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Experts and national consultants' recommendations regarding management of patients treated for migraine with comorbid depression. Epidemiology. Pathomechanism. Comorbidity. Part 1

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Summary

Coexistence of migraine and depression is a significant clinical problem. Health examination surveys indicate that patients who suffer from migraine are more likely to develop depression than the general population. The inverse relationship is also observed. The etiopathogenesis of both migraine and depression is not fully understood and is probably multifactorial and complex. Neurotransmission disorders, the immune system, and genetic predisposition are considered in the literature. The authors present etiopathogenetic theories of both diseases and their prevalence. They analyze data on the comorbidity of these conditions and discuss likely underlying factors. They describe clinical predictors of depression onset in people with migraine.

Key words: migraine, depression

Introduction

Neurological disorders are an important cause of disability and death worldwide. Globally, due to a growing number of people and ageing population, the burden of these disorders has increased significantly over the past 25 years [1]. The most common neurological disorders worldwide are various types of headaches, including tension headache, migraine, and pain as a consequence of misuse of medicines. Migraine is one of the best defined pain syndromes and is associated with the highest number of disability-adjusted life years (DALYs) [1].

Although this disease entity has been present since the beginning of mankind, it is only recently that significant progress has been made in the understanding of its pathomechanism, which has allowed new aspects of therapy to be indicated. More than 40 years ago, the trigeminovascular theory was formulated as the key mechanism in generating the symptoms typical of migraine.

Migraine is a health problem that has a significant impact on the individual and society in general. It often leads to moderate or severe disability and disrupts family life, interpersonal relationships, and work life [2]. The social costs of migraine are high for many reasons; they include lack of productivity at work, poorer functioning in daily life, the need for medication, and the use of various medical services. An additional problem is the comorbidity of migraine with other conditions, including mental, neurological, vascular and cardiovascular disorders [2].

Migraine epidemiology

Migraine is a spontaneous headache with significant prevalence; it is also the second most common neurological disorder associated with the highest health burden [3]. The significant prevalence of migraine, its unfavourable impact on the quality of life and the considerable impairment of the patients' and their family members' daily functioning have led to a situation where the World Health Organization listed it among the top twenty diseases that negatively affect human life [4].

In adults, migraine is more common in women (approximately 15–18% of the population) than in men (6–8%) [5]. It manifests in early adolescence and tends to gradually subside after the fifth decade of life. Before puberty, it occurs with equal frequency in both sexes (incidence rate of approx. 4%) [6, 7]. In adults, migraine onset is observed in the second or third decade of life – in 90% of patients the first episode takes place before the age of 40 and only in about 3% of patients older than 60. It most often appears before the age of 35. The incidence of migraine after the age of 50 has been reported rarely, but the disease is still observed at this age in half of the patients previously affected by it. After the age of 65, 2.5% of women and 7.4% of men suffer from migraine. In the European population, the incidence of migraine has been studied, among others, in the Danish population. The sick rate

totals 8.1 per 1,000 persons per year and is six times higher in women compared to men [8].

The International Classification of Headache Disorders distinguishes several clinical forms of migraine – the most widespread being migraine with and without aura. Migraine without aura is more common in women than migraine with aura [9]. Chronic migraine occurs in about 2.5% of people suffering from migraine, more often in women than in men (3:1). The risk of episodic migraine transformation into chronic migraine is higher in women than in men without relation to the misuse of antimigraine medicines [10]. However, there are studies that do not support any association between the development of chronic migraine and the gender of the patient. The reported prevalence rate of chronic migraine is higher in headache treatment centres. It occurs in 25% of patients, mainly in women [11]. Data from other headache centres indicate that migraine occurs in approximately 14% of patients who report for consultation due to chronic headaches [12].

The prevalence of headache episodes is variable over the course of the disease and is characterised by individual biological rhythms. Nearly 75% of migraine patients experience fewer than four attacks per month [13]. According to research conducted in Poland, 48% of patients experience at least one migraine episode per month and 24% have more than two such episodes monthly. The average duration of a migraine attack is one day, but some 20% of patients struggle with attacks lasting 2–3 days. Migraine episodes last longer in women than in men. As many as 71% of women report attacks lasting longer than 24 hours, whereas episodes of this duration are reported by 48% of male patients [14].

Few epidemiological studies of migraine have been conducted in Poland so far [15]. The most recent indicate that nearly 10% of the population, or about four million people, suffer from migraine [16]. However, most of them do not receive regular medical care, which negatively affects the quality and efficacy of treatment. These patients self-medicate with over-the-counter common painkillers. Studies also show that migraine is nearly three times more common in women than in men. The prevalence of the disease among residents of cities of all sizes and rural residents is similar. Its adverse effect on the quality of life and limitation of the patient's daily functioning, as well as the unfavourable impact of the disease on the life of the patient's whole family and his or her ability to perform professional work have been proven. Frequent co-occurrence of neurotic disorders and depression in people affected by chronic headache is one of the consequences of these phenomena [17].

Most epidemiological studies have indicated that migraine is more common in groups of people with lower income [18]. Migraine prevalence decreases with increasing income and better education of the patients. Such observations have also been confirmed in national studies [16].

Migraine negatively affects the lives of patients by causing frequent inability to work. About 10% of patients are forced to change jobs because of migraine attacks.

The same number of patients give up work entirely. This problem is also significant from an economic point of view. Studies show that the medical costs and losses caused by sickness absence due to headaches run into millions of Euros per year and consume a significant proportion of all health care expenditure. Moreover, it has been calculated that a migraine patient misses 2 to 4 days of work per month and takes an average of 2.5 painkillers during a single attack. The direct and indirect costs of migraine treatment are greater in women than in men. In the United States alone, these costs have been estimated at about USD 27 billion [19]. This figure is likely to be underestimated due to the fact that people with migraine are less likely to be professionally active, more likely to be unemployed or do not work full time.

Depression epidemiology

Depression is a widespread mental disorder. It is also one of the most common causes of health-related disability. Almost 350 million people worldwide are affected by depression and this number is still increasing [20]. The lifetime prevalence of the disease is 14–18%. Depression most commonly affects young people between the age of 20 and 40. Among all European countries, the highest percentage of people suffering from depression (more than 5%) is observed in Portugal, Finland, Estonia, Sweden, and Lithuania [20]. In the population of the European Union, the difference in terms of gender remains at about 2%, with 3.1% of men and 5.3% of women suffering from depression. Most depressed women are Portuguese and Finnish (more than 6.5%), while men suffer from depression most often in Lithuania and Finland (4%). Taking these figures into account, the epidemiological situation in Poland looks quite optimistic – 3.2% of women and 2.4% of men suffered from depression in our country in 2017 [22]; however, this may be rather due to the underestimation of the problem and reduced social awareness of mental disorders [20]. It is worth noting that depression is a significant risk factor for suicide death [19]. Data from the National Health Fund report [20] also indicate a high demand for antidepressants. In 2018, 1.28 million people in Poland used prescriptions for reimbursed antidepressants and, of this group, 69.3% were women [20]. Between 2013 and 2018, the number of patients who used prescriptions for reimbursed antidepressants increased by almost 35% [20]. It is particularly alarming that the number of patients under 18 taking reimbursed drugs in this group doubled. The total financial costs associated with the prescriptions for reimbursed antidepressants totalled PLN 232.5 million in 2018 and the amount increased by 28.5% compared to 2013 [20].

Migraine pathomechanism

Migraine aetiology has not been fully studied. According to current medical knowledge, it can be considered a genetically determined channelopathy, which depends on

several genes [21]. Migraine is characterised by a propensity for increased vasomotor activity, caused by paroxysmal changes in the central nervous system (CNS). The vascular system, the trigeminal nerve and its nuclei in the brainstem, as well as cortical centres, which form the so-called functional trigeminovascular system, interact in the pathomechanism of migraine attack development. The individual components of this system are influenced by genetic and environmental factors that modify their activity.

Activation of the trigeminovascular system

During a migraine attack, cortical spreading depression (CSD) leads to cerebral vascular hyperactivity [22]. This phenomenon is directly related to the formation of migraine aura. A reduction in arterial blood flow spreads from the occipital region of the brain through the entire hemisphere to the frontal region at a rate of approximately 2–3 mm/min. This leads to the activation of the trigeminovascular system. It is also worth remembering that brainstem changes are considered to be the neuronal generator of migraine attacks [22].

Metabolic changes

During migraine aura, a slowdown of metabolic processes involving magnesium ions is observed in the occipital region of the brain. A deficiency of these ions consequently leads to impaired oxidative phosphorylation in cell mitochondria, resulting in the inhibition of adenosine triphosphate (ATP) synthesis. Additionally, a decreased magnesium concentration is accompanied by an increased concentration of calcium and glutamate in nerve cells as well as by the release of potassium ions, nitric oxide, arachidonic acid, prostaglandins, and amino acids from arachnoid cells [23].

An increased activity of the nucleus and trigeminal nerve leads to the release of vasoactive neuropeptides, including substance P, calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP), outside the vascular bed [24, 25].

Role of calcitonin gene-related peptide (CGRP)

Activation of the trigeminovascular system stimulates nociceptive neurons on the blood vessels of the dura mater, which release various neuropeptides and cause the characteristic throbbing migraine pain [26, 27]. Signalling molecules associated with migraine pain generation are: 5-hydroxytryptamine (5-HT), substance P, nitric oxide, and calcitonin gene-related peptide (CGRP) [24, 26-29]. CGRP is a neuropeptide consisting of 37 amino acids encoded by the calcitonin gene and is a potent vasodilator that is released by trigeminal nerve endings entwining blood vessels in the meninges [29]. The binding of CGRP to the receptor for CGRP has both peripheral and central effects; peripheral binding is thought to lead to sensitisation and stimulation of

trigeminal nociceptive neurons, leading to migraine pain, while central binding may modulate pain transmission [30-35].

CGRP is believed to be one of the most potent vasodilators. It also plays an important role in several other processes, including modulation of nociception and neurogenic inflammation. Cell bodies of the trigeminal ganglion are the main source of CGRP in the trigeminovascular system.

An altered balance between parasympathetic and sympathetic nervous system tone in cerebral meninges and/or a lower nociceptive threshold may trigger the activation of trigeminovascular signals from the thalamus to the cortex [36]. Then trigeminal nerve activation causes the release of CGRP from perivascular nerve endings. By taking part in nociceptive transmission, CGRP also acts as a neurotransmitter in the trigeminal ganglion and secondary neurons in the caudal part of the trigeminal nerve nucleus [32]. CGRP-induced mast cell degranulation is also thought to sustain inflammation by activating and sensitising nociceptors in the meninges. Stimulation of neurogenic inflammation in the meningeal blood vessels is a key mechanism responsible for the effects that CGRP exerts in migraine [33].

Neurogenic inflammation

Extravasation of proteins beyond the vascular bed within the arachnoid has been confirmed in experimental studies and in migraine patients. This is one of the elements of neurogenic inflammation formation [34]. This process is inhibited by the 5-HT1B/D serotonin receptor agonists, i.e. triptans. In turn, histamine is released from arachnoid mast cells, and increased platelet aggregation in the venous hilar vessels takes place, from which serotonin (5-HT) is released. The consequence of this is vasospasm. There is a sharp increase in serotonin concentration during a migraine attack, whereas it is constant and small between attacks. The concentration of 5-HT in platelets, rising 24 hours before an episode, decreases by 50% from its value at the onset of the attack, and increases again to baseline values during the inter-attack period. There is a rapid increase in the excretion of 5-hydroxyindoleacetic acid, which is the main metabolite of serotonin [35].

The pathomechanism of migraine formation also emphasises the involvement of the dopaminergic system. Dopamine D1 and D2 receptors have been found in the trigeminal nerve and its nucleus. In turn, the number of D3 and D4 receptors is elevated in peripheral blood lymphocytes. Before and during a migraine attack, symptoms indicating hyperreactivity of postsynaptic dopamine receptors, such as yawning, lack of appetite, nausea and vomiting, appear. Experimental studies have confirmed the inhibitory effect of dopaminergic neurons on nociceptive transmission in the trigeminal nerve [36]. In summary, the aetiology of migraine is complex and multifactorial [37].

Depression pathomechanism

The actual cause of depression is complex and multifactorial, including dysfunctions of the serotonergic system resulting from changes in the functioning of the hypothalamic-pituitary-adrenal axis and the immune system [38]. The neurodevelopmental theory integrates all previous theories [39]. According to its assumptions, a series of mechanisms in the course of ontogenesis determines vulnerability to depression in adulthood. During the prenatal period, the impact of factors such as infections, the pregnant woman's exposure to stressors, and her ability to cope may – through epigenetic mechanisms – determine lifelong susceptibility. In subsequent stages of individual development – early childhood and adolescence – the formation of personality traits, symmetrical development of nervous and immunological systems are observed. The last pathways connecting the limbic system, the amygdala and the prefrontal cortex are formed, which significantly determines the body's reactivity in a threatening situation. Infections, stressors and personal experiences during this period holistically affect the developed coping mechanisms. If this process leads to the establishment of a tendency to react with fear in many non-threatening life situations, it causes overactivity of the HPA axis and a chronic inflammatory process (neuroinflammation) and, consequently, a reduction in the size of the areas responsible for the regulation of emotions and behaviour. As a result, anhedonia, lowered mood, fatigue and somatic symptoms are noticed [40]. Hence, we observe clinical symptoms of depression [38].

The mechanisms described above affect, among others, the regulation of the pituitary-hypothalamic-adrenal axis activity, the levels of biogenic amines, glutamate and GABA, dysfunction of specific areas of the central nervous system, neurotrophic and neurotoxic processes, and disturbances of circadian rhythms. These mechanisms together contribute to the aetiology of depression and its clinical picture.

Common pathomechanism of migraine and depression

Depression is the most common mental illness accompanying migraine, and the risk of depression in migraine headache sufferers far exceeds that of the general population [2]. Here is a brief summary of the mechanisms mentioned in the literature that are potentially common to these disease entities.

Substance P is the mediator of aseptic inflammation within the dura mater of the brain [41]. The literature emphasises that the likely cause of migraine headaches includes changes in the width and permeability of blood vessels [42]. Protein P is a neuropeptide that mediates the spread of inflammation [42] and changes in vascular permeability, which may induce inflammatory changes observed in depression.

Structural and functional changes in both diseases observed in migraine and affective disorders in neuroimaging studies are also highlighted in the literature [43], in

particular concerning the centres responsible for pain modulation, i.e. the amygdala, anterior cingulate cortex, and periaqueductal grey matter [43].

A dysfunction of the serotonergic system may be another common pathogenetic mechanism [44]. It has been reported in the literature that the phenomenon of chronically reduced serotonin availability (characteristic of depressive disorders) may predispose to 'cortical spreading depression' and increase the sensitivity of pain-transmission pathways (trigeminal nerve, vascularisation). The amount of serotonin increases during attacks and decreases between migraine episodes.

A possible common genetic cause is also indicated. Namely, a polymorphism in the gene that encodes the 5-HT transporter is probably associated with both diseases [44, 45]. It is worth noting that medicines used in migraine – triptans – act as 5-HT agonists, while drugs used to treat depressive disorders – SSRIs – can be used as migraine preventers. Abnormalities in the GABAergic system are also observed – it is indicated in the literature that reduced levels of GABA in the cerebrospinal fluid are found in patients with migraine co-occurring with depression compared to those without depression [46]. A dysfunction of the dopaminergic system has also been pointed out, especially in the patients suffering from migraine with aura with comorbid depression and anxiety [47]. Furthermore, endocrine disorders have been described, including in the pituitary-hypothalamic-adrenal axis, i.e. elevated proinflammatory cytokines, impaired feedback, and sex hormones, mainly estrogens. Dresler et al. [44] point out that the observed phenomenon of migraine-depression comorbidity probably has a multifactorial basis; perhaps genetics also plays a role, more precisely a polygenic basis of inherited susceptibility [48].

Migraine and depression – common comorbidity

Epidemiological studies of comorbidity have shown that migraine often coexists with depression. This association is particularly strong in chronic migraine [49, 50].

Research on the comorbidity of depression has shown that migraine is three times more common among patients who suffer from depression than in the general population (33% vs. 11%) [51]. Among patients with moderate depression, migraine with aura occurs in 16.7%, while migraine without aura in 21.1%. Similar results were observed in Polish patients [16].

Studies on the development and dynamics of comorbidity over time have shown that patients with features of major depression have a three – to four-fold increased risk of developing migraine over two consecutive years compared with non-depressed individuals. In turn, the risk of depression in a migraine sufferer is 2.4 to 5.8 times higher than in the 'healthy' population [52]. The risk of major depression occurrence within two years in people with severe headaches is 2.7 times higher than in people without severe headaches. It is as much as 5.8 times higher in the population with diagnosed migraine than in people without migraine and other severe headaches [52].

However, depression is not the only psychiatric condition that coexists with migraine at an increased rate in comparison to the general population. Other psychiatric conditions which are comorbid with migraine, especially chronic migraine, include anxiety syndrome (51–58%), post-traumatic stress disorder (9–43%), childhood trauma (58%), as well as various addiction conditions during adult life (33%) [43].

It is important to note that depression is a strong risk factor for the transformation of episodic migraine into chronic migraine.

The mechanisms underlying the frequent coexistence of migraine and depression and other psychiatric conditions are not clear. However, the literature draws attention to the involvement of the prefrontal cortex area of the left cerebral hemisphere in the pathomechanism of both diseases. Reduced activity of this region has been observed in magnetic resonance functional images in the two diseases discussed [53].

It is clear that a patient being treated by a psychiatrist for depression or anxiety syndrome with the presence of headaches should also be consulted by a neurologist for coexisting migraine, and conversely, migraine patients – especially those suffering from chronic migraine – should be consulted by a psychiatrist if depression is suspected [50-55].

Summary – clinical predictors of depression onset in people with migraine

Migraine often coexists with various chronic diseases. These include various neurological diseases, e.g. epilepsy, restless legs syndrome, vascular diseases, e.g. acute stroke, cerebral small vessel disease, cardiovascular diseases, e.g. ischaemic heart disease, mitral valve prolapse, patent foramen ovale, and psychiatric diseases [2]. Among psychiatric diseases, depression is the most common comorbidity with migraine [2], followed by anxiety disorders, panic attacks, and bipolar disorder. A cross-sectional study and meta-analysis of 12 clinical trials published in 2011 [49] found that depressive symptoms are present in 8.6% to 47.9% of people with diagnosed migraine; the prevalence of depression in people without a diagnosis of migraine is two to four times lower, ranging from 3.4% to 24.4%.

Both the risk of migraine and the risk of depression are thought to be genetically determined; in both cases they are conditioned by the summative influence of a large number of diverse genetic variants with little individual impact on the development of these diseases [56, 57]. Interestingly, genetic risk variants common to both conditions have also been identified. In contrast, an Australian study has shown a different profile of genetic risk variants for migraine with comorbid depression and for migraine without comorbid depression [57].

A repeatedly confirmed risk factor for depression in patients with migraine is the presence of migraine aura. For example, a Norwegian population-based survey of 9,000 people with migraine documented that women who have migraine with aura are more than twice as likely to have depressive symptoms than women who have

migraine without aura (OR = 2.24; 95% CI: 1.57-3.18). No such dependencies were found in men [58].

The frequency and severity of migraine pain is also important. For example, individuals who experience frequent migraine attacks of very high intensity have been found to have up to a 30-fold increased risk of depression compared to individuals with only episodic headaches [59]. Another factor that increases the risk of depression in migraine patients is the co-occurrence of chronic daily headaches [49].

In an Italian study designed to identify the factors that distinguish migraine with coexisting depression and migraine without depression, it has been shown that among the studied features (demographics, duration of migraine and duration of a migraine attack, number of migraine attacks per month, pain intensity, presence of aura, presence of throbbing pain, presence of photophobia, phonophobia, osmophobia, nausea/vomiting, autonomic symptoms, sensitivity to various provoking factors, BMI, smoking, comorbidities, current treatment), migraine and depression comorbidity is characterised by higher incidence of allodynia during an acute pain attack, higher sensitivity to various factors provoking migraine attacks and higher frequency of migraine attacks [60].

The development of depression in migraine patients is also affected by low economic status and single life resulting from divorce, separation or widowhood. The impact of adverse childhood experiences, prior depression, and female gender at the onset of depression in people with migraine has also been demonstrated [61].

It should be emphasised that it is possible to screen for depression in patients with migraine using a variety of simple questionnaire tools, e.g. Patient Health Questionnaire (PHQ-9), which may be particularly useful in people characterised by the presence of the above-mentioned features indicating the risk of depression.

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