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Delva I. I.

MIGRAINE AND CEREBROVASCULAR DISEASES

Poltava State Medical University (Poltava, Ukraine)
iryna.delva@gmail.com

In the last decade, much attention has been paid to migraine as a factor that can influence the occurrence of cerebrovascular pathology as well as modify its further course. Objective - to analyze the literature data on the associations between migraine and acute cerebrovascular events. The relationships between migraine and an increased risk of ischemic stroke is evident in female patients, especially in women under 45 years who use oral contraceptives and (or) smoke. In men, the association between migraine and the risk of ischemic stroke up to now remains unclear. The vast majority of studies indicate reliable relationships between migraine and the risk of hemorrhagic stroke, especially in women under 45 years and in cases of migraine with aura. The mechanisms connecting migraine with stroke are not fully understood and, most likely, are multifactorial. Presence of migraine aura doubles the risk of ischemic stroke. A number of studies have shown that migraine is associated with an accelerated development of atherosclerotic lesions in cerebral arteries. It was revealed a common genetic predisposition for migraine and ischemic stroke. Several observational studies have shown that patients with migraine with aura have significantly increased prevalence of patent foramen ovale. It had been found associations between migraine without aura and increased risk of cerebral dissections. Several studies have found associations between migraine and atrial fibrillation, more pronounced in migraine with aura. Understanding the relationships between migraine and cerebrovascular pathology is important for the development of effective tools for primary prevention of cerebrovascular diseases in this category of individuals.

Key words: *migraine, strokes, risk factors, etiopathogenesis.*

Connection of the publication with planned research works.

The work is a fragment of the research «Optimization of diagnosis, prognosis and prevention of neuropsychological disorders in organic diseases of the nervous system», state registration number 0120U 104165.

Introduction.

Migraine is a common type of primary headache affecting about 20% of the population [1]. In the last decade, much attention has been paid to migraine as a factor that can influence the occurrence of cerebrovascular pathology as well as modify its further course.

The aim of the study.

To analyze the literature data on the associations between migraine and acute cerebrovascular disorders.

Main part.

Numerous studies, including results of 5 meta-analyses, found that migraine (especially migraine with aura) is associated with an increased risk of ischemic stroke [2-6]. In migraine patients, the risk of ischemic stroke is higher in cases of migraine attacks presence during the last year [7] and, especially, during periods of increased frequency of migraine attacks [8]. The relationships between migraine and an increased risk of ischemic stroke is evident in female patients, especially in women under 45 years who use oral contraceptives and (or) smoke [2, 3]. In men, the association between migraine and the risk of ischemic stroke up to now remains unclear [2]. In the elderly, migraine is a proven risk factor for ischemic stroke only in patients smoke [9].

In migraine with aura, the risk of transient ischemic attacks is increased [10, 11]. However, this issue needs further clarification, since in some cases it is quite difficult to distinguish a migraine aura from a transient ischemic attack, especially in patients over 60 years old (among whom the prevalence of both transient ischemic attacks and migraine attacks with aura without headache is increased [12]). The most important distinction between a transient ischemic attack and a migraine aura is the sudden onset of symptoms in patients with vascular risk factors, while aura in a migraine attack has a gradual development of symptoms.

Neuroimaging studies have found that migraine with aura is associated with an increased probability of "silent" cerebral infarctions, especially in the vertebrobasilar arterial territory [13-15], regardless of other vascular risk factors and antimigraine drugs uses [13, 16-18].

The vast majority of studies indicate reliable relationships between migraine and the risk of hemorrhagic stroke [6, 19, 20-23], especially in women under 45 years [21] and in cases of migraine with aura [6, 19, 22]. In addition, there are reports that the presence of migraine is associated with increased mortality rates in hemorrhagic strokes [22]. The mechanisms that increase the risk of hemorrhagic stroke in migraine have not yet been elucidated and are partially explained by the increased risk of intracranial aneurysms in patients with migraine [24, 25].

Connection "migraine - cerebrovascular pathology" can also be mediated through other, rarer conditions - reversible cerebral vasoconstrictor syndrome and SMART syndrome.

Migraine patients have an increased risk of reversible cerebral vasoconstrictor syndrome [26]. Reversible cerebral vasoconstrictor syndrome is a clinical and radiological phenomenon characterized by acute, severe headache (often in combination with convulsions and neurological deficits) and multifocal constriction of cerebral arteries with spontaneous resolution within the next 3 months (according to cerebral angiography). In a significant number of cases, reversible cerebral vasoconstrictor syndrome can be complicated by ischemic strokes, intracerebral and subarachnoid hemorrhages [26].

SMART syndrome (stroke-like migraine attacks after radiation therapy) is a rare pathological condition with transient hemispheric neurological symptoms, migraine-like headache attacks, and epileptic seizures that appear in patients several years after radiation therapy for brain tumors [27]. SMART syndrome has specific MRI features:

hyperintensive changes in cerebral gyri at the site of radiation therapy on T2 and FLAIR images, thickening of the cerebral cortex with contrast accumulation in these areas [28]. As a rule, SMART syndrome is self-limiting condition that gradually resolves over several weeks.

The problem of antimigraine medications on the occurrence of acute cerebrovascular disorders deserves special attention. Some drugs for abortive migraine therapy - ergotamine alkaloids and triptans have vasoconstrictor properties. Excessive intake of ergotamine drugs increases the risk of ischemic stroke, so their use is contraindicated in patients with a history of strokes and myocardial infarction [29]. Also, triptans should be used with caution in patients who have vascular risk factors [30], moreover in patients who had ischemic stroke, transient ischemic attack, unstable angina, and a history of acute coronary syndrome, these drugs are contraindicated [31].

As mentioned above, associations between migraine and ischemic stroke are most pronounced in women of childbearing age [8]. The risk of ischemic stroke is increased in women who have migraine with aura and use oral contraceptives [32] and (or) have concomitant vascular risk factors [33] and (or) smoke tobacco [34]. It is important that the increased risk of ischemic stroke in women with migraine is directly correlated with the dosage of estrogens in oral contraceptives [35, 36]. From a practical point of view, a woman who has migraine with aura, who smokes and (or) has any clinical manifestations of coagulation disorders (history of thromboembolism, spontaneous abortions, malignant neoplasms, etc.) should be considered as patient with increased risk of stroke and, consequently should not has been recommended the use of oral contraceptives [37, 38]. If the start of oral contraceptives usage coincides in time with manifestation of a migraine aura in patients who have migraine without aura or with manifestation of a new and (or) prolonged aura in patients who have migraine with aura, it is necessary to revise the expedience of these drugs usage [37].

Physiological changes during pregnancy and the postpartum period (venous stasis, peripheral edema, hypercoagulation, etc.) are accompanied by an increased risk of strokes [39]. The vast majority of women have a decrease in the frequency and intensity of migraine attacks during pregnancy [39]. During pregnancy, women with a history of migraine have an increased risk of pathological conditions that are complicated by strokes (preeclampsia, gestational hypertension, venous thromboembolism), and this risk is most significant in the cases of unchanged frequency and intensity of migraine attacks during pregnancy [40].

The mechanisms connecting migraine with stroke are not fully understood and, most likely, are multifactorial. Among the most significant factors are spreading cortical depression, endothelial dysfunction, genetic factors, migrainous infarction, patent foramen ovale, dissections of cerebral arteries, atrial fibrillation.

Presence of migraine aura doubles the risk of ischemic stroke [2-6]. At present, the basis of migraine aura is considered to be the spreading cortical depression - an electrophysiological phenomenon in the form of intense depolarization of the membranes of neurons and glial cells, that spreads in a wave-like manner over the cerebral cortex [41]. In spreading cortical depression, initial neuronal activation is associated with a short period of cerebral hyperperfusion (1-2 minutes), followed by a longer (1-2 hours) neuronal suppression and decreasing of cerebral blood flow in these areas by 20-30% [42]. As a rule, decreasing of cerebral blood flow during cortical depression is not critical for cell membranes ischemic damage, however, in some cases, the level of hypoperfusion may exceed the hypoxic threshold. In experiments on animals, spreading cortical depression is reduced by pharmacological agents (analgesics, sedatives, NMDA receptor antagonists, etc.) and neuromodulation technologies (transcranial magnetic stimulation, vagal nerve stimulation, etc.) [43-46]. Therefore, there are theoretical assumptions that if effective methods of prevention and early correction of spreading cortical depression would be available in clinical practice, it could be possible to reduce risk of ischemic stroke in patients who have migraine with aura [37].

A number of studies have shown that migraine is associated with endothelial dysfunction [47] and, consequently, with an accelerated development of atherosclerotic lesions in cerebral arteries [47, 48]. However, this issue is contradictory, because for assessment of atherosclerosis progression in patients with migraine, a prospective follow-up is necessary [49].

From genetics point of view, migraine is a multifactorial phenomenon, in which the role of genetic component in the risk of disease is more than 40% [50]. Based on the results of a polygenomic study, it was revealed a common predisposition for migraine and ischemic stroke, especially pronounced for atherothrombotic and cardioembolic stroke subtypes [50, 51]. In addition, some monogenic diseases in their clinical phenotype have as migraine as well as ischemic stroke: CADASIL syndrome, MELAS syndrome, familial hemiplegic migraine, retinal vasculopathy with cerebral leukodystrophy, etc.

Migrainous infarction, according to the International classification of headache disorders of the 3rd revision, is a condition that occurs in a patient with «Migraine with aura» and typical of previous attacks except that one or more aura symptoms persists for >60 minutes, if neuroimaging demonstrates ischemic infarction in a relevant area and this condition is not better accounted for by another ICHD-3 diagnosis [52]. Migrainous infarction is quite rare and accounts for about 0.5% of all ischemic strokes [53]. The exact pathophysiological mechanisms of migrainous infarction are not yet known, but it is assumed that they are based on a critical decrease of cerebral blood flow during a prolonged aura. In most cases, migraine infarcts develop in the posterior circulation system, which corresponds to the most frequent type of migraine aura - visual [54]. The diagnosis of migraine infarction is complicated by the fact that in patients who have migraine with aura, primary cerebral ischemia can provoke migraine-like attacks and imitate a migraine attack with aura [55]. Therefore, migrainous infarction, by its definition, is a diagnosis of exclusion and cannot be established without providing an appropriate diagnostic search in order to exclude other possible causes of cerebral ischemic damage [56].

The foramen ovale is the hole in the atrial septum of the fetus that closes within a few days after the birth. Patent foramen ovale leads to constant or periodic (due to transient increasing of pressure in the right atrium) blood flow from the right half of the heart to the left that can lead to “paradoxical embolism” and embolic stroke. Several observational studies have shown that patients with migraine with aura have significantly increased prevalence of patent foramen ovale [57, 58]. It is not yet

known whether it is the cause-and-effect relationship or whether it is simply the result of an independent coexistence of these two conditions. It is assumed that through patent foramen ovale, mechanical or chemical irritants (small particles, air bubbles, various substances) circulating in the venous system can directly flow in the arterial system and cause a spreading cortical depression and, subsequently, a migraine attack with aura. Observational studies have shown that endovascular closure of patent foramen ovale is accompanied by a significant reduction in the frequency of migraine attacks [59-63]. From a practical point of view, migraine is not an indication for patent foramen ovale screening, except for cases of migraine attacks with atypical aura or frequent migraine attacks with aura [37].

Dissection of the cerebral arteries is the most common cause of strokes in young patients. It had been found associations between migraine without aura and increased risk of cerebral dissections, especially in men and in young patients [64]. Throughout clinical signs of cerebral dissections, headache occurs much more often in patients with migraine [65]. In addition, dissections of cerebral arteries can cause migraine-like attacks due to the release of biologically active substances from the damaged endothelium at the site of arterial dissection, which provoke spreading cortical depression and a migraine attack with aura.

Several studies have found associations between migraine and atrial fibrillation, more pronounced in migraine with aura [19, 66] and in women [19]. Some clinical reports describe cases of atrial fibrillation paroxysms during a migraine attack, the cause of which is considered to be an acute disturbances of autonomic regulation [67, 68]. On the other hand, catheter ablation of atrial fibrillation is accompanied by decreasing of frequency and intensity of migraine attacks [69].

Conclusions.

Migraine, especially migraine with aura, is associated with an increased risk of acute cerebrovascular disorders, mainly ischemic stroke and transient ischemic attack. The pathophysiological mechanisms mediating these associations are complex and up to now is not fully understood. From a practical point of view, there are currently no personalized biomarkers for predicting stroke risk in migraine patients. However, understanding the relationship between migraine and cerebrovascular pathology is important for the development of effective tools of primary prevention of acute cerebrovascular events in this category of patients.

Prospects for further research.

Further studies should be devoted to detailing of the clinical course of acute cerebrovascular events as well as post-stroke functional recovery in patients with different types of migraines.

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МІГРЕНЬ ТА ЦЕРЕБРОВАСКУЛЯРНІ ЗАХВОРЮВАННЯ

Дельва І. І.

Резюме. В останній час велика увага приділяється мігрені як чиннику, що може впливати на виникнення ішемічних і геморагічних інсультів, транзиторних ішемічних атак, лейкоареозу. Достовірні зв'язки між мігренню та підвищеним ризиком інсультів зафіксовані в осіб жіночої статі, які мають мігрень з аурою, і ці асоціації найбільш виражені у жінок до 45 років, при умові вживання оральних контрацептивів та (або) при тютюнопалінні. Механізми, що пов'язують мігрень з інсультом до кінця не є вивченими і, скоріш за все, є мультифакторіальними. Препарати абортивної терапії мігрені – алкалоїди ерготаміну та триптани мають вазоконстрикторні властивості і можуть збільшувати ризик ішемічного інсульту. Кортикальна депресія, що поширюється – це інтенсивна, хвилеподібна деполяризація мембран нейронів та гліальних клітин з вторинним зниженням церебральної перфузії; зниження мозкового кровотоку в ділянці кортикальної депресії може перевищувати критичний поріг та приводити до мігренозного інфаркту. За результатами полігеномного пошуку виявлена спільна спадкова схильність до мігрені та ішемічного інсульту, особливо виражена при його атеротромботичному та кардіоемболічному підтипах. У пацієнтів з мігренню з аурою достовірно збільшена розповсюдженість відкритого овального отвору; вважається, що при відкритому овальному отворі механічні або хімічні подразники, що циркулюють у венозній системі можуть безпосередньо проникати в артеріальний кровотік і викликати мігренозний напад з аурою. Зафіксовані асоціації між мігренню без аури та ризиком виникнення дисекцій магістральних артерій голови, особливо у представників чоловічої статі та у пацієнтів молодого віку. Виявлені асоціації між нападами мігрені та пароксизмами фибриляції передсердь, особливо виражені при мігрені з аурою та у пацієнтів жіночої статі.

Таким чином, мігрень (особливо мігрень з аурою) асоціюється з підвищеним ризиком гострих порушень мозкового кровообігу, переважно ішемічного інсульту та транзиторної ішемічної атаки. Розуміння зв'язків між мігренню та цереброваскулярною патологією є важливим для розробки ефективних засобів первинної профілактики цереброваскулярних захворювань у цієї категорії осіб.

Ключові слова: мігрень, інсульти, фактори ризику, етіопатогенез.

MIGRAINE AND CEREBROVASCULAR DISEASES

Delva I. I.

Abstract. In the last decade, much attention is paid to migraine as a risk factor of cerebrovascular pathology. There is increased risk of stroke and transient ischemic attack in females who have migraine with aura, this risk is highest in women under 45 years who use oral contraceptives and (or) smoke. The mechanisms that mediate increased risk of stroke in migraine patients up to now are still not completely defined and, most likely, are multifactorial. Drugs for the abortive therapy of migraine – ergotamine alkaloids and triptans have vasoconstrictor properties and by that way may increase the risk of ischemic stroke. Spreading cortical depression is an intense depolarization of neurons and glial cells membranes that spreads in a wave-like manner throughout the cerebral cortex with secondary decreasing of cerebral perfusion; decreased cerebral blood flow during cortical depression may exceed a critical threshold and lead to migrainous infarction. According to polygenomic search, it was found the common hereditary predisposition to migraine and ischemic stroke, highest in atherothrombotic and cardioembolic strokes. In patients with migraine with aura, the prevalence of patent foramen ovale is significantly increased; it is assumed that through patent foramen ovale mechanical or chemical stimuli can directly come from venous system to the arterial system and cause a migraine attack with aura. There are associations between migraine without aura and the risk of cerebral arteries dissections, particularly in males and younger patients. Also it was revealed associations between migraine attacks and paroxysms of atrial fibrillation, especially in females who have migraine with aura.

Thus, migraine, especially migraine with aura, is associated with an increased risk of strokes, mainly ischemic stroke. Understanding the relationships between migraine and cerebrovascular pathology is important for effective primary prevention of cerebrovascular diseases in migraine patients.

Key words: migraine, stroke, risk factors, etiopathogenesis.

ORCID and contributionship:
Delva I. I.: 0000-0002-2795-4897 ABCDEF

Corresponding author
Delva Iryna Ivanivna
Poltava State Medical University
Ukraine, 36000, Poltava, 23 Shevchenko str.
Tel.: +380957108584
E-mail: iryna.delva@gmail.com

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