary. We followed 17 families in which mothers had migraine (four with aura, 13 without aura). Two of them had Ehlers-Danlos syndrome, two had Marfan syndrome, and seven had joint hypermobility syndrome. By age 45, migraine attacks had gradually stopped in eight women, and by age 55, in almost all of them. In three cases, attacks resumed, less pronounced, due to late bedtime or emotional stress. The health status of 15 children in these families was monitored. Seven (all girls) developed migraine attacks without aura during puberty and adulthood. The 15 had connective tissue dysplasia, including three with Ehlers-Danlos syndrome. One 29-year-old boy was diagnosed with nonspecific ulcerative colitis due to Ehlers-Danlos syndrome, mitral valve prolapse, and arrhythmia.

Pathogenesis

The anatomical and physiological substrate of migraine is the trigeminovascular system. Within it, nociceptive transmission leads to the occurrence of migraine pain [8, 9]. The occurrence of migraine is due to the activation and sensitization of first-order trigeminovascular neurons. The afferent fibers of these neurons innervate the meninges and their vessels and provide projection structures to the central nervous system. Activation of the neurons releases vasoactive peptides and induces local inflammatory responses [10, 11]. This process, in turn, sensitizes and releases second-order neurons in the brainstem and then third-order neurons in the thalamus until nociceptive impulses reach somatosensory and other cortical areas involved in pain perception.

Treatment of migraine patients

In the management of patients with migraine, many specialists can be involved: a therapist (general practitioner), a neurologist, a neuro-ophthalmologist, a psychologist, a gynecologist (menstrual migraine), functional diagnostics specialists, alternative treatment methods, etc. It is important to organize regular and psychological problems. However, the effectiveness of non-invasive neuromodulatory devices, biohazard therapy, acupuncture, physical therapy, chiropractic, and diet has not been reliably proven. In our opinion, these methods are used only as distraction procedures in neurotic patients.

Avoid unnecessary tests. The American Headache Society, as part of the American Board of Internal Medicine's (ABIM) Choosing Wisely campaign, has published a list of five commonly performed tests or procedures that are not always necessary in the treatment of migraine and headache [20-22]:

a. Do not perform neuroimaging studies in patients with stable headache who meet criteria for migraine;

b. Do not perform CT scans for headaches except in emergency situations, when magnetic resonance imaging is available;

c. Surgical removal of migraine trigger points is not recommended outside of clinical trials;

d. Do not prescribe medications containing opioids or barbiturates as first-line treatment for recurrent headaches;

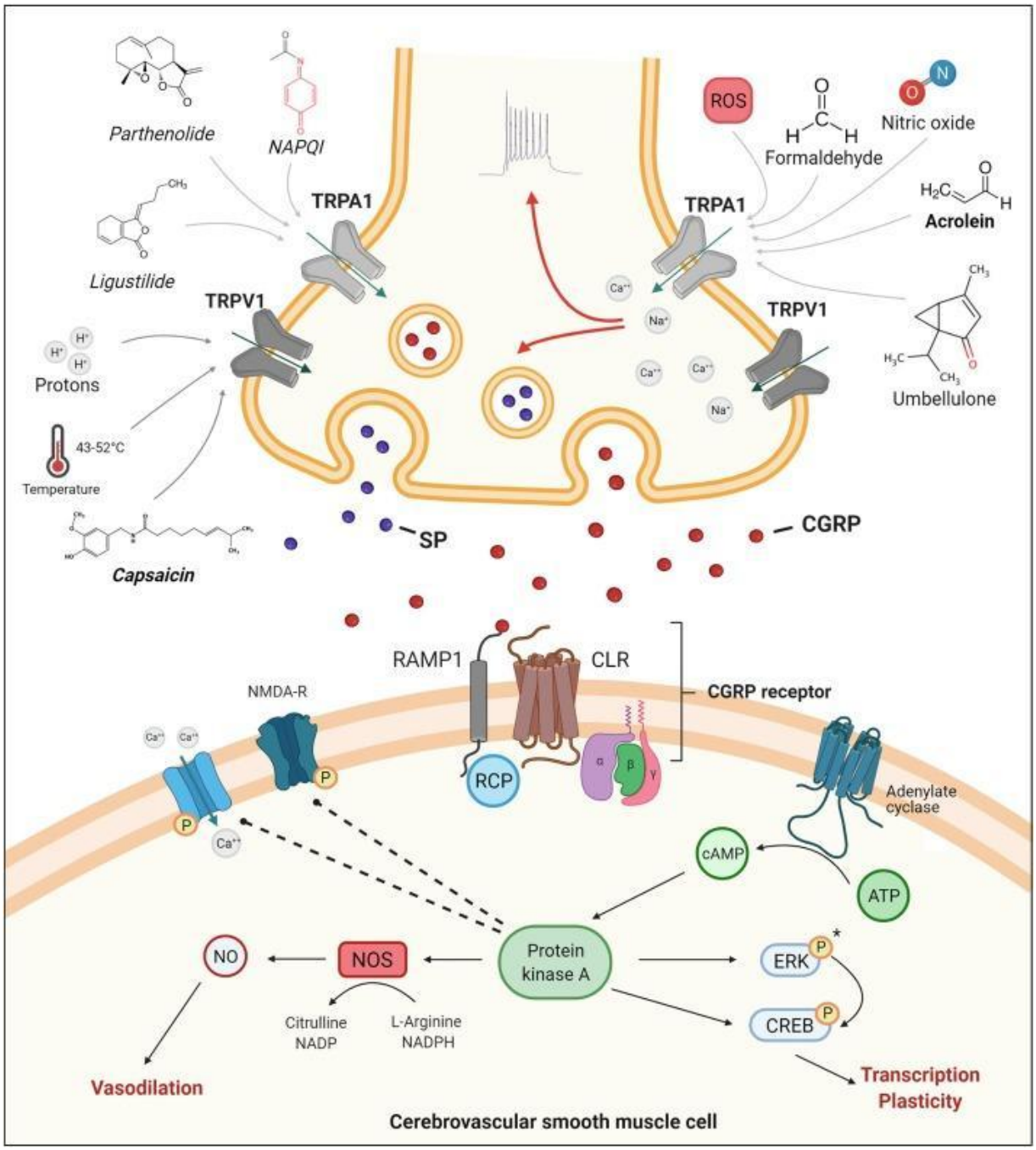
e. Long-term or frequent use of over-the-counter pain medications for headaches is not recommended.

Drug therapy is the mainstay of migraine treatment. In general, drugs used in clinical practice for pain relief or treatment should be prescribed at the onset of a migraine attack, if their effectiveness is significantly higher than that taken later [3]. Analgesics and/or nonsteroidal anti-inflammatory drugs (NSAIDs) can be prescribed as a first-line treatment for mild attacks of pain. Acetylsalicylic acid, ibuprofen, diclofenac are preferred. Prokinetics (domperidone) can be used. Serotonin receptor agonists of the 5HT type (triptans) - second-line drugs - are effective in stopping an attack. Triptans

are useful in patients with severe attacks and severe adaptation, as well as in long-term migraine, when the effectiveness of other drugs has decreased. If the treatment of three migraine attacks is unsuccessful, it is recommended to switch from one triptan to another. If an oral triptan does not provide adequate pain relief, a combination of an oral triptan and a short-acting NSAID (such as naproxen) is recommended. Subcutaneous injections of sumatriptan are the most effective for ineffective oral forms, vomiting, and rapidly increasing headache.

You should be aware of the risks of drug overdose with frequent and daily headaches.

Preventive treatment. Migraine is a recurrent disease and may require preventive treatment. The goal is not to cure migraine, but to reduce the frequency, duration, or severity of migraine attacks. Preventive treatment is initiated during individual treatment [21]. This treatment is usually recommended for patients who have migraines at least two days per month and who have a reduced quality of life despite treatment. Antihypertensive drugs (beta-blockers, candesartan), antidepressants (e.g. amitriptyline), anticonvulsants (topiramate, sodium valproate), and calcium channel blockers are commonly used.



Conclusion: The mechanisms that trigger migraine attacks are unclear. Some data support a peripheral origin at the perivascular level of the trigeminal nerve. Other evidence points to a central nervous system origin associated with neuronal dysfunction in the brainstem and diencephalon. Migraine may be the result of impaired glucose metabolism in the brain. Migraine occurs as a result of mitochondrial dysfunction in the brain, resulting in decreased glucose levels in the brain and reduced gray matter volume in some areas of the brain. In addition, peripheral insulin resistance may spread to the brain, leading to cerebral insulin resistance. This condition suppresses insulin receptors on astrocytes and neurons, leading to decreased glucose uptake and glycogen synthesis, mainly during times of high metabolic demand [12]. A characteristic feature of migraine is its recurrence. Patients often describe triggers (certain foods, fasting, stress, sleep disturbances) that trigger migraine attacks. But retrospective evaluation is limited by extremely subjective, biased, and false attributions. Post hoc, ergo propter hoc (after that - because of this; Latin) is a logical fallacy that forces a person to accept a temporally random sequence of events as causally related.

In the experiment, only three out of 27 patients could be induced by triggering factors. In clinical models of migraine, signaling molecules that trigger the attack have been identified. These molecules are potent vasodilator compounds widely distributed in the trigeminovascular system: calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide 38 (PACAP-38), nitric oxide. With the introduction of nitric oxide (induced by trinitroglycerin), migraine occurs in 80% of patients, with CGRP infusion - in 57%, and PACAP-38 - in 58% [13-15]. An increase in the concentration of intracellular cyclic guanosine monophosphate (cGMP), CGRP and PACAP-38 leads to an increase in intracellular cyclic adenosine monophosphate (cAMP5). Activation of cAMP and cGMP indirectly leads to the opening of ATP-sensitive potassium channels. Modulation of nociceptive transmission through ion (mainly potassium) channels may be a universal pathway in the genesis of migraine attacks [16-18]. Indeed, after intravenous administration of the potassium ATP channel activator leukromacaline, all patients with migraine develop an attack of the disease. It is likely that during a migraine attack, potassium ATP channels open in smooth muscle cells in the walls of intracranial arteries, which leads to vasodilation. The perivascular afferent branches of the trigeminal nerve are activated, nociceptive impulses are generated. The latter are transmitted to subcortical structures and the cerebral cortex, and pain sensation occurs. An increase in the extracellular concentration of not only potassium, but also other cations activates and sensitizes the perivascular primary afferent neurons of the trigeminal nerve. Modulatory activity of ion channels has also been described in other paroxysmal pain disorders, such as familial episodic pain syndrome.

Clinical models of migraine based on molecules of the trigeminovascular system open up prospects for the development of specific migraine treatments. In particular, the use of nitrogen synthase inhibitors, CGRP or its receptor antagonists is proposed. In the future, it is possible to use drugs that affect PACAP-38 or pituitary adenylate cyclase. Monoclonal antibodies to polypeptide type I receptor (PAC1) and PACAP-38 have been used in the experiment for the prevention and treatment of migraine [19-21].

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