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PATHOPHYSIOLOGY OF MIGRAINE - FROM MOLECULAR TO PERSONALIZED MEDICINE

PATOFIZIOLOGIJA MIGRENE – OD MOLEKULARNE DO PERSONALIZOVANE MEDICINE

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Summary

Introduction. Understanding of migraine pathophysiology has substantially improved over the last two decades. As a result, migraine is now mainly considered to be a disorder of the brain, rather than one of the vasculature or the meninges. **Pathophysiology.** Although it remains speculative how exactly they relate to each other, the following three processes are important in migraine: 1. *Cortical spreading depression* is a wave of intense depolarization, it starts in the occipital lobe, propagates through the brain and is followed by a period of suppressed activity. 2. *Activation of the trigeminovascular system* causes the release of neuropeptides (e.g. calcitonin gene-related peptide, substance P) from the peripheral trigeminal nerve endings. These neuropeptides are thought to play a role in causing and maintaining headache. 3. *Sensitization of peripheral and central brain areas*, it is thought that pulsating quality of migraine headache is caused by a process of peripheral sensitization. Cutaneous allodynia is a marker of central sensitization. **Link between Aura and Headache.** The view that the aura is caused by cortical spreading depression has become generally accepted, and the same is true for the view that activation of the trigeminovascular system underlies migraine headache. However, the relationship between the aura and the activation of the trigeminovascular system and the start of headache remains elusive. **Genetics of Migraine.** One of the most important aspects of the pathophysiology of migraine is the hereditary nature of the disorder. **Conclusion.** Identification of polymorphisms and genetic biomarkers should help us to understand migraine pathophysiology better and thus enable the development of specific, effective "individually-tailored treatment" for each particular migraine patient (personalized medicine).

Key words: Migraine Disorders; Pathology; Physiology; Headache; Individualized Medicine; Genetic Markers; Polymorphism, Genetic

Introduction

Migraine is a complex disorder of the central nervous system that affects a large part of population, and thus incurs a substantial economic burden on society [1]. This disorder of the nervous system is characterized by severe, recurrent, unilateral pulsating headaches that are usually ac-

Sažetak

Uvod. Razumevanje patofizioloških mehanizama migrene je značajno unapređeno tokom poslednje dve decenije. Rezultat toga je da se migrena sada uglavnom smatra poremećajem koji je pre u vezi sa mozgom, nego sa krvnim sudovima ili moždanim omotačima. **Patofiziologija migrene.** Postoji sve više dokaza da patofiziološki mehanizmi migrene uključuju tri procesa, mada nije tačno objašnjeno kakvi su tačni odnosi između njih: 1. *Širenje kortikalne depresije*, predstavlja talas intenzivne depolarizacije koji počinje iz okcipitalnog režnja, propagira se kroz mozak a nakon kojeg sledi period smanjene moždane aktivnosti. 2. *Aktivacija trigemino-vaskularnog sistema*, izaziva oslobađanje neuropeptida (npr. peptid udružen sa genom kalcitonina, supstancija P) iz perifernih trigeminalnih nervnih završetaka. Misli se da ovi neuropeptidi imaju ulogu u izazivanju i održavanju glavobolje. 3. *Periferna i centralna senzitivizacija*. Smatra se da je pulsirajuća priroda glavobolje rezultat periferne senzitivizacije. Kožna alodinija je marker centralne senzitivizacije. **Veza između aure i glavobolje.** Smatra se da proces širenja kortikalne depresije predstavlja neurofiziološki supstrat aure, a da je u osnovi nastanka glavobolje aktivacija trigeminalno-vaskularnog sistema. Međutim, odnos između aure i aktivacije trigeminalno-vaskularnog sistema ostaje nejasan. **Genetika i migrena.** Jedna od najznačajnijih karakteristika patofizioloških mehanizama migrene je nasledna priroda ove bolesti. **Zaključak.** Identifikacija polimorfizma i genetskih biomarkera će pomoći boljem razumevanju patofiziologije migrene te bi trebalo da omogući razvoj specifičnog i efikasnog „individualno-skrojenog” tretmana za svakog pojedinačnog bolesnika sa migrenom (personalizovana medicina).

Cljučne reči: Migrena; Patologija; Fiziologija; Glavobolja; Personalizovana medicina; Genetski markeri; Genetski polimorfizam

companied by nausea, vomiting, photophobia and phonophobia. The prodrome (premonitory symptom) often occurs before the headache, during which the patients experience the symptoms like changes in mood or behavior, excessive tiredness, yawning and phonophobia [2]. If the headache is unilaterally localized, it may fluctuate between sides during the attack or between the attacks. Ac-

Abbreviations

VIP	– vasoactive intestinal polypeptide
PAG	– periaqueductal gray matter
CSD	– Cortical Spreading Depression
TGVS	– trigeminovascular system

cording to the International Headache Society diagnostic criteria, a patient must experience at least five attacks fulfilling above-mentioned criteria before the diagnosis of migraine can be made [2]. The frequency of attacks, severity of the pain and duration of the headache is variable from person to person. Medium frequency is about one attack per month and the average duration is approximately 48 hours (ranging from 24 to 72 hours). In 15-30% of people with migraines, an attack of reversible neurological symptoms lasting shorter than 60 minutes immediately precedes the headache [2,3]. This transient focal neurological phenomenon is called aura, and it mainly consists of visual symptoms. The most common triggers for development of migraine headache are stress, change in hormone level and change in sleep routine or sleep disorders [4].

Pathophysiology of Migraine

High variability of clinical features of migraine, a lot of triggering factors ("triggers") and numerous functional and biological abnormalities have led to the development of many theories about the pathophysiology of migraine. Pathophysiological ideas have evolved within a limited number of paradigms, notably the vascular, neurogenic, neurotransmitter, and genetic/molecular biological paradigm [5].

Due to pulsating quality of headache, migraine was thought to be a vascular disorder during the entire 20th century [6]. Today many facts disprove the vascular theory of the origin of migraine attack: intracranial powerful vasodilator, called vasoactive intestinal polypeptide (VIP), does not cause migraine [7,8]; intracranial vasodilatation occurs secondary to painful stimulation of the head [9,10]; the substances that do not cause constriction of the blood vessels, like e.g. aspirin, may abort a migraine attack [11].

Those who advocate the neurogenic and neurotransmitter theories claim that the brainstem dysfunction is a major cause of headaches (the brainstem is a "migraine generator") [12]. The neuromodulatory structures, such as periaqueductal gray matter (PAG), locus coeruleus and nucleus raphe, modulate the transmission of ascendant pain signals.

Functional brain imaging with positron emission tomography (PET) can reveal activation of these brain areas during an acute attack, and an electrical stimulation of the PAG can provoke headaches which are similar to migraine headaches [12].

Today, however, most researchers accept and support the neurovascular (neurogenic inflammation) theory of migraine, which assumes that the nervous mechanisms cause activation of the cranial (meningeal) blood vessels which then cause

the pain and promote further nerve activation [10]. These authors suggest that neural activation releases vasoactive neurotransmitters from their afferent processes, which in turn provoke inflammatory changes in the cerebral blood vessels. It is assumed that the following processes underlie occurrence of the migraine attack:

1. Cortical Spreading Depression (CSD);
2. Activation of the trigeminovascular system;
3. Sensitization of peripheral and central brain areas.

Sensitization process guides the patient's cerebral cortex into a state of hyperexcitability and consequently causes repeated, chronic pain conditions, which ultimately leads to the transformation of episodic migraine to chronic form of migraine [9].

1. Cortical Spreading Depression in Migraine Aura

Previous research indicated that cortical spreading depression (CSD) is the substrate of migraine aura. This phenomenon was first described by Lea in 1944 [13]. CSD is a slowly propagating wave of sustained neuronal depolarization, which starts in the occipital lobe, extends through the cerebral cortex (2-5 mm/minute) and is followed by potent, relatively long-lasting neural suppression. This corresponds to the progression of aura symptoms and it may explain the relationship between aura and some of the migraine consequences (positive and negative symptoms) [14].

2. Activation of Trigeminovascular System

The trigeminovascular system (TGVS) consists of meningeal blood vessels which are innervated by the first (ophthalmic) branch of the trigeminal nerve. The trigeminal nerve is projected in the brainstem nuclei, such as the trigeminal nucleus caudalis, which provides projections on several higher brain centers, including the thalamus, hypothalamus and cortex. Activation of the TGVS stimulates the release of neuropeptides (e.g. CGRP – calcitonin gene-related peptide; substance P, VIP) from peripheral endings of the trigeminal nerve [15] which cause the vascular and inflammatory changes associated with migraine pain. It is believed that these neuropeptides play a role in causing a sterile neurogenically driven inflammation of the meningeal blood vessels wall (the dura mater) and in maintaining the migraine pain [10,16]. The trigeminal afferent fibers transmit pain signals through the brain stem to several brain centers involved in pain perception [9]. The fact that headache is interrupted when the ipsilateral trigeminal denervation is made is only one of several proofs that TGVS activation is important in the development of headache [16].

3. Sensitization of Peripheral and Central Brain Areas

It is believed that the pulsating (throbbing) quality of migraine headaches and the aggravation of

symptoms by physical activity are caused by the process of peripheral sensitization [16,17]. Another important symptom, which is often seen in migraine patients, is a cutaneous allodynia, i.e. a feeling of pain caused by non-noxious stimuli. Allodynia is believed to be a result of the process of central sensitization of the neurons in the caudal trigeminal nucleus which receive input signals from the dura mater and skin [9]. Central sensitization plays an important role in the later stages of migraine attacks and introduces the brain into the state of the excessive sensitivity, i.e. "*perpetuum migraine*" [18].

Central and peripheral sensitization introduces the patient into the state of hyperexcitability of the cerebral cortex. Neurophysiological methods have recently shown that in patients with a chronic form of migraine, there is an increased excitability in somatosensory and visual cortices (determined by measuring the amplitude of evoked potentials and habituation). Finally, it confirms the view that the brain is more excitable and more vigilant in migraine patients than in people without migraines. In addition, such a "migraine" brain is not capable of extinguishing the sensory stimuli quickly and completely, which makes it suitable for "sensory overload" and the beginning of the next ictal (painful) period [18,19]. Sensitization process is just one of the pathophysiological mechanisms which lead to the transformation of migraine attacks from acute to acute recurrent, chronic non-progressive and chronic progressive form of migraine [20].

Link between Aura and Headache

It is believed that the process of cortical spreading depression is closely associated with aura and aura progression (a neurophysiological substrate of aura), while the TGVS activation underlies the migraine headache. However, the mechanisms by which CSD activates the trigeminovascular system remain unclear. Experiments performed on animals have shown that CSD may activate trigeminal nociceptors by the release of H^+ , K^+ , arachidonic acid and nitric oxide in the extracellular space of the neocortex. These agents can cause depolarization of perivascular trigeminal nerve endings and trigger an antidromic activation of the trigeminal sensory pathways [16].

Disadvantages of Neurovascular Theory

The broad clinical spectrum of migraine has posed a challenge to understanding of the underlying pathophysiology and molecular genetics. For example, it is difficult to find a pathophysiological link between a headache, which is not symptomatic, and symptoms like nausea, photophobia, or hypotension. The disadvantages of this theory are twofold: 1) how to explain the fact that most people with migraine do not have aura (it is assumed that in these patients the CSD process takes place in the

subcortical structures) and 2) the contemporary concept of the pathogenesis of migraine, particularly CSD, does not focus on the precise onset of the migraine attack [3,20]. Neither aura nor headache represents the proper onset of an attack. The primary or causal physiological change underlying the migraine occurs during the prodromal phase, between the stimuli which provoke headaches and the onset of the prodrome. Therefore, a key pathophysiological mechanism underlying migraine has yet to be identified [20]. Due to the fact that migraine attacks occur during or after the stress, and more frequently in women than in men, it seems logical that the neuroendocrine system also plays an important role in activating the mechanisms controlling vascular integrity and antinociception during migraine attacks [21]. Therefore, neurological, hormonal and vascular genes are important factors in the pathophysiology of migraine and the focus of many current clinical and basic studies [22].

Genetics and Migraine

One of the most important aspects of the migraine pathophysiology is that it is hereditary by nature [23]. The polygenic nature of migraine suggests the idea that multiple disorders are present in the pathogenesis of migraine. By now, however, genetic loci or causative genes involved in migraine (with or without aura) have not been identified. Common forms of migraine (with or without aura) have been linked to chromosomes 4q21-q24, 5q21, 6p12.2-p21.1, 11q24, 14q21.2-q22.3, 15q11-q13 [23]. The use of genome-wide analysis, which allows simultaneous analysis of many DNA variants, led to the discovery of the first gene variant for common migraine [23]. The mutation, which is located on chromosome 8q22, affects the expression of *metadherin* and thereby regulates the expression of the glutamate transporter gene *SLC1A2*, which encodes a major glutamate transporter in the brain. Shortly thereafter another mutation linked to migraine with aura was discovered [4]. The mutation described is a *frameshift mutation* in the *KCNK18* gene, which encodes the TRESK two-pore domain (K2P) potassium channel. The studies suggest that decreased activity in TRESK may increase the risk of migraine. However, more studies with larger patient samples are required to establish the clinical relevance of this finding [24,25].

Investigations in patients suffering from familial hemiplegic migraine have led to the discovery of three mutations (*CACNA1A*, *ATP1A2* and *SCN1A*), all of which code for alterations in ion channels which are involved in ion and neurotransmitter transport in the brain. In this way, by using the research from the genetic perspective, it has been shown that migraine can be considered as a channelopathy. The laboratory model was created by using a knock-in mouse (R192Q) resembling one of the known familial hemiplegic migraine mutations

(CACNA1A), and thus allowed the systematic investigation of its pathophysiological consequences in several *in vivo* models relevant to migraine [24].

Today most authors believe that the genetic diversity is the key pathogenetic mechanism of migraine [20,24]. Genes investigated are, for example, implicated in serotonin and dopamine metabolism, neurogenic inflammation, vascular function, and hormone regulation. The most important candidate genes, whose polymorphism is important for the occurrence of migraine, are: Tumor necrosis factor-alpha (TNF-alpha), Tumor necrosis factor-beta (TNF-beta, or lymphotoxin alpha), the methylenetetrahydrofolate reductase gene (MTHFR), Estrogen receptor-1 gene (ESR-1) and Wolfram gene (WFS1) [26]. A strong association was observed between migraine and the polymorphism in the gene for dopamine transport (DAT, DRD₂, DRD₄) as well as in the insulin receptor gene ("single nucleotide polymorphisms - SNP"), which indicates a possible role for dopamine transporters and insulin receptors in the pathogenesis of migraine [27]. The researchers hope that, thanks to the science of genomics and proteomics, they will manage to get insight into a part of diversity, and thus enable personalized medicine to make progress in the current treatment of patients with migraine [28,29].

Personalized Medicine

The path by which the science about migraine has been approaching personalized medicine has gone from clinical observations to modern understanding of the molecular and genetic mechanisms. Within personalized medicine, i.e. medical practice which enables personalized solutions for the individuals, different tools will be used (genotyping, risk assessments, etc.) to determine the probability that an individual will get a certain type of migraine (prediction of disease through genetic testing) [30]. Based on the obtained results it will be possible to suggest preventive measures. As we enter the era of personalized drug therapy, we will be able to identify

not only the best drug to be administered to a particular patient, but also the most effective and safest dosage from the outset of therapy (pharmacogenomics). Therefore, personalized medicine is the way how to improve quality in health care [31].

Conclusion

Migraine is more than a headache. There are several theories about the pathophysiological mechanisms of migraine. The probable causal algorithms underlying the pathophysiology of migraine are the state of hyperexcitability of cerebral cortex, cortical spreading depression, sterile neurovascular inflammation of meningeal blood vessels, the activation of trigeminovascular system and sensitization (peripheral and central). However, none of the therapeutic strategies is effective for each and every patient, not even for the same patient in different migraine episodes. Therefore, it is not surprising that so many people with migraine are dissatisfied with their treatment; they even opt for discontinuing it although migraine disables them progressively. For this reason, personalized medicine (pharmacogenomics - "individually tailored medicine") will have safe and scientifically based future.

After identifying the genetic diversity between the patients, the doctor will be able to answer the question why some drugs work better or worse in some patients, and finally to apply individually tailored and effective treatment of migraine. Other benefits from personalized medicine are the discovery of new targets for the treatment of migraine.

Paradoxically, migraine research develops in reverse direction - from clinical observations to modern understanding of its basic molecular and genetic mechanisms. Identification of polymorphisms and genetic biomarkers should improve understanding of migraine pathophysiology and thus enable better choice of specific, effective "individually-tailored treatment" for each particular migraine patient (personalized medicine).

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