Psychiatr. Pol. 2023; 57(2): 405–419
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/143982

Common pathomechanism of migraine and depression

Katarzyna Wachowska[1], Katarzyna Bliźniewska-Kowalska[1], Jarosław Sławek[2], Monika Adamczyk-Sowa[3], Agata Szulc[4], Michael Maes[5], Su Kuan-Pin[6,7], Piotr Gałecki[1]

[1] Department of Adult Psychiatry, Medical University of Lodz, Poland

[2] Department of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland

Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland

[3] Department of Neurology, Medical Faculty in Zabrze, Medical University of Silesia, Katowice, Poland

[4] Department of Psychiatry, Faculty of Health Sciences, Medical University of Warsaw, Poland

[5] Department of Psychiatry, Chulalongkorn University, Bangkok, Thailand

[6] College of Medicine, China Medical University, Taiwan

[7] An-Nan Hospital, China Medical University, Tainan, Taiwan

Summary

Migraine and depression often coexist and constitute an important clinical problem. Both disorders are associated with the necessity of chronic treatment, and their mutual coexistence contributes to the phenomenon of drug resistance. Influencing the functioning of patients, they also cause numerous social consequences – affecting the quality of life and achievement of personal goals of patients. This review presents factors that may explain the common pathomechanisms of depression and migraine. Structural and functional disturbances of the central nervous system (CNS), disturbances in the neurotransmitter systems, inflammatory theories, hormonal disturbances, as well as a possible genetic basis were taken into account. Due to the fact that both depression and migraine have a multifactorial etiology and at the present stage of scientific research it is difficult to clearly determine which factor is the most important, such a broad overview has been presented. It is also difficult to determine which of the above-mentioned factors, well documented in international studies, only coexist, and which of them may have a cause-and-effect relationship in the described disorders. Further research into the comorbidity and causes of migraine and depression seems to be worth considering.

Key words: depression, migraine, pathomechanism

Introduction

Depression is the most commonly diagnosed mental disorder, and patients with this diagnosis often receive treatment for a variety of comorbid medical conditions, including inflammatory disorders and those associated with chronic pain. It has been observed in a part of scientific research that depression is the most common illness accompanying migraine [1] and affects up to 28% of people suffering from migraine headaches [2]. The risk of developing depression in people suffering from migraine significantly exceeds the risk for the general population [2, 3]. People suffering from migraine have a 2–4 times higher risk of developing depression [4–6]. This risk becomes even greater when migraine is accompanied by an aura, especially in the female population [7]. The observed comorbidity of depression and migraine also applies to children and adolescents [8].

An episode of depression can occur during unipolar depressive disorders as well as constitute an element of bipolar disorder – in both cases its coexistence with migraine is observed [9]. Although the research results are not clear in this matter, the coexistence of both disorders may indicate the presence of bipolar disorder spectrum (BD) [9, 10]. Due to the differences in the etiopathogenesis of bipolar disorder and depression, and the clear diagnostic delineation of these disorders in the ICD-11 and DSM-5, the presented issues will only concern depression in the course of unipolar disorders.

Both depression and migraine are important medical and social problems. They significantly affect the quality of life and hinder the patients from achieving their professional and personal goals. Studies have shown that depression co-occurring with migraine may lead to the transition of episodic headaches into chronic ones [5, 11], and also make it difficult to achieve and maintain remission [12].

Already in the 1990s, numerous links were observed between depression and migraine. Patients suffering from depression are three times more likely to develop migraines than healthy people. Additionally, depression is a risk factor for more severe course of migraines and worse response to treatment [13]. The literature considers both the cause-effect relationship between these diseases and the relation of a common etiology of disorders. This paper aims to present common pathogenetic mechanisms of the described diseases and to search for answers about possible causes of the observed dependencies.

Diagnosis and pathogenesis of migraine

Migraine is a neurological disease, the prevalence of which affects approximately 15-18% of women and 6–7% of men [14]. This is a disruptive headache with or without an aura. There are episodic and chronic migraines. Table 1 presents the diagnostic criteria for migraine [15, 16].

Table 1. **Migraine diagnostic criteria according the International Classification of Headache Disorders 3rd edition (ICHD-3) [15, 16]**

Migraine without aura	Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location – at least at the beginning of the attack, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Diagnostic criteria: A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: 1) unilateral location 2) pulsating quality 3) moderate or severe pain intensity 4) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis.
Migraine with aura	Description (aura): Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Diagnostic criteria: A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1) visual 2) sensory 3) speech and/or language 4) motor 5) brainstem 6) retinal C. At least three of the following six characteristics: 1) at least one aura symptom spreads gradually over ≥5 minutes and/or two or more aura symptoms occur in succession 2) each individual aura symptom lasts 5–60 minutes 3) at least one aura symptom is unilateral 4) the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.

table continued on the next page

Chronic migraine	Description: Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache. Diagnostic criteria: A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura C. On ≥8 days/month for >3 months, fulfilling any of the following[2]: 1) criteria C and D for migraine without aura 2) criteria B and C for migraine with aura 3) believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis

The theories describing the presumed pathomechanism of the occurrence of a migraine headache attack include: vascular theory, neuronal theory, inflammation of the nervous tissue, biochemical theory, central sensitization theory, and genetic background [17]. The vascular theory assumes that the symptoms of migraine are caused by vasoconstriction (vasoconstriction of the occipital area during the visual aura), followed by their relaxation/ vasodilatation accompanied by hyperperfusion and perivascular edema, which are to be the cause of severe pain [17]. The neuronal theory identifies the source of migraine headaches as disturbances in the brain's bioelectrical activity, the presence of cortical spreading depression (CSD), accompanied by dilation of the meningeal arteries and edema, which increases the excitability of nerve fibers and pain [17]. Another hypothesis is that sterile inflammation of the nervous tissue (neuroinflammation) is the cause of migraine. Increasing the secretion of inflammatory factors by the vessels of the meninges stimulates the sensory nerves, especially the trigeminal nerve. Activation of the fiber endings of this nerve causes the secretion of pro-inflammatory substances and neuropeptides, such as substance P (SP) and the calcitonin gene-related peptide (CGRP), which favors the expansion and permeability of blood vessels of the meninges and the formation of an inflammatory reaction [17]. The biochemical theory is based primarily on disturbances in serotonergic transmission. There is also a hypothesis about disorders of the autonomic system (sympathetic insufficiency) in patients with migraine. It explains the symptoms occurring in patients with migraine (vasomotor and heart rhythm disturbances, nausea, vomiting and diarrhea). As in the case of depression, there are many theories that integrate those preliminary hypotheses [17].

Shared elements in the pathomechanism of depression and migraine

The literature distinguishes the main areas with shared etiopathogenetic factors, which include:

- CNS morphological and functional disorders;
- systems of neurotransmitters and their receptors;
- inflammatory factors (neuroinflammation);
- hormonal regulation;
- environmental factors, with particular emphasis on stress;
- personality, temperament;
- genetic predispositions.

All these factors are briefly presented below.

Structural and functional disorders in the central nervous system

The literature describes the structural and functional changes observed in neuroimaging in patients with migraine and affective disorders. Chronic pain and depression often exhibit common biological connections related to specific brain function or central nervous system sensitization [18]. They concern in particular the centers responsible for pain modulation, such as: the amygdala, the anterior part of the cingulate cortex and the periaqueductal gray matter [19]. At the same time, these areas belong to the limbic system, considered to be the so-called emotional brain, responsible for the regulation of emotions [20]. Examinations of the CNS in a group of patients with migraine and depression showed changes in structure observed macroscopically (reduced total brain volume, reduced volume of gray and white matter and reduced amount of cerebrospinal fluid) [21], microscopically (changes in caudate nucleus homogeneity), and in activation of certain brain areas (left medial prefrontal cortex – left mPFC – part of a wider functional network connected, inter alia, with the thalamus, insula and left medial gyrus) leading to changes in the cognitive functioning of patients [13, 22, 23]. Also in patients suffering from depression, without concomitant headaches, dysfunction in the frontal lobes, especially in the prefrontal cortex (which does not properly inhibit the functioning of subcortical emotional systems) is observed [24].

Moreover, Tao et al. [25] showed that the hypoechogenicity of the brain stem raphe area correlates with the occurrence of depressive symptoms in patients suffering from migraines. It seems not meaningless that the most abundant neurotransmitter in the dorsal raphe nucleus (DRN) is serotonin, a monoamine with a proven role in the pathogenesis of depression [26, 27].

Research indicates increased activity, and at the same time smaller size, of the lateral habenula (LHb) in patients with depression [28]. This structure is a messenger node that connects the limbic structures of the forebrain (“emotional brain”) and the

prefrontal cortex with the aminergic centers of the midbrain, including the above-mentioned dorsal raphe nucleus (DRN). It is also involved in the transmission of pain. The nociceptive stimuli (pain stimuli), that reach it through afferent fibers from the lateral part of the hypothalamus, from the dorsal horns of the spinal cord and from the trigeminal nucleus, which plays an important role in the pathogenesis of migraine, increases its activity. A significant increase in the excitability of LHb neurons results in increased inhibition of DRN and a decrease in the level of serotonin, modulating the activity of the limbic system and the prefrontal cortex. In response to reduced stimulation, the central nucleus of the amygdala (CeA) stimulates LHb even more by secreting glutamate (Figure 1) [28–32].

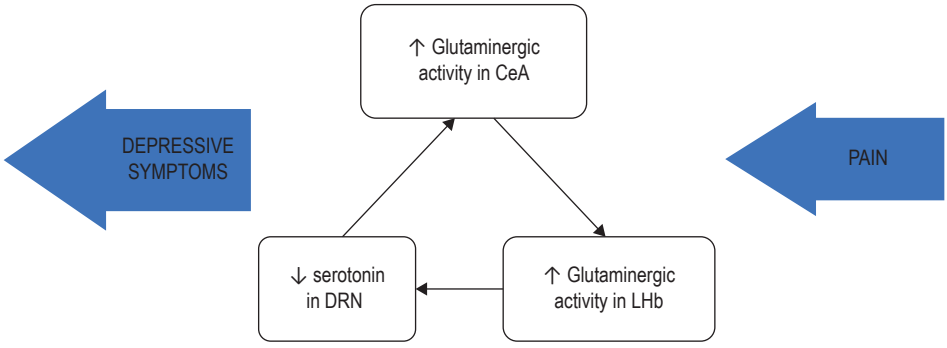

Figure 1. **Scheme of common central pathomechanisms of chronic pain and depression**

DRN – dorsal raphe nucleus; LHb – lateral habenula; CeA – central nucleus of the amygdala.

System of neurotransmiters and their receptors

Abnormalities in the serotonergic system are observed in both depression and migraine [12]. The phenomenon of chronically reduced availability of serotonin (characteristic of depressive disorders) may increase the sensitivity of pain pathways – induced by the so-called cortical spreading depression (CSD) [33]. An increased amount of serotonin (5-HT) is also observed during attacks and its decreased amount between migraine attacks [13]. A possible genetic background is also indicated – the polymorphism of the gene encoding the 5-HT transporter is probably associated with both diseases [12]. It is worth emphasizing that the drugs used in the acute treatment of migraine – triptans – are 5-HT1 receptor agonists. Triptans are thought to terminate the attack of migraine by: modulating the trigeminal nociceptive pathways, partly also by inhibiting the release of the calcitonin gene-related peptide (CGRP) by activating serotonin receptors [34]. Additionally, although they are not first-line drugs, selective serotonin reuptake inhibitors (SSRIs) used in the treatment of depression, as well as

drugs from an older group – tricyclic antidepressants (e.g., amitriptyline) – are used in the prevention of migraine [13]

Calcitonin gene-related peptide (CGRP) is a molecule with proven importance in the pathogenesis of migraine. It is found in two isoforms – alpha (α) and beta (β). CGRPα is present mainly in the central (mainly areas related to the transmission of pain stimuli and their sensory processing) and the peripheral nervous system (the most abundant neurotransmitter in the trigeminal nerve), and β in the intestinal sensory neurons [34]. Factors such as ischemia, injury or hyperthermia affecting the central nervous system (CNS) increase the expression (upregulation) of CGRP, which has numerous neuroprotective functions, including enhancing anti-apoptotic signaling and increasing the secretion of certain neurotrophins (NGF – nerve growth factor, IGF-1 – insulin-like growth factor, bFGF – basic fibroblast growth factor), thus supports the neurogenesis [35]. In view of the neurogenic theory, stating that impaired neurogenesis in the dentate gyrus of the hippocampus is one of the factors causing depression, it could be concluded that CGRP plays a role in the pathogenesis of this mental disorder.

Keeping in mind the neuroprotective function of this peptide, it may seem surprising that CGRP sometimes facilitates apoptosis of hippocampal neurons [36]. However, this only happens under conditions where these nerve cells would otherwise become necrotic through toxic damage, and the accumulation of necrotic debris would contribute to microglia activation and acute phase responses [37]. CGRP thus protects against an enhanced immune response within the CNS. This feature of CGRP can be compared to the role of brain-derived neurotrophic factor (BDNF), which in case of mild lesions counteracts neuronal apoptosis, and when the damage is very severe, it intensifies this process. Due to the importance of the area of the hippocampus in the pathogenesis of depression, it can be concluded that in the case of a strong damaging stressor (e.g., ischemia), CGRP may also contribute to the intensification of depressive symptoms (e.g., post-stroke depression) [35, 38].

Research confirms that the level of CGRP is elevated in the frontal cortex, hippocampus and amygdala (but not in the hypothalamus) of rats being a genetic animal model of depression (Flinders-sensitive line rats, FSL) [39]. Angelucci et al. [39] observed that antidepressants did not affect the level of CGRP. Other animal studies also suggest that the expression of CGRP in the hippocampus may be associated with depressive symptoms and an increase in the expression of nerve growth factor (NGF) [40].

Increased CGRP is also observed in patients with migraine. This neuropeptide is also elevated in the peripheral blood of migraineurs between their headache attacks. Intravenous CGRP infusion may induce symptoms of migraine headaches [34].

CGRP has many functions, including reduction of brain oedema and possibly stimulation of antioxidant defenses. The calcitonin gene-related peptide also supports the action of the blood-brain barrier (BBB) by inhibiting, inter alia, influx of neutrophils and monocytes to the brain [35]. It also shows its activity peripherally. It is a peptide that strongly dilates blood vessels, promoting the development of inflammation. It may

also increase the concentration of cAMP, thus inhibiting the release of TNF-α (anti-inflammatory effect) [41, 42].

Also other neurotransmitter systems have been described as a possible basis for the coexistence of these two described disorders. A decreased level of GABA in the cerebrospinal fluid was observed in patients with migraine with coexisting depression compared to those without depression [43]. Disturbances in the functioning of the dopaminergic and melatonergic system, especially in patients suffering from migraines with aura with comorbid depression (also in the course of bipolar disorder) and anxiety, are observed. [44, 45].

Inflammatory factors

Chronic migraine pain and depression are conditions that are highly comorbid and present with overlapping clinical presentations. Both disorders are associated with common pathological biological pathways in neuroinflammation, which can be reversed by the use of proper, for example, anti-inflammatory treatment [46]. In migraine, activated trigeminal nerves release CGRP and substance P, as well as other neurotransmitters (such as serotonin). CGRP dilates blood vessels, and substance P increases vascular permeability, facilitating the influx of cells and inflammatory factors [42].

Research suggests that the inflammation within the nervous tissue (neuroinflammation) connects three key elements in the pathogenesis of depression, such as: reduced

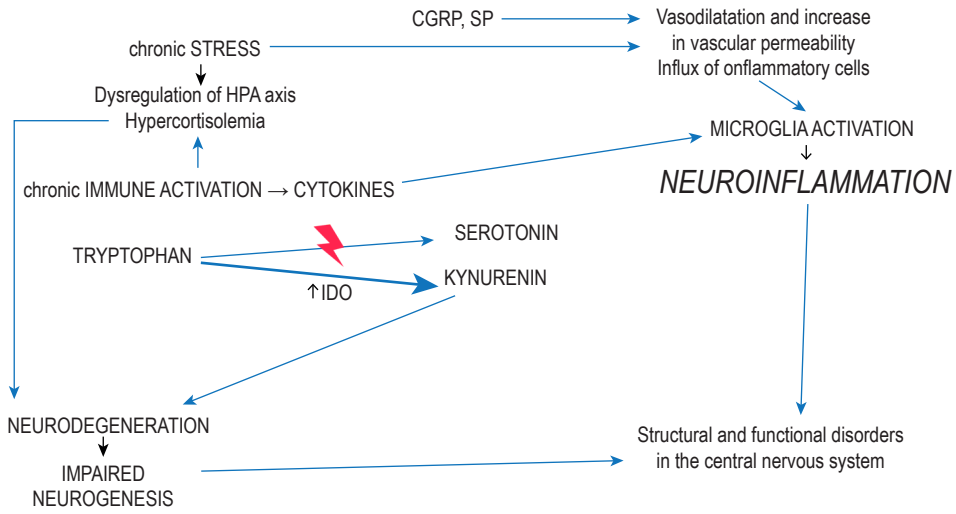

Figure 2. **Inflammation as a common element in the pathomechanism of migraine and depression**

IDO – indoleamine-2,3-dioxygenase, an enzyme present in microglia, astrocytes and neurons; CGRP – calcitonin gene-related peptide; SP – substance P

availability of serotonin in the CNS, dysregulation of the HPA (hypothalamus-pituitary-adrenal) axis and disturbances of neurogenesis within the hippocampus [47]. Under increased immune system activity inflammatory factors cause excessive activation of IDO (indoleamine-2,3-dioxygenase), an enzyme present in microglia, astrocytes and neurons, catabolizing the conversion of tryptophan into neurotoxic kynurenine (KYN), thus reducing the availability of tryptophan for the production of serotonin. Kynurenine, in turn, influences the intensification of neurodegenerative processes [48]. Similarly, long-term stress leading to dysregulation of the hypothalamic-pituitary-adrenal axis (HPA axis), the effect of which is chronic hypercortisolemia, also has neurotoxic effects [49]. Both of these processes damage nervous tissue, influencing neurogenesis in the dentate gyrus of the hippocampus [47]. This cascade can be triggered by any chronic inflammation in which cytokines crossing the blood-brain barrier lead to the activation of microglia and the development of inflammation [47]. In depression, the "source" of inflammation is rather peripheral. However, recent data also indicate that primary microglia activation, caused by the direct effects of chronic stress on blood vessel function, may lead to the development of depression (Figure 2). At this point we might see many similarities to the inflammatory pathomechanism of migraine headaches described above. Studies have also confirmed disturbances in the concentration of pro-inflammatory cytokines (e.g., an increase of IL-6) in patients with headaches [17, 50].

Hormonal factors

In addition to the previously described dysregulation of the stress axis, other hormonal disorders also underlie both depression and migraines. In the case of both of these disorders, due to the significantly higher incidence in women, sex hormones are the main area of research. Estrogens have a multidirectional effect on the neurotransmitter systems, including on the synthesis of serotonin and norepinephrine, key monoamines in the pathogenesis of depression. In addition, they influence the production of enkephalins and the release of GABA, which in turn is crucial in controlling pain transmission. Additionally, a low level of estrogens may be a factor contributing to the phenomenon of cortical spreading depression (CSD) [13]. Progesterone, on the other hand, modulates the expression of genes encoding monoamine oxidases – thus regulating the level of the enzyme that breaks down serotonin. At the same time, the metabolites of progesterone interact with GABA-A receptors and have an analgesic effect [13].

Psychological factors

Bhatia and Gupta [51], in a study on the comorbidity among Indian population, they indicated the personality profile of patients suffering from migraine, including anankastic, dysthymic, histrionic, and anxiety features among the most common ones. The literature indicates personality correlates favoring the development of both depression and migraine. It is primarily neuroticism – measured with the Eysenck's EPQR [6] questionnaire), but

also harm avoidance (HA) – measured with the TCI questionnaire. HA is described as excessive alert, anxiety and passive behavior in response to events [52]. It is easy to notice that the areas of the two described features actually constitute different terms of the generally understood neuroticism in psychology, the features of anxiety – referring to the neurodevelopmental theory of depression [53]. This theory assumes that factors such as biological and psychological stressors that trigger an inflammatory response in the form of cytokines, interacting at an early stage of development (also in prenatal development), cause changes in gene expression through epigenetic mechanisms, and thus altered patterns are then passed on to the next generations by inheritance [53]

Genetic background

Studies conducted in a group of twins [54] showed an increased risk of both: developing depression in relatives of a person suffering from migraine headaches and developing migraine in relatives of depressive patients (the risk was greater in the latter option). The relationship was also more pronounced in the case of monozygotic twins than in the case of dizygotic twins, which further confirms the common genetic background of these disorders [54]. Research focused on the search for an explanation of the observed relationship indicates the possibility of the existence of genetically conditioned vulnerability which is triggered by environmental factors. Specific candidate genes are taken into account, including CNR1 (the gene encoding the cannabinoid receptor), DRD2 (the gene encoding the receptor of the dopaminergic system) or SLC6A4 [13, 51]. The literature also describes studies on polymorphic sites of genes, such as the MTHFR gene responsible for encoding enzymes in the pathways associated with homocysteine and folic acid derivatives, as well as other SNPs (single nucleotide polymorphisms) [13, 55]. Regarding homocysteine, it is worth noting that disorders related to the increased concentration of this amino acid in the blood serum may lead to endothelial dysfunction and, consequently, promote the phenomenon of cortical spreading depression (CSD) [13]. Dresler [12] points out that the observed phenomenon of the coexistence of migraine with depression is probably multifactorial, and the confirmed genetic relationship considered in many studies probably has the dimension of polygenic inheritance of susceptibility [12, 54].

Recapitulation

The coexistence of migraine and depression is a major clinical challenge and is associated with great suffering and deterioration of the quality of life. Experts and national consultants in the field of neurology and psychiatry drew attention to the problem of the coexistence of these disorders. They presented a study on the management of patients treated for migraine with comorbid depression, emphasizing the validity of neurological consultations in terms of migraine coexistence in patients with depressive and anxiety disorders, and psychiatric consultations in patients suffering from chronic migraine, when depression is suspected [56, 57].

The discussed coexistence also contributes to the phenomenon of drug resistance. Scientists are working on new medications that could be effective in the treatment of both migraine and recurrent depressive disorders. An example of such targeted therapy is erenumab – a human monoclonal antibody that competes strongly and specifically for binding to the receptor of the peptide related to the calcitonin gene (CGRP), which has a proven role in the etiopathogenesis of migraine, as well as a potential role in the development of depression [58]. In clinical trials of the described drug, its use not only reduced the symptoms of migraine but also resulted in an improvement in the general functioning of patients [59, 60].

It is worth noting that both depression and migraine have a multifactorial etiology and at the present stage of scientific research it is difficult to clearly define which factor is the most important. It is also difficult to determine which of the above observations, well documented in studies from many parts of the world, are only the coexistence of two factors, and which have a cause-effect relationship in the described disorders.

References

1. Bigal ME, Lipton RB. *The epidemiology, burden, and comorbidities of migraine*. Neurol. Clin. 2009; 27(2): 321–334. Doi: 10.1016/j.ncl.2008.11.011.
2. Moschiano F, D'Amico D, Canavero I, Pan I, Micieli G, Bussone G. *Migraine and depression: Common pathogenetic and therapeutic ground?* Neurol. Sci. 2011; 32(Suppl 1): S85–88. Doi: 10.1007/s10072-011-0545-0.
3. Molgat CV, Patten SB. *Comorbidity of major depression and migraine – A Canadian population-based study*. Can. J. Psychiatry. 2005; 50(13): 832–837. Doi: 10.1177/070674370505001305.
4. Hamelsky SW, Lipton RB. *Psychiatric comorbidity of migraine*. Headache. 2006; 46(9): 1327–1333. Doi: 10.1111/j.1526-4610.2006.00576.x.
5. Antonaci F, Nappi G, Galli F, Manzoni GC, Calabresi P, Costa A. *Migraine and psychiatric comorbidity: A review of clinical findings*. J. Headache Pain. 2011; 12(2): 115–125. Doi: 10.1007/s10194-010-0282-4.
6. Breslau N, Andreski P. *Migraine, personality, and psychiatric comorbidity*. Headache. 1995; 35(7): 382–386. Doi: 10.1111/j.1526-4610.1995.hed3507382.x.
7. Oedegaard KJ, Neckelmann D, Mykletun A, Dahl AA, Zwart JA, Hagen K et al. *Migraine with and without aura: Association with depression and anxiety disorder in a population-based study. The HUNT Study*. Cephalalgia. 2006; 26(1): 1–6. Doi: 10.1111/j.1468-2982.2005.00974.x.
8. Dindo LN, Recober A, Haddad R, Calarge CA. *Comorbidity of migraine, major depressive disorder, and generalized anxiety disorder in adolescents and young adults*. Int. J. Behav. Med. 2017; 24(4): 528–534. Doi: 10.1007/s12529-016-9620-5.
9. Breslau N, Merikangas K, Bowden CL. *Comorbidity of migraine and major affective disorders*. Neurology. 1994; 44(10 Suppl 7): S17–22.
10. Oedegaard KJ, Fasmer OB. *Is migraine in unipolar depressed patients a bipolar spectrum trait?* J. Affect. Disord. 2005; 84(2–3): 233–242. Doi: 10.1016/j.jad.2003.11.007.
11. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC et al. *Depression and risk of transformation of episodic to chronic migraine*. J. Headache Pain. 2012; 13(8): 615–624. Doi: 10.1007/s10194-012-0479-9.

12. Dresler T, Caratozzolo S, Guldolf K, Huhn JI, Loiacono C, Niiberg-Pikksööt T et al.; European Headache Federation School of Advanced Studies (EHF-SAS). *Understanding the nature of psychiatric comorbidity in migraine: A systematic review focused on interactions and treatment implications*. J. Headache Pain. 2019; 20(1): 51. Doi: 10.1186/s10194-019-0988-x.
13. Zhang Q, Shao A, Jiang Z, Tsai H, Liu W. *The exploration of mechanisms of comorbidity between migraine and depression*. J. Cell Mol. Med. 2019; 23(7): 4505–4513. Doi: 10.1111/jcmm.14390.
14. Amoozegar F. *Depression comorbidity in migraine*. Int. Rev. Psychiatry. 2017; 29(5): 504–515. Doi: 10.1080/09540261.2017.1326882.
15. Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders, 3*rd *edition*. Cephalalgia. 2018; 38(1): 1–211. Doi: 10.1177/0333102417738202.
16. Rożniecki JJ, Stępień A. Domitrz I. *Leczenie migreny przewlekłej—zalecenia opracowane przez Grupę Ekspertów Polskiego Towarzystwa Bólów Głowy i Sekcji Badania Bólu Polskiego Towarzystwa Neurologicznego na podstawie międzynarodowych zaleceń i najnowszej literatury.* Pol Prz Neurol. 2018; 14(2): 60-66.
17. Zgorzalewicz M. *Patomechanism of migraine headache*. Child Neurology. 2005; 14(28): 7–14.
18. Satyanarayanan SK, Shih YH, Wen YR, Palani M, Lin YW, Su H et al. *miR-200a-3p modulates gene expression in comorbid pain and depression: Molecular implication for central sensitization*. Brain Behav. Immun. 2019; 82: 230–238. Doi: 10.1016/j.bbi.2019.08.190.
19. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, Powers S, Schwedt TJ, Lipton R et al. *Migraine and its psychiatric comorbidities*. J. Neurol. Neurosurg. Psychiatry. 2016; 87(7): 741–749. Doi: 10.1136/jnnp-2015-312233.
20. Rajmohan V, Mohandas E. *The limbic system*. Indian J. Psychiatry. 2007; 49(2): 132–139. Doi: 10.4103/0019-5545.33264.
21. Gudmundsson LS, Scher AI, Sigurdsson S, Geerlings MI, Vidal JS, Eiriksdottir G et al. *Migraine, depression, and brain volume: The AGES-Reykjavik Study*. Neurology. 2013; 80(23): 2138–2144. Doi: 10.1212/WNL.0b013e318295d69e.
22. Ma M, Zhang J, Chen N, Guo J, Zhang Y, He L. *Exploration of intrinsic brain activity in migraine with and without comorbid depression*. J. Headache Pain. 2018; 19(1): 48. Doi: 10.1186/s10194-018-0876-9.
23. Jahangir S, Adjepong D, Al-Shami HA, Malik BH. *Is there an association between migraine and major depressive disorder? A Narrative Review*. Cureus. 2020; 12(6): e8551. Doi: 10.7759/cureus.8551.
24. Gałecka M, Bliźniewska-Kowalska K, Maes M, Su KP, Gałecki P. *Update on the neurodevelopmental theory of depression: Is there any 'unconscious code'?* Pharmacol. Rep. 2021; 73(2): 346–356. Doi: 10.1007/s43440-020-00202-2.
25. Tao WW, Cai XT, Shen J, Shi XG, Wang Y. *Hypoechogenicity of brainstem raphe correlates with depression in migraine patients*. J. Headache Pain. 2019; 20(1): 53. Doi: 10.1186/s10194-019-1011-2.
26. Warner-Schmidt J. *Treating the brain deep down: Short-circuiting depression*. Nat. Med. 2013; 19(6): 680–681. Doi: 10.1038/nm.3215.
27. Michelsen KA, Prickaerts J, Steinbusch HW. *The dorsal raphe nucleus and serotonin: Implications for neuroplasticity linked to major depression and Alzheimer's disease*. Prog. Brain Res. 2008; 172: 233–264. Doi: 10.1016/S0079-6123(08)00912-6.
28. Ranft K, Dobrowolny H, Krell D, Bielau H, Bogerts B, Bernstein HG. *Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia*. Psychol. Med. 2010; 40(4): 557–567. Doi: 10.1017/S0033291709990821.

29. Tappe-Theodor A, Kuner R. *A common ground for pain and depression*. Nat. Neurosci. 2019; 22(10): 1612–1614. Doi: 10.1038/s41593-019-0499-8.

30. Browne CA, Hammack R, Lucki I. *Dysregulation of the lateral habenula in major depressive disorder*. Front. Synaptic Neurosci. 2018; 10: 46. Doi: 10.3389/fnsyn.2018.00046.

31. Zhang G, Guo J, Yang J. *The lateral habenula: Role in chronic pain and depression*. Transl. Perioper. Pain Med. 2020; 7(4): 271–278.

32. Zhou W, Jin Y, Meng Q, Zhu X, Bai T, Tian Y et al. *Publisher correction: A neural circuit for comorbid depressive symptoms in chronic pain*. Nat. Neurosci. 2019; 22(11): 1945. Doi: 10.1038/s41593-019-0522-0. Erratum for: Nat. Neurosci. 2019; 22(10): 1649–1658.

33. Supornsilpchai W, Sanguanrangsirikul S, Maneesri S, Srikiatkhachorn A. *Serotonin depletion, cortical spreading depression, and trigeminal nociception*. Headache. 2006; 46(1): 34–39. Doi: 10.1111/j.1526-4610.2006.00310.x.

34. Levin M, Silberstein SD, Gilbert R, Lucas S, Munsie L, Garrelts A et al. *Basic considerations for the use of monoclonal antibodies in migraine*. Headache. 2018; 58(10): 1689–1696. Doi: 10.1111/head.13439.

35. Borkum JM. *CGRP and brain functioning: Cautions for migraine treatment*. Headache. 2019; 59(8): 1339–1357. Doi: 10.1111/head.13591.

36. Park S-H, Sim Y-B, Kim C-H, Lee J-K, Lee J-H, Suh H-W. *Role of α-CGRP in the regulation of neurotoxic responses induced by kainic acid in mice*. Peptides. 2013; 44: 158–162. Doi: 10.1016/j.peptides.2013.04.001.

37. Bulloch K, Milner TA, Prasad A, Hsu M, Buzsaki G, McEwen BS. *Induction of calcitonin gene-related peptide-like immunoreactivity in hippocampal neurons following ischemia: A putative regional modulator of the CNS injury/immune response*. Exp. Neurol. 1998; 150(2): 195–205. Doi: 10.1006/exnr.1997.6765.

38. Shao B, Zhou YL, Wang H, Lin YS. *The role of calcitonin gene-related peptide in post-stroke depression in chronic mild stress-treated ischemic rats*. Physiol. Behav. 2015; 139: 224–230. Doi: 10.1016/j.physbeh.2014.11.049.

39. Angelucci F, Ellenbroek BA, El Khoury A, Mathé AA. *CGRP in a gene-environment interaction model for depression: Effects of antidepressant treatment*. Acta Neuropsychiatr. 2019; 31(2): 93–99. Doi: 10.1017/neu.2018.31.

40. Hashikawa-Hobara N, Ogawa T, Sakamoto Y, Matsuo Y, Ogawa M, Zamami Y et al. *Calcitonin gene-related peptide pre-administration acts as a novel antidepressant in stressed mice*. Sci. Rep. 2015; 5: 12559. Doi: 10.1038/srep12559.

41. Pociecha K, Przejczowska-Pomierny K, Cios A, Wyska E. *Contemporary concepts in studies on cyclic AMP and its role in the inflammatory reaction*. Postepy Hig. Med. Dosw. (Online). 2015; 69: 777–798. Doi: 10.5604/17322693.1161412.

42. Kuzawińska O, Lis K, Cessak G, Białkowiec-Iskra E. *The role of the CGRP in the pathogenesis and treatment of migraine*. Farmakoter. Psychiatr. Neurol. 2015; 31(2): 127–140. Doi: 10.17393/fpn.2015.10.001.

43. Vieira DS, Naffah-Mazacoratti MG, Zukerman E, Senne Soares CA, Alonso EO, Faulhaber MH et al. *Cerebrospinal fluid GABA levels in chronic migraine with and without depression*. Brain Res. 2006; 1090(1): 197–201. Doi: 10.1016/j.brainres.2006.03.051.

44. Peroutka SJ, Price SC, Wilhoit TL, Jones KW. *Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI Alleles*. Mol. Med. 1998; 4(1): 14–21.

45. Tseng PT, Yang CP, Su KP, Chen TY, Wu YC, Tu YK et al. *The association between melatonin and episodic migraine: A pilot network meta-analysis of randomized controlled trials to compare*

the prophylactic effects with exogenous melatonin supplementation and pharmacotherapy. J. Pineal. Res. 2020; 69(2): e12663. Doi: 10.1111/jpi.12663.

46. Lin YW, Chou AIW, Su H, Su KP. *Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: The common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids*. Brain Behav. Immun. 2020; 89: 604–614. Doi: 10.1016/j.bbi.2020.06.033.
47. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B et al. *Neuroinflammation and depression: A review*. Eur. J. Neurosci. 2021; 53(1): 151–171. Doi: 10.1111/ejn.14720.
48. Ogyu K, Kubo K, Noda Y, Iwata Y, Tsugawa S, Omura Y et al. *Kynurenine pathway in depression: A systematic review and meta-analysis*. Neurosci. Biobehav. Rev. 2018; 6(90): 16–25. Doi: 10.1016/j.neubiorev.2018.03.023.
49. Whittle S, Yap MB, Sheeber L, Dudgeon P, Yücel M, Pantelis C et al. *Hippocampal volume and sensitivity to maternal aggressive behavior: A prospective study of adolescent depressive symptoms*. Dev. Psychopathol. 2011; 23(1): 115–129. Doi: 10.1017/S0954579410000684.
50. Gergont A, Kaciński M. *Stężenie interleukiny-6 we krwi u dzieci z samoistnymi bólami głowy*. Neurol. Neurochir. Pol. 2005: 39(4 Supl. 1): S1–S8.
51. Bhatia MS, Gupta R. *Migraine: Clinical pattern and psychiatric comorbidity*. Ind. Psychiatry. J. 2012; 21(1): 18–21. Doi: 10.4103/0972-6748.110943.
52. Mongini F, Fassino S, Rota E, Deregibus A, Levi M, Monticone D et al. *The temperament and character inventory in women with migraine*. J. Headache Pain. 2005; 6: 247–249.
53. Kowalczyk M, Szemraj J, Bliźniewska K, Maes M, Berk M, Su KP et al. *An immune gate of depression – Early neuroimmune development in the formation of the underlying depressive disorder*. Pharmacol. Rep. 2019; 71(6): 1299–1307. Doi: 10.1016/j.pharep.2019.05.022.
54. Yang Y, Ligthart L, Terwindt GM, Boomsma DI, Rodrigez-Acevedo AJ, Nyholt DR. *Genetic epidemiology of migraine and depression*. Cephalgia. 2016; 36(7): 679–691. Doi: 10.1177/0333102416638520.
55. Yang Y, Zhao H, Boomsma DI, Ligthart L, Belin AC, Smith GD et al. *Molecular genetic overlap between migraine and major depressive disorder*. Eur. J. Hum. Genet. 2018; 26(8): 1202–1216. Doi: 10.1038/s41431-018-0150-2.
56. Stępień A, Domitrz I, Kozubski W, Rejdak K, Rożniecki J, Słowik A et al. *Experts and national consultants' recommendations regarding management of patients treated for migraine with comorbid depression. Epidemiology. Pathomechanism. Comorbidity. Part 1*. Psychiatr. Pol. ONLINE FIRST Nr 237: 1–14. Published ahead of print 14 July 2021. www.psychiatriapolska.pl. ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE). DOI: https://doi.org/10.12740/PP/OnlineFirst/13648.
57. Stępień A, Domitrz I, Kozubski W, Rejdak K, Rożniecki J, Słowik A et al. *Experts and national consultants' recommendations regarding management of patients treated for migraine with comorbid depression. Diagnosis. Therapeutic strategies. Part 2*. Psychiatr. Pol. ONLINE FIRST Nr 243: 1–18. Published ahead of print 20 July 2021. www.psychiatriapolska.pl. ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE). DOI: https://doi.org/10.12740/PP/OnlineFirst/139596.
58. De Matteis E, Guglielmetti M, Ornello R, Spuntarelli V, Martelletti P, Sacco S. *Targeting CGRP for migraine treatment: Mechanisms, antibodies, small molecules, perspectives*. Expert Rev. Neurother. 2020; 20(6): 627–641. Doi: 10.1080/14737175.2020.1772758.
59. Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick DW, Xue F et al. *Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial*. Eur. J. Neurol. 2021; 28(5): 1716–1725. Doi: 10.1111/ene.14715.

60. Andreou AP, Fuccaro M, Lambru G. *The role of erenumab in the treatment of migraine*. Ther. Adv. Neurol. Disord. 2020; 13: 1756286420927119. Doi: 10.1177/1756286420927119.

Address: Katarzyna Wachowska
Department of Adult Psychiatry
Medical University of Lodz
91-229 Łódź, Aleksandrowska Street 159
e-mail: katarzyna.wachowska@umed.lodz.pl