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MIGRAINE AND CARDIOVASCULAR DISORDERS

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ABSTRACT

From a clinical point of view, differentiation of numerous forms of migraine depends on the accompanying diseases with prevailing cardiovascular symptoms. However, many pathophysiological interactions between migraine and cardiovascular disturbances remain insufficiently clarified yet. During the fits of migraine, the patients complain from palpitation, angina pectoris, tachycardia, anxiety, and feeling of fear. ECG examination reveals non-specific changes of T-wave and either elevation, or reduction of ST-segment. It has been supposed that the fit is due to a spasm of coronary vessels ('coronary migraine'). In migraine patients, there is a relationship between serotonin (5-HT) and the sympathetic nerves under pathological conditions. During the period between the migraine seizures there is an increase by two times but during the seizure itself by four times of the plasma levels of norepinephrine, serum dopamine, beta-hydroxylase, systolic and diastolic arterial blood pressure and heart rate in comparison with these parameters in healthy controls. The new class of 5-HT 1B/1d antagonists and ergotamine as well can induce vasoconstriction by stimulation of 5-HT receptors of the peripheral vessels. The low relative share of myocardial infarctions in migraine patients along with the higher one of angina pectoris results from the coronary spasm accompanying every migraine fit and from the increased arterial resistance. There is a familial predisposition between migraine and Raynaud's disease, systemic lupus erythematosus, and acute myocardial infarction as risk factor for the manifestation of migraine fits. Coronary ischemia plays an important role in these cases and requires the discussion of an adequate therapeutic and protective approach.

Key words: migraine, serotonin, coronary ischemia, hypertension, treatment

INTRODUCTION

Nature and duration of neurological symptoms are of essential clinical value when differentiating the numerous forms of migraine. This point of view is important for the analysis of the accompanying somatic diseases and especially of those with prevailing cardiovascular symptoms. Knowledge and clinical experience in this field define the indications and contraindications in the treatment of migraine (3,5).

Biochemistry of migraine

Biochemical and pathobiochemical relations between migraine and cardiovascular diseases.

Circulating serotonin (5-hydroxytryptamine, 5-HT) accumulated in platelets plays a neurotransmitter role in the brain. Under certain circumstances, it is capable of influencing upon the vascular wall (7). Amines are involved in the regulation of vascular tone by acting on the cardiovascular receptors and activating them either towards vasodilatation, or towards vasoconstriction. It has been shown that 5-HT is metabolized or accumulated in the endothelial cells close to the sympathetic nerve endings. The barrier function of endothelium prevents the penetration of vasoactive substances such as 5-HT into the vascular wall while, at capillary level, the endothelial cell hampers their penetration through the tissues playing the role of blood-brain barrier (16). The role of 5-HT to pass, to accumulate and, when possible, to liberate itself in the endings of the sympathetic nerves is clarified. The sympathetic nerves regulate the blood flow in the vessels in dependence of 5-HT variations as the outcome can be reversible.

Some recent investigations suggest a relationship between 5-HT and the sympathetic nerves under pathological conditions. For instance, the increase of 5-HT threshold in both blood and cerebrospinal fluid of experimental animals with subarachnoid hemorrhage leads to a multifold enhancement of the vascular constriction effect of nervous fibres and their reflection on the cerebral vessels underlying the brain vasoconstriction (13). In migraine patients during the period between the seizures there is an increase by two times but during the seizure itself by four times of the plasma levels of norepinephrine, serum dopamine, beta-hydroxylase, systolic and diastolic arterial blood pressure and heart rate in comparison with these parameters in healthy

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controls. These abnormalities indicate the involvement of the sympathetic nervous system.

After its liberation from enterochromaffin cells, mainly from platelets, 5-HT interacts with cardiovascular tissues. The indol amine is a substance proved in the heart and blood vessels of mammals including man. The amount of 5-HT is by 6 times smaller in the heart than that of norepinephrine. The physiological role of 5-HT remains insufficiently clarified yet; however, because of its relation with the amines it could be involved in the pathogenesis of certain heart diseases.

Clinical symptoms in migraine and cardiovascular diseases

More than 60 years ago, Fitz-Haugh (8) noted that approximately 27 per cent of migraine patients complained from the side of the heart (pain, fits of palpitation, etc.). These symptoms may accompany the fits of migraine or represent their equivalents. In such cases, the author suggested the nomination of 'overintestinal migraine' that was used in practice for a while by various authors. This syndrome is extraordinarily rare being observed a total of two times among 1000 patients (19). Such generalizations are an expression of a particularly careful selection of the patients with cardiovascular complaints. Leon-Solomayor described 12 cases, 10 females and two males (12). In the course of long lasting diseases in migraine patients he established during the fits a series of symptoms such as palpitation, angina pectoris, tachycardia, bradycardia, anxiety and feeling of fear. The ECG-examination during the fit demonstrated non-specific changes of T-wave and either elevation, or decrease of ST-segment. The coronary arteriography of 6 patients failed to demonstrate any vascular alterations at all. This author supposed that the fit resulted from a spasm of the coronary vessels ('coronary migraine'). Besides during the fit of migraine one has described paroxysmal disorders of the heart rhythm emerging independently of headache. Already in 1925, attention was paid to the relation between the paroxysmal tachycardia and migraine (21). A female patient presenting with crises of paroxysmal tachycardia not only during the fit of migraine but also in the fit-free period was reported (17). ECG changes were established in 13 of 49 migraine patients only (2). The following findings were found out in 57 migraine patients examined during the disease-free intervals and in 10 ones examined during the fits: i) normocardia in 61,4 per cent but tendency towards bradycardia and tachycardia - in 38,6 per cent of the cases; ii) abnormal ECG recordings in 38,6 per cent of the cases; iii) myocardial ischemia, low voltage of the curves, high amplitudes of T- and P-waves belonged to the most common abnormal signs (1). ECG data do not suggest any essential pathological aberrations in the heart activity related with the pathogenesis of migraine. They are, however, necessary for the administration and control of treatment, especially in adult and senile patients, in hypertensive patients as well as when ergotamine and contemporary antimigraine drugs are used.

Smyth and Winter (20) note that the observations of heart rate, respiration and skin galvanic response do not reveal any typical features in migraine patients. Therefore, the primary mechanisms of migraine do not reflect considerably on the peripheral and autonomic activity. Belov and Uzunov (1) conclude that in migraine the adrenergic reactivity estimated by means of skin-vegetative tests is higher than the cholinergic one. However, ECG data indicate reverse correlations: more common bradycardia than tachycardia. Besides there is ECG evidence of certain hyperkaliemia despite the absent electrolyte disbalance. These changes could be related with the abnormalities of the vegetative innervation and probable biochemical disturbances that require further investigations within the complex of migraine-accompanying pathophysiological mechanisms.

The relation between hypertension and migraine has been first suggested by Walker in 1959 (22). The study of 375 migraine patients of whom 60 males and 315 females demonstrates a tendency towards an increasing of the arterial pressure in dependence on the duration of migraine (4). Other authors report that anamnesis of hypertension is by twofold more common in patients with classical migraine (6).

Relationship between antimigraine drugs and cardiovascular disorders

Some antimigraine drugs induce spasm of the coronary vessels and could explain the occurrence of medicamentous complications such as chest pain and frequent heart attacks in some migraine patients. The drugs represent a risk factor for the preliminarily damaged arterial vessels in heart diseases such as Prinzmetal's angina or angina pectoris leading to vasospasm in response to treatment although there are no coronary scleroses at all (11,15). The patients presenting with high cholesterol levels or with arterial hypertension should be examined prior to the antimigraine treatment in order to avoid the aforementioned complications. The cases with organ donation and the reflection of the new medicaments on the arterial vessels are of interest, indeed. Testing of old vessels by ergotamine, methysergid and their metabolites such as methylergotamine as well as by the new means such as sumatriptan, naratriptan, zolmitriptan and rizatriptan establishes that this effect is less significant concerning the new drugs, relatively long lasting (90-min long) concerning the old means such as dihydroergotamine and ergotamine but short lasting (up to 30-min long) concerning the triptanes. The administration of sumatriptan leads to the feeling of stress and severity in the chest, chest pain and symptoms of angina pectoris in 50 per cent of the patients (15,19).

The new class of 5-HT 1B/1d antagonists and ergotamine as well can induce vasoconstriction by stimulation of 5-HT receptors of the peripheral vessels. The cardiovascular effect of Zomig in a dose of 20 mg and of ergotamine in a dose of 2 mg orally alone or in combination was studied in a double-blind, placebo-controlled trial of 12 healthy subjects. Arterial blood pressure, systolic blood pressure of the

thumb and hand, bioimpedance cardiography, brachial arterial diameter and velocity of peripheral blood flow by Doppler were examined. Both drugs lead to a small extent to vasoconstriction, increasing of the diastolic blood pressure and the speed of the blood flow as well as reduction of the arterial diameter of the thumb and hand. There is no significant difference in the heart minute volume, heart rate and ECG changes. Both medicaments are well tolerated in their combination as ergotamine does not show any significant effect on zolmitriptan pharmacokinetics (7,23). The therapeutic effect on the fit of migraine, from a modern viewpoint, is based on the hypothesis about the presence of two kinds of serotonin receptors - of 1b and 1d types that mediate the antimigraine effect in acute fits. The different receptors lead to a differentiated approach in the treatment of migraine. For instance, ergotamines interrupt the fit of migraine; however, they affect some other receptors such as adrenergic and dopamine ones. The new drugs such as sumatriptan and noratriptan act specifically on type 1 serotonin receptors. Their influence is related with shunting of the dilated vessels during the fit of migraine more outlined in those in the head and less in the cranium and eyes resulting in cerebral ischemia. Similar mechanisms are detected in the heart consisting in vasoconstriction and closure of collateral channels thus inducing an unfavourable side effect. In this way the contraindications emerge. They are the following: pregnancy, peripheral vascular diseases, cardiovascular diseases such as angina pectoris, heart attacks, coronary spasm and uncontrolled hypertension. Besides sumatriptan should not be combined with ergotamine in migraine (13,15,23).

The patients with pulmonary symptoms occur equally often with cardiovascular symptoms or risk factors. The risk of pains in the chest and neck in the course of sumatriptan therapy is more seldom when compared with that in cardiovascular diseases (8,11). This fact raises the hypothesis that these are the reason for heart ischemia after sumatriptan therapy. The latter induces ECG changes consisting of transitory ischemia as well as angina pectoris, arrhythmia, myocardial infarction and death in isolated cases when the drug is applied for the first time (9). However, neither the pathogenesis of the cardiovascular diseases, nor their relationship with the administered treatment and the primary disease has become clear. A clinical case of a 56-year-old female patient with migraine was presented. She developed the symptoms of a myocardial infarction soon after the introduction of sumatriptan although her anamnesis was normal. After catheterization for ischemic heart disease no pathological alterations were detected suggesting that sumatriptan has induced coronary spasm and myocardial infarction (11).

The investigations of the risk factors for cardiovascular complications demonstrate arterial hypertension in 36 per cent, cardiopathy in 24 per cent, diabetes mellitus in 12 per cent, tobacco smoking in 8 per cent, polycythemia in 4 per cent, hyperlipemia in 16 per cent, and chronic ethylism in 4 per cent. The anamnesis reveals migraine without evidence of epileptic seizures in 29 per cent and ECG changes in 12 per cent, of which nonspecific ones in 24 per cent of the cases (20-22). In a 34-year old woman with aortic and mitral valve defect after ergotamine misuse the picture of dyspnea was established after a long history of a peripheral vascular disease. Heart insufficiency advanced rapidly and, surgically, a fibroblast proliferation of the mitral valve was detected.

There is evidence of cardiovascular diseases combined with a risk of migraine fits. In this aspect, associations were drawn of parallel relationships between the patients with migraine and those with cardiovascular diseases. The familial and individual anamnesis in a group of patients with cardiovascular diseases and migraine show a significant risk of mutual risk existence of these two disease groups. In two females a paradoxical cardioembolic stroke during a migraine fit defining the migraine as risk factors (18). A familial predisposition between migraine and Raynaud's disease as a risk factor for the manifestation of migraine fits.

Because sumatriptan leads to coronary spasm in the patients with coronary risk its therapeutic application should carefully be specified. The investigation of 186 patients with systemic lupus erythematosus demonstrates a risk for the occurrence of migraine fits in 39 per cent while the screening of the general population detects a risk of 13-18 per cent for the females and of 2-6 per cent for the males. It is not influenced by the systemic treatment of the systemic lupus erythematosus, neither provokes migraine fits. These authors suggest the search for symptoms in this disease (10). Other authors interviewed 85 males and 15 females at a mean age of 54,7 years and demonstrated the development of an acute myocardial infarction. There was evidence of myocardial infarctions in 6 per cent of the cases. Of them, migraine fits were present in 66,7 per cent along with anamnesis of angina pectoris while in the patients without migraine this occurred in 17 per cent of the cases only (14).

It could be concluded that the low relative share of myocardial infarctions in migraine patients along with the higher share of the angina pectoris results from the coronary spasm accompanying every migraine fit and from the increased arterial resistance. Ischemia plays an important role in these cases and requires the discussion of an adequate therapeutic and protective approach.

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