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ATHEROTHROMBOSIS AS A NEUROLOGICAL PROBLEM**SUMMARY**

The author presents the problem of atherothrombosis in neurological aspect.

Key words: atherothrombosis, neurology.

STRESZCZENIE

Autor omawia problematykę aterotrombozy w aspekcie neurologicznym.

Słowa kluczowe: aterotromboza, neurologia.

Atherothrombosis is a secondary result of atheromatosis (chronic inflammatory process of aorta and medium size arteries, like carotid, coronary, iliac and renal) and disturbances of coagulability, with formation of thrombus, because of rupture of atheromatous plate, adhesion, activation and aggregation of blood platelets, accumulation of fibrinogen fibers. During initial phase, macrophages, cholesterol, lipoproteids of low density (LDL), foamy cells (macrophages coated by oxidated LDL) are deposited between intima and endothelium of arteries. „Fatty streaks” formed on the internal part of the artery, represent the early phase of atheromatous process. Then fibrous elements of connective tissue set in, which leads to formation of isolated element called an atheromatous plate. The discontinuity of plate, caused mechanically by blood flow, may lead to intravascular coagulation. It leads to stenosis or total occlusion of cerebral, coronary or peripheral arteries [1-4]. Clinical result of such process is cerebral stroke, cardiac infarction or disease of peripheral arteries.

„Atherothrombosis – the disease of whole life” [1] – this statement is applicable to multispecialist and long – lasting studies. The risk factors of atherothrombosis play a vital part, including dyslipidemia (apolipoprotein ratio – ApoB/ApoA1), nicotine, psychosocial environmental factors, abdominal obesity, arterial hypertension, bad diet (not enough fruit and vegetables supply), lack of physical activity, diabetes, and even lack of some „therapeutic” doses of alcohol [1]. The last recommendation is controversial, because – among other things – the flavonoids are present not only in wine,

while drinking up to 200 ml of red wine every day may also lead to addiction. It is characteristic that among risk factors of heart infarction in younger age groups, especially in men, the nicotinism and dietary deficiencies [1] play the most important role. Unfortunately, passive smokers are also exposed, which depends on time of daily exposure on toxic action of nicotine. Atherothrombosis is strictly combined with atheromatous process, starting as early as in fetal life, with susceptibility to specific risk factors, and peculiar „programming” of pathological process. Atheromatous process has a generalized character, with some predisposition to bigger vessels (carotid coronary, iliac, renal arteries). In many autopsy studies of children aged 1-13 years, dead because of rupture of cerebral aneurysm, accidents or neoplasm, fatty streaks were found in abdominal aorta and in main arteries. In a group of above 10 years, atheromatous plates were also found. It is worth stressing that hypercholesterolemia of mother is of great importance in programming of children's susceptibility to risk factors of atheromatosis. Therefore, by modern criteria, it is a problem which applies – to some degree – to the pediatricians [2].

The influence of genes in a process of atherothrombosis including – so called one – and polygene reasons, are emphasized. Polymorphism of genes is also stressed. There is also a possibility to use of pharmacogenetics, based on the method of therapy dependent on genotype, which can be beneficial on limitation of risk factors of cerebral strokes or cardiac infarcts [3-8].

It is claimed lately, that atherothrombosis is related to metabolic syndrome, connected with abdominal type obesity, which is also one of factors causing not only cardiovascular but also cerebro – vascular disorders. There are 20% adult persons with abdominal obesity in Poland [7].

Among atheromatous complications there are mainly cerebral strokes and cardiac infarcts. In patients with cerebral strokes, typical risk factors include: arterial hypertension, coronary disease, atrial fibrillation, diabetes, hyperlipidemia and nicotinism. In a group of stroke patients aged above 70 years, there are similar ones: hypertension, atrial fibrillation, nicotinism, diabetes. Among stroke patients aged below 50 years („young adults”) the order of risk factors is different: nicotinism, hypertension, diabetes, coronary disease, primary vasculopathies, systemic diseases of connective tissue, genetic disorders.

There are also other reasons of ischemic cerebral stroke in patients below 50 years: delamination of carotid artery, vasculitis, antiphospholipid syndrome, CADASIL, MELAS, Snedon's syndrome. Genetic disorders in stroke patients below 50 years include: hyperhomocysteinemia, coagulation disorders, CADASIL (cerebral autosomal dominant inherited arteriopathy with subcortical infarcts and leukoencephalopathy), Gene (protein: mutation of gene Notch 3 on chromosome 19. Localisation on cytogenic map: 19 p 13, 2-13, 1 MIM 125 310). Phenotype variant, based on familial occurrence of migraine was also defined: CADASIL M (M – migraine). Clinically: recurrent subcortical infarcts and transient cerebral ischemia, without known risk factors and without MELAS Syndrome. Disease is related to mitochondria, controlled

by 2 genomes: mitochondria own dezoksyrybonucleid acid – mtDNA, and nuclear – mDNA. There are some point mutations and many rearrangements of mtDNA. Mitochondrial encephalomyopathy with lactic acidosis and stroke – like epizodes. This syndrome can also cause progressive external opthalmoplegia (PEO), because of deposits of mutated mtDNA in muscles, known in classification as A 32 439. In more than 80% patients it is a molecular defect, as a point mutation in t RNA gene. The mutation A 32 434 is considered one of the most frequent mutations of mtDNA, and is connected – in addition to MELAS – also with PSO, isolated diabetes and diabetes with coexistent deafness [8-15].

Cerebral strokes above 75 years – the aged patients consist 50-60% of all strokes. There are 60-70 thousand cases of stroke in Poland every year. The mortality in this age group is higher than in younger groups, also in comparison with cardiac infarcts. The basic reason of strokes in this group of patients is atherothrombosis. There are also therapeutic limitations, like thrombolytic therapy, which can be used up to 80 years. This group of strokes will increase, together with prolonged life of general population, which can bring not only diagnostic – therapeutic, but also social challenges. Significant percentage of these patients will be included in the group of invalids, requiring special care, especially with dementive syndromes (atherothrombosis).

The results of atherothrombosis in children have somewhat different patomechanism, prevalence and clinical picture. In the world scale, the morbidity of vascular diseases in children is difficult to assess. In the USA it is assessed as 2,52 per 100 000 children. For comparison, intracranial tumors have an index about 5,0 per 100 000 children. There are more reasons of vascular lesions in children than in adults, and they are more various. Atheromathosis (in progeria) is also on the list of reasons, which thus means atherothrombosis, as a reason of mainly arterial thrombi. These latter ones include, first of all, intracranial branches of carotid internal artery, more rarely – cervical part of this artery, or spinal artery. It is a characteristic phenomenon, that coagulability disorders can be secondary, after completed thrombosis. It is emphasized, that the deficiencies of the 5-th Leiden factor, Protein S and C may be the components predisposing to the formation of thrombus. Clinical picture depends on localisation and size of thrombotic process. Typical is hemiplegia or hemiparesis with other disorders (aphasia), depending on age – when there is a coexistent teleangiectasia with the occlusion of arteries of the base of the skull (moya – moya disease) or with bilateral thrombotic process in carotid arteries, then headache with alternating and recurrent hemiplegia or hemiparesis occurs. In children, the thrombotic processes are often secondary – in the course of many inflammatory processes (diseases of connective tissue, shingles, bacterial infections of respiratory tract, infections of cervical lymph glands) more rarely – injures (carotid arteries). Yet more rarely Syphilis and tuberculosis can be a reason of thrombosis of cerebral vessels in children. Surely there are many other reasons which can constrict or injure the cerebral arteries in children, with secondary cerebral vascular disorders. Among them, there are thalassemia (sickle cell anemia), generalized inflammatory processes – including digestive tract migraine,

tumors (mainly of lymphatic – reticular system). There are also rare cases predisposed to congenital lesion of vascular walls, like the dissecting aneurysm. Cerebral lacunar state In children, except typical factors („cardiogenic”, fat, bacterie, parasites, air, tumor, foreign body) can also be a result of displacement of „organized thrombus”. In such cases, magnetic resonance (MR) reveals multiple cerebral infarcts with internal bleeding in some of them. MR technique with „diffusion” and FLAIR imaging makes possible the quick diagnosis of cerebral stroke. Control MR studies reveal the evolution of pathologic changes in stroke, with distinct demarcation of stroke zone.

USG examination is of great importance in diagnosis of stroke in children, especially in newborns and premature infants. Neuroimaging studies, including MR, angio – MR, computerized tomography (CT) and cerebral angiography are a significant importance in diagnosis of ischemic stroke in children. In MR, diffusion – perfusion imaging technique has a great diagnostic significance, because it reveals clear – cut and „over – acute” ischemia of cerebral area, not shown by classic technique of spin echo (SE) imaging. Cerebral angiography during early phase of stroke reveals closed artery, and in consecutive control studies reveals possible recanalisation of the artery. After stroke, especially in case of paroxysmal disorders of consciousness or convulsions, it is necessary to perform repeated EEG studies, with digital (computerised) technique, program of detection of spikes and seizures and of mapping technique.

The treatment of ischemic stroke in children is different than in adults. Usually there is a necessity of intravenous hydration, use of antibiotics and decreasing of possible intracranial hypertension at the same time. Administration of anticoagulants is limited mainly to cases of „progressive stroke”. Anastomosis of external and internal carotid artery is carried out rarely (because of small diameter of the vessels), and bilateral cervical sympathectomy is sometimes performed [9-11].

In adults, the treatment of ischemic strokes connected with atherothrombosis is complex, and depends on coexisting diseases [16]. It is important, if the atheromatous – thrombotic stroke is „progressive”, developing or completed – with fixed neurological deficit.

The National Institute of Health in the USA (NIH) recommends thrombolytic therapy even in progressive stroke, under the stated criteria. These drugs include alteplase (tissue plasminogen activator t-PA) and urokinase, although adequate studies were not performed in this group. In such cases, mainly in the insufficiency of vertebro – basilar region, it is considered to administer intraarterial thrombolysis, even over 12 hours from the onset. Complex therapy of this type of stroke is connected mainly to acute phase of completed ischemic stroke, fulfilling necessary criteria of NIH (less than 3 hours from the onset of stroke, exclusion of cerebral hemorrhage or extensive ischemic infarct by CT, proper coagulation system, hematocrit and thrombocytes values. The drug is administered intravenously, at a dose of 0,9 mg/kg, during 1 min the first 10%, then the remaining dose during 60 min. Neurologic control: every hour during the first 6 hours of therapy, then every 2 hours during the first 24 hours. There is also an important requirement, that the centre where t-PA is administered should

include neurosurgery (intervention in the case of intracerebral hematoma) and interventional cardiology departments.

There are also so – called neuroprotective drugs (protecting neurocytes) that are tried in stroke – like receptor NMDA blockers: aptiganel (cerestat), selfotel, Mk – 801, glutamate releasing inhibitor – lubelusol and enlimomab, intercellular adhesion molecule antibody ICAM. Citycholine and clomethiasol were also tried [17]. There are also some „vascular” drugs, used intravenously as well as orally, that seem to have some clinical importance, despite lack genuine theoretical studies of its real action in this type of cases. During recent years, a lot of „mechanical” devices trying to remove or suck out the thrombus (laser, cork screw methaod, gamma radiation) were tried. Complex objectivity of usefulness of these methods needs many more years of clinical observations [17, 18].

Use of combined antithrombotic and antiplatelet therapy in cardiology is diverse, including acute coronary syndrome, atrial fibrillation, pulmonary embolia, before planned angioplasty and in prevention of „thrombotic – embolic incidents in patients with valvular heart lesions” [19-20].

Such metod of treatment with oral antithrombotic (acenocumarol) and antiplatelet (aspirin with clopidogrel or ticlopidine) drugs is in cardiology – relatively safe are useful. In neurologic therapy of ischemic strokes it is not so simple. Usually we are forced to use only one form of oral therapy. Currently we have been practically forced to withdraw ticlopidine, although the drug acted perfectly, because of hemorrhagic complications. There is also an operative therapy, e. g. removing of thrombi (endarterectomy) from carotid arteries [20-21]. Cerebral arteries are slighthy different than other arteries, but they are influenced by the same pathologic processes like heart and other vessels.

Characteristic for small cerebral arteries is so – called hardening (arteriosclerosis), that is one of causal factors for strokes of somewhat different clinical picture.

Genetic factors of cerebral strokes, including their indirect connection on risk factors is emphasized more often. One reliable syndrom of „direct genetic reason” is – up to now – CADASIL. The other cases are rather the results of individual – genetic and environmental factors mutual interactions [8].

Short description of problem of atherothrombosis connected with arteriosclerosis process, presented in this work, concerns the whole population, including children as well, that sets new challenges, not only in research, but also in diagnostic – clinical field.

As the researches emphasize, indeed it is a problem of the whole life, concerning many specialties, especially the specialist of vacular – cardiac and cerebral diseases.

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