**Migraine and the endocannabinoid system: a stormy relationship**

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ABSTRACT

Migraine is a common neurological disorder characterized by peripheral and central sensitization. Trigemino-vascular system is involved in the genesis of the migraine attack. CGRP is one of the main determinants of the migraine pain. CGRP-targeting drugs like anti-CGRP monoclonal antibodies and CGRP-receptor antagonists named “gepants” are effective and safe drugs recently introduced into clinical practice. The endocannabinoid system is a lipid-based neurotransmitter complex that has been linked to migraine. CB1 receptor is localized in the presynaptic synapses of the trigeminal terminals and is activated by the endocannabinoid anandamide. It acts as a negative regulator of the CGRP release. Anandamide has been found in reduced amounts in subjects suffering from migraine.

Keywords—migraine; headache; chronic migraine; medication overuse headache; endocannabinoids; endocannabinoid system; anandamide; 2-arachidonoylglycerol.

**I. INTRODUCTION**

 Migraine without aura (1.1) is defined by the International Classification of Headache Disorder Third Edition (IHS-3) as a recurrent headache that occurs with at least 5 attacks lasting 4-72 hours. Typical features of headache are unilateral localization, pulsating quality of pain, moderate to severe intensity, exacerbation following routine physical activity, and association with neurovegetative symptoms such as nausea, vomiting, photophobia, and phonophobia [1]. Migraine with aura (1.2), on the other hand, is characterized by recurrent attacks, lasting between 5 and 60 minutes of completely reversible unilateral central nervous system symptoms of visual, sensory, speech symptoms that usually develop gradually and are usually followed by headache that meets the characteristics of a migraine [1]. Based on the frequency of attacks, migraine can be classified into episodic and chronic. Episodic migraine is characterized by 1-14 monthly migraine days. Chronic migraine (1.3; CM) is defined as a headache that occurs for 15 days or more per month for at least three months, which, on at least 8 days per month, has the characteristics of a migraine. If a patient consumes many symptomatic drugs for pain control, he will develop a medication overuse headache (8.2; MOH) in the long run. MOH due to excessive use of acetaminophen (8.2.3.1) or nonsteroidal anti-inflammatory drugs (NSAIDs) (8.2.3.2) is defined by taking more than 15 drugs per month, while MOH due to excessive use of triptans (8.2.2) occurs when the person takes more than 10 triptans per month [1].

The diagnosis of migraine, as it is a primary headache, is basically clinical, relying on the collection of the patient's medical history and through the exclusion of secondary forms of headache. The patient should undergo a general physical examination and neurological examination, which must be normal to suppose a primary headache [2]. A headache diary is usually requested to assess the frequency of attacks. Pain intensity is determined by the patient's completion of a visual analog scale (VAS) or numeric rating scale (NRS). Instrumental analysis and other visits, such as a magnetic resonance imaging of the brain (MRI), both with or without contrast agents, an ultrasonography of supra-aortic trunks, a complete ophthalmological examination, blood pressure tests, may be necessary to exclude a secondary cause of headache.

Migraine represents one of the most disabling neurological disorders in most age groups. It ranks second in the world as a cause of disability in the 10-24 age group and fifth in the 25-49 age group as attested by the Global Burden of Disease 2019 [3]. Migraine, therefore, affects a population of education and working age, which is the most productive component of society. It afflicts people in the most active period of their lives, leading to a significant loss of productive capacity from both personal and social perspectives. Epidemiological studies have attempted to estimate the prevalence and incidence of migraine by means of various methodologies, concluding that it affects about 14 percent of the population, while chronic migraine affects 4.6 percent of people [4]. Migraine most prevalently affects the female sex, with a female-to-male ratio of 3:1 [5]. According to the latest global epidemiological estimates, in 2019, the global incidence of migraine was 87.6 million new cases/year, an increase of 40.1% since 1990 [6].

**II. ETIOPATHOGENESIS**

The pathogenesis of migraine has yet to be fully explained. Since it is a complex disease, both genetic and environmental factors are involved. Genetic inheritance of migraine is polygenic. The only exception is familial hemiplegic migraine (FHM), for which a single-gene Mendelian inheritance involving 4 genes (*CACNA1A, ATP1A2*, *SCN1A, PRRT2*) has been established, determining four forms of this rare disease respectively (FHM1, FHM2, FHM3, FHM4) [7].

A prominent role in the pathogenesis of the migraine attack is attributed to the activation of the trigeminal vascular system. The trigeminal nerve is composed of fiber Aδ and fiber C, which innervate the intracranial arteries, including the vessels of the meninges and the dura mater [8]. Various triggers of migraine attack, including alterations in sleep-wake rhythm, fasting, weather variations, certain foods, psychophysical stress, can activate the trigeminal nerve endings both in an orthodromic way (from the peripheral stimuli to the central structure) and in an antidromic way (from the central areas to the periphery). The debate about the origin of the migraine attack is still ongoing. There are arguments both pros and cons regarding its peripheral or central origin. Particularly, the sensory nerve fibers activated in migraine are in the periphery, differently cortical spreading depression, the widely accepted mechanism of aura is a typical central trigger of migraine [9]. Anyway, sensitization of the first-order trigeminal sensory neuron occurs, which in turn results in sensitization of second- and third-order neurons that make synapses in the thalamus and carry pain information directly to areas of the somatosensory cortex [5].

The search for a biological correlate of migraine has a long history. Since its discovery in 1982, calcitonin gene-related peptide (CGRP) has been characterized as a major player in the migraine attack. CGRP-α is derived from alternative splicing of the calcitonin gene. Its receptor consists of a transmembrane G-protein-coupled protein (calcitonin receptor like receptor, CALCRL), which binds to the receptor activity modifying protein (RAMP1) to form a heterotrimer. CGRP is released from trigeminal nerve endings peripherally and produces arterial vasodilation of extra-cranial meningeal vessels. CGRP is released during a migraine attack (1990). Whereas, in 1993-1994 it was demonstrated that triptans, specifically sumatriptan, serotonin 5-HT1B/D receptor agonist drugs, can block the release of CGRP from the trigeminal nerve endings and concomitantly extinguish pain during a migraine attack. Based on experimental observations on the role of CGRP in the genesis of migraine attack, monoclonal antibodies that block CGRP peptide or its receptor have been developed. These drugs are: erenumab (antibody directed against the CGRP receptor), galcanezumab, fremanezumab, and eptinezumab (antibodies that directly block CGRP peptide). Monoclonal antibodies for migraine prevention have been found to be safe and well-tolerated in most patients in both clinical and real-world studies [8]. Other CGRP drugs called “gepants”, which are small molecule CGRP receptor antagonists, are approved or under investigation in the US and UE market: these are ubrogepant, rimegepant, atogepant (with oral administration) and zavegepant (with intranasal or subcutaneous administration). Ubrogepant has been studied for acute treatment, whereas atogepant has been developed for migraine prevention; finally, rimegepant can be used for both acute and preventive therapy [10].

**III. ENDOCANNABINOID SYSTEM AND MIGRAINE**

The endocannabinoid system is a complex lipid network comprising endogenous ligands, cannabinoid receptors, and enzymes that catalyze the formation and degradation of endocannabinoids. The effects of endocannabinoids are mediated mainly by CB1 and CB2 cannabinoid receptors, but other receptors also mediate some actions of endocannabinoids, particularly acylethanolamides. CB1 and CB2 endocannabinoid receptors are receptors coupled to Gi/o inhibitory proteins. Consequently, their activation inhibits adenylate cyclase and some voltage-dependent calcium channels. CB1 receptors are abundant in the central nervous system: cortex, basal nuclei, hippocampus, and cerebellum. Most receptors are expressed on axon terminals and in pre-terminal segments. CB2 receptors, on the other hand, are found mainly in cells of the immune system, microglia, and vessels [11].

Alterations in the endocannabinoid system have been associated with numerous neuropsychiatric disorders, including substance abuse [12]. There is evidence that alterations in the endocannabinoid system are present in CM and MOH [13–18]. Specifically, in subjects with CM and MOH, a deficit of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) has been shown in plasma and cerebrospinal fluid (CSF) [13,16]. Early studies in humans have confirmed the presence of a clear alteration of the endocannabinoid system in migraine subjects. Italian authors analyzed AEA and 2-AG levels in platelets extracted from the plasma of 20 CM patients, 20 MOH patients, compared with 20 healthy controls. The results showed a strong reduction in 2-AG and AEA levels in CM and MOH patients compared with healthy controls (p < 0.0001 for both), but with no significant differences between the two groups of patients. In addition, the 2-AG content in the platelets of patients and control subjects was 20 times higher than that of AEA. In both groups, endocannabinoid levels were significantly lower in females than in migraineurs males [16]. Moreover, the levels of AEA, 2-AG and CGRP in CSF of subjects with CM and probable CM or MOH were studied. AEA concentrations were significantly lower than controls, while CGRP concentrations were higher, with a negative correlation between the two variables for both CM and probable CM or MOH [13].

The deficiency of the endocannabinoid system in chronic migraine configures a possible therapeutic strategy for the treatment of chronic pain. A new challenge is restoring deficient endocannabinoid transmission by inhibiting the enzymes responsible for the degradation of AEA and 2-AG [17]. To date, pharmacological inhibition of the fatty acid amide hydrolase enzyme (FAAH), which metabolizes AEA has been tested in preclinical models as a possible target for migraine [19,20]. In conclusion, the deficit of the endocannabinoid system involved in pain regulation in the peripheral nervous system appears to be one of the pathogenic mechanisms of migraine onset. Future research in this field could explain the complex interplay between migraine pain and the endocannabinoid components.

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