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Helicobacter pylori infection and arteriosclerosis

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Abstract

The hypothesis regarding the relationship between *Helicobacter pylori* infection and the development of arteriosclerosis is not clearly demonstrated and needs validation even though many clinical trials conducted in this area in recent years seem to support this etiopathology. *H. pylori* is a Gram-negative, microaerophilic bacterium, usually found in the stomach, widespread in the environment. Infections often occurs even in early childhood. As a result of infection a chronic inflammation develops with concomitant elevated levels of C-reactive protein (CRP). It has long been known that atherosclerosis is a chronic disease of the arteries with underlying inflammation. The formation of atherosclerotic plaques may also begin in childhood. There are more than one mechanism that may affect disease development. Lipopolysaccharides of *H. pylori* by stimulating the secretion of Tumor Necrosis Factor (TNF) by macrophages inhibits lipoprotein lipase activity, which results in an increase in serum triglycerides and a decrease in serum High-density Lipoprotein (HDL) cholesterol. The second mechanism leading to an increased risk of arteriosclerosis may be associated with a chronic inflammation of the gastric mucosa which may lead to impaired absorption of many nutrients, including vitamins B6, B12 and folic acid, the deficiency of which results in secondary hyperhomocysteinemia. Elevated levels of homocysteine are a strong risk factor for atherosclerosis. Lastly, in the serum of patients with *H. pylori* infection, elevated values of number of important factors from the point of view of atherosclerotic plaques formation are found. These include CRP, interleukin 6 (IL-6), interleukin 8 (IL-8), TNF-α, fibrinogen, type 1 plasminogen tissue activator inhibitor and Willebrand factor. Taking into account the above-mentioned correlations, it seems reasonable to continue research focusing on many pathomechanisms that may help explaining the cause and relationship of *H. pylori* infection to the development of atherosclerosis. Clinical trials conducted on the pediatric population, could contribute to the broadening of medical knowledge in this area, as well as to the modification of preventive and therapeutic recommendations for atherosclerosis and its consequences.

Keywords: Helicobacter pylori; arteriosclerosis; inflammatory markers; cholesterol; homocysteine; inflammatory cytocines.

Introduction

Helicobacter pylori is a pathogenic gram-negative helical-shaped rod, discovered by Warren and Marshall in 1982, inhabiting the surface of epithelial cells of the gastric mucosa [5, 11]. It is one of the most widespread pathogenic bacteria in the world. WHO estimates that it is infected by up to 70% of people in developing countries and 30% in developed countries. The infection occurs through food, most often in early childhood. From then on, it can last a lifetime [11]. It is a known factor causing gastritis, as well as leading to peptic ulcer disease (about 60% of cases are associated with this bacterium) and duodenum (infection occurs in about 95% of cases) and gastric cancer [6]. The relationship between H. pylori and the above-mentioned disease entities is documented and it is not in doubt, whereas recently there have been suspicions about the association of this bacterium with other diseases outside the digestive system. H. pylori is suspected, among others for association with diseases such as bronchiectasis, ischemic heart disease, asthma, IgA-associated vasculitis, autoimmune thrombocytopenia, autoimmune thyroiditis, Parkinson's disease, chronic obstructive pulmonary disease, idiopathic chronic urticaria, delaying growth, cirrhosis. There are also reports in the world literature on the relationship between H. pylori infection and an increased risk of atherosclerotic disease [1,3,7,8].

Pathophysiology

Currently, atherosclerosis is considered to be a chronic inflammatory disease of the arteries, the essence of which is an excessive, inflammatory - proliferative response to damage to the vessel wall. The atherosclerotic process is initiated already in the early childhood. In the formation of atherosclerotic plaque, a key role is attributed to factors inducing an inflammatory process damaging endothelium - this is the first stage of the atherosclerotic process. The factors that trigger endothelial dysfunction include, among others: oxidative stress, hyperhomocysteinemia, hyperglycemia, oxygen free radicals from tobacco smoke, hypercholesterolemia [2,10]. An increasingly important role in this process is also attributed to infectious factors (bacterial and viral), such as: Chlamydia pneumoniae, mycobacteria, H. pylori, herpesviruses, cytomegaloviruses [1,3,8,10].

The elements constituting the structure of primary atherosclerotic lesions are the lipids accumulating in the inner membrane of the vessels and phagocytic cells such as macrophages derived from peripheral blood and central membrane myocytes. Activated myocytes synthesize extracellular connective tissue elements (collagen, proteoglycans, elastins), which then accumulate within the atherosclerotic plaque. In this way, plaques with a predominance of connective tissue over lipid compounds are formed. The structure of this type of plaques is stable. They form for about 20-30 years. The plaque increment takes place towards the lumen of the vessel, gradually leading to its narrowing, which consequently causes blood flow disorders [2,4]. Unstable changes arise as a result of the intensification of the inflammatory process in the wall of the vessel. In such plaques there is an increased proportion of inflammatory cells, such as macrophages and T lymphocytes. In the destabilization of atherosclerotic plaque, an important role is played by activated IFN-gamma lymphocytes, which inactivates myocytes, leading to inhibition of their proliferation and collagen synthesis. At the same time, it stimulates macrophages, a source of metalloproteinases (MMPs) responsible for the degradation of connective tissue elements. The fibrous layer of the plaque becomes thinner and thinner. The acute episodes of ischemia occur as a result of the detachment of unstable atherosclerotic plaques, which when flowing with the blood stream close the light of small blood vessels [2,4,8].

Numerous studies have demonstrated the association of inflammation with the destabilization of plaques in the arteries. A close correlation was found between elevated levels of inflammatory markers such as CRP, alpha 1-antitrypsin or fibrinogen and the risk of acute cardiovascular events [1,3,8]. Elevated LDL-cholesterol alone does not pose a risk for ischemic

episode, whereas the coexistence of hypercholesterolemia with elevated levels of inflammation markers (of which the CRP protein is best known and proven) clearly raises this risk. As can be seen from many studies, generalized inflammation may occur during H. pylori infection, as evidenced by elevated CRP levels in these patients [3.5].

Lipids

Studies conducted in the world indicate that chronic infection of Helicobacter pylori may affect the development of atherosclerotic disease through several mechanisms. It is believed that lipopolysaccharides of H. pylori rods stimulate secretion by macrophages of TNF-alpha with an inhibitory activity of lipoprotein lipase, which results in an increase in triglycerides and a decrease in serum HDL-cholesterol [3]. These are known as strong risk factors for atherosclerosis. The results of studies showing elevated levels of total cholesterol, LDL cholesterol and triglycerides, and reduced HDL cholesterol in the serum of patients infected with this bacterium are repeated [1,3,7].

Homocysteine

In addition, chronic inflammation of the gastric mucosa that occurs in the course of H. pylori infection may cause the impairment of the absorption of many vitamins, including vitamin B6, B12 and folic acid. These elements are essential for methionine metabolism, which results in their deficiency resulting in elevated levels of homocysteine [1,9,10]. Homocysteine is one of the factors damaging the wall of blood vessels, so its high level contributes to the initiation of the atherosclerotic process. In addition, its elevated concentrations are responsible for the extensive pro-thrombotic processes in the blood vessels.

Cytokines

In addition, the concentration of other inflammatory cytokines, mainly IL-6, IL-8 and TNF-α, as well as CRP, fibrinogen, tissue inhibitor type 1 plasminogen activator and von Willebrand factor, which is a sensitive overt index, is present in the sera of people infected with this bacterium. clinically atherosclerosis and is a prognostic factor for the occurrence of acute coronary syndrome. TNF-alpha along with IL-1 stimulates the production of adhesion molecules across the vascular endothelium, thereby contributing to the onset of atherosclerotic process [1,3,10], and the elevated concentration of CRP also contributes to the initiation and progression of atherosclerotic process [10].

Conclusion

The relationship between Helicobacter pylori infection and atherosclerotic disease seems to be confirmed, however, it remains in the research phase. It should be noted that atherosclerosis begins in childhood, and most cases in childhood are also in H. pylori. The conducted research could, therefore, contribute to the introduction of appropriate diagnostics targeted at the same time for bacterial infections, such as H. pylori, and markers of atherosclerotic disease, also in the group of pediatric patients. Confirmation of a cause and effect relationship between them could give grounds for the implementation of adequate and early (already in childhood) prophylaxis of atherosclerotic disease (eg eradication of H. pylori), and modification of therapeutic recommendations, which could improve the results of atherosclerosis treatment and thus reduce the amount of acute ischemic episodes in adult patients.

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