Interleukin-6 in cardiovascular disorders

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Abstract

Interleukin-6 (IL-6) belongs to the cytokine group and is produced by monocytes and macrophages under the influence of interleukin-1 (IL-1) and other proinflammatory cytokines. IL-6 shows multidirectional action, including stimulation of B lymphocytes to transform into plasma cells. It is also a proinflammatory factor and stimulates the production of other proteins of acute phase. Adipocytes are also the source of IL-6, which may be the reason for obese people to have higher concentrations of acute phase protein (CRP, C-reactive protein). Cortisol, released physiologically under stress, is a factor affecting the increased secretion of IL-6 into the bloodstream. Interleukin-6 is a marker of vascular endothelial dysfunction. It's concentration correlate with acute cardiovascular events in adults, however the reports on the role of IL-6 in the development of vascular diseases in children are very few. The authors present an overview and discussion of the current data on the significance of IL-6,especially in the context of the occurrence of inflammatory processes, vascular endothelial dysfunction and atherosclerosis, and consequently – cardiovascular diseases.

Key words:

interleukin-6, atherogenesis, inflammation, ischemic heart disease, ischemic stroke

Introduction

Cardiovascular diseases (ischemic heart disease, ischemic stroke) on the atherosclerotic background are still the main cause of high mortality. Atherosclerosis is a chronic inflammatory disease which etiology is multifactorial. The inflammation occurring in the progress of the atherogenesis is the result of the impact of inflammatory mediators, among others: cytokines, chemokines, adhesion molecules, as well as proteolytic enzymes [1-4]. Proinflammatory proteins, i.e. interleukin-6 (IL-6) as well as tumor necrosis factor alpha (TNF-α) contribute to the growth of atherosclerotic plaques. Under the influence of cytokines, chemokines and growth factors (including fibroblast growth factor – FGF, insulin-like growth factor-1 - IGF-1, transforming growth factor – TGF), smooth muscle cells differentiate, migrate from the middle membrane to the inner endothelium layer and begin to synthesize extracellular matrix proteins (mainly collagen and elastin) and also form a fibrous cap around the lipid core of the plaque, which contributes to the increase of atherosclerotic plaque. Elevated levels of some inflammation factors are associated with unfavorable prognosis and more frequent appearance of acute cardiovascular events such as myocardial infarction and ischemic stroke. Interleukin-6 is a protein consisting of 212 amino acids and the gene encoding IL-6 is mapped on chromosome 7 [5]. The increase in IL-6 concentration occurs immediately after the initiation of inflammation or in response to tissue damage and is a "warning signal" for the entire organism [6]. For the first time, the association between IL-6 concentration and a specific disorder was demonstrated by the example of a patient with myxoma and clinical presentation of fever, polyarthritis with antinuclear antibodies, elevated acute phase protein (CRP) and hypergammaglobulinemia [7].

The aim of the present review was to analyze the available literature data on the role of interleukin-6 in etiopathogenesis of cardiovascular diseases, including ischemic heart disease, myocardial infarction and ischemic stroke.

Interleukin-6 – inflammation indicator

Indicators of chronic inflammation predisposing to atherosclerosis and myocardial infarction, besides membrane adhesion proteins, are among others cytokine and C-reactive protein (CRP). Interleukin-6 (IL-6) is the major cytokine of inflammation with pleiotropic activity. It is responsible for stimulating synthesis in hepatocytes of all acute phase proteins involved in the inflammatory response, namely: C-reactive protein, fibrinogen, serum amyloid A, α1-chymotrypsin and haptoglobin [8]. It also stimulates the differentiation of B-cells. Interleukin-6 is involved in bone metabolism, the immune response of the body, neuronal development and hematopoiesis [9]. IL-6 can actively promote the atherogenesis, both directly by inducing vascular endothelial dysfunction, monocyte/macrophage recruitment, extracellular matrix degradation as well as indirectly – by stimulating coagulation factors synthesis. Figure 1 shows the role of interleukin-6 in the atherogenesis. IL-6 is mainly produced by activated macrophages, and to a lesser extent, fibroblasts and vascular endothelial cells. A significant source of interleukin-6 is also adipose tissue, over 30% of IL-6 circulating in the blood of healthy people comes from adipocytes [10]. Earlier data showed a higher concentration of IL-6, adiponectin and leptin in patients with stroke compared to controls [11]. The authors also demonstrated a significant correlation between leptin level and interleukin-6 level in patients after ischemic stroke.

In addition, IL-6 levels correlate with the body mass index, which may explain how overweight/obesity increases the risk of ischemic heart disease (IHD). The secretion of IL-6 is increased by TNF-α, endothelin-1 or hypotension and angiotensin II in macrophages and smooth muscle cells [12,13]. In addition, cortisol released physiologically under stress increases secretion of IL-6 into the bloodstream. IL-6 plays a role in the regulation of lipid metabolism, a process important for the pathogenesis of atherosclerosis [14]. It was found that IL-6 reduces the activity of lipoprotein lipase in adipose tissue, which leads to a decrease in triacylglycerol absorption [15].

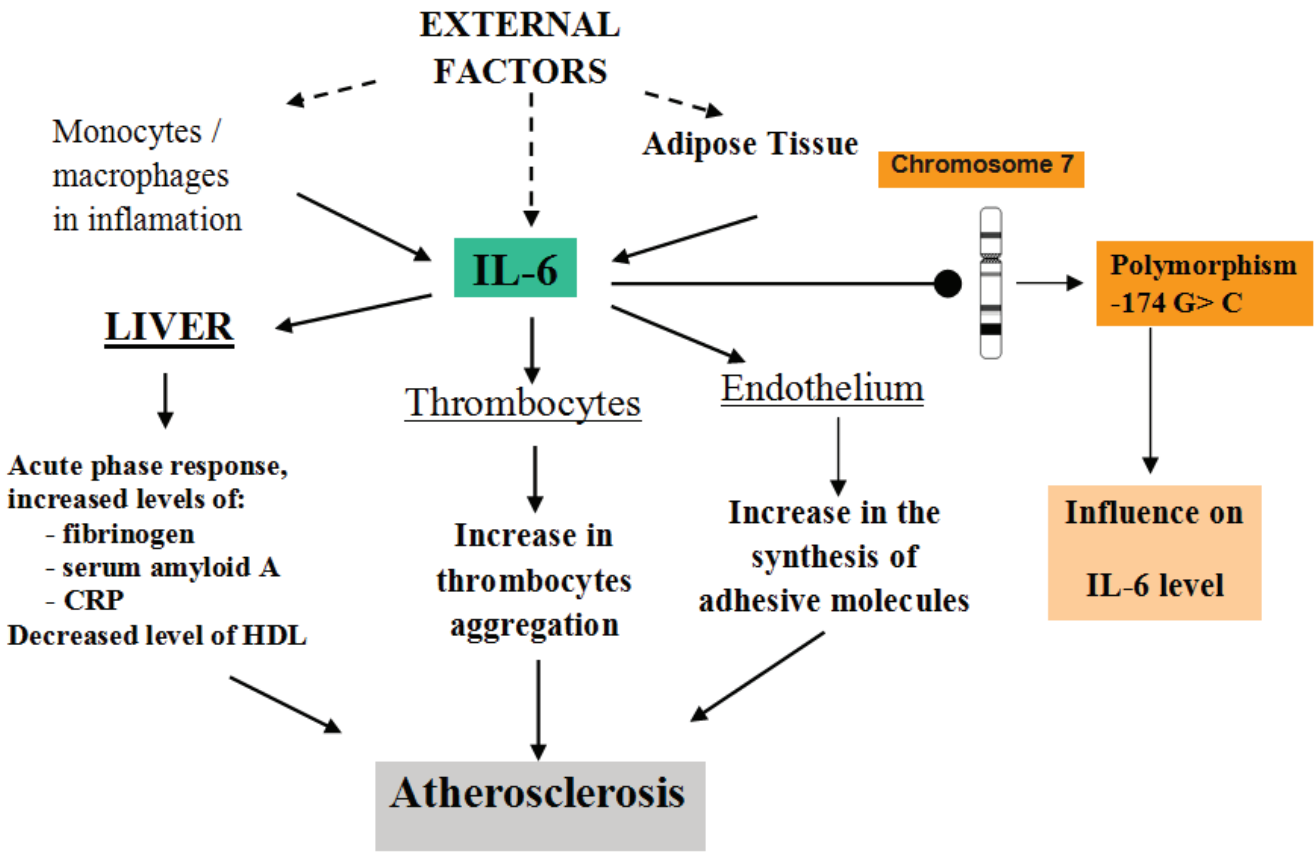

Fig. 1.
The role of interleukin-6 in the atherosclerotic process

Abbreviations:
IL-6 – interleukin-6, CRP – C-reactive protein, HDL – high-density lipoproteins

This can lead to a permanent increase of lipid levels in blood serum. Experimental research in mice with excluded IL-6 gene showed that they have worse leukocyte recruitment to sites of inflammation [16]. The inflammatory response to the interleukin-1 given to animals is reduced, but may be improved by local injection of interleukin-6. This suggests that locally produced IL-6 plays a role in the regulation of leukocyte accumulation. It was also observed that IL-6, as a ligand of the glycoprotein 130 receptor (gp130), causes a significant increase in the production of plasminogen activator inhibitor-1 (PAI-1) in the culture of human adipose tissue [17]. Dong et al. [18] revealed that IL-6 determines the increase of PAI-1 expression in hepatocytes through a specific promoter region containing protein binding C/EBPs (CCAAT/enhancer-binding proteins). In HepG2 cells, IL-6 activates several signaling pathways: Janus kinase (JAK), extra-cellular signal-regulated kinase (ERK), p38/mitogen-activated protein kinase (MAPK) and phosphoinositide (PI)3-kinase/Akt [19].

IL-6 in ischemic heart disease

The concentration of proinflammatory cytokines, including IL-6, is low in the healthy heart. However, in myocardial infarction, their levels depend on the area of necrosis, namely in infarction with a small extent, they can quickly return to normal level, and with a large extent – they last longer. A high level of interleukin-6 seems to be a predisposing factor for myocardial infarction.

In the research on a group of 100 patients from Saudi Arabia, a higher levels of IL-6 were observed in patients with confirmed IHD than in the control group [20]. Similarly, IL-6 levels are higher in patients with unstable angina than in patients with stable one [21,22]. Wainstein et al. [23] showed that serum IL-6 level above 1 pg/ml is a predictor of ischemic heart disease and an indicator of the severity of atherosclerotic disease. In addition, patients with ischemic heart disease and IL-6 level above 2.16 pg/ml had a higher mortality rate [24]. Elevated levels

of IL-6 are also observed in people with pulmonary hypertension [25]. In the pulmonary placenta, the production of IL-6 is reduced by β-blockers but increased by β-mimetics [26]. The concentration of IL-6 in plasma may also be influenced by atherosclerosis risk factors such as smoking or psychological stress [27,28]. In addition, the amount of IL-6 can be genetically determined. The gene for interleukin-6 is located on chromosome 7 in the p21-p14 locus. A common polymorphism consisting of the substitution of guanine by cytosine in the position −174 IL-6 gene (−174G> C) contains a cAMP binding site and determines the efficiency of transcription and plasma IL-6 level. It is located close to the site that affects the binding of the glucocorticoid receptor and has the ability to inhibit transcription. The G>C change creates a potential binding site for the nuclear transcription factor NF-1, which belongs to the family of transcription factors active in many cell types [29]. The G allele of the −174G> C polymorphism of the *IL6* gene is associated with higher protein production than the C allele. This has been revealed in *in vitro* research. HeLa cells, into which the vector containing the G allele was inserted, have an increased response to stimulation with lipopolysaccharide or interleukin-1 than the cells with the C allele [30]. Data on the impact of −174G> C polymorphism on plasma IL-6 level indicate that people with the C allele have lower protein levels [30,31]. Research on a different group of patients show opposite correlation - people who are homozygous for the C-allele have the highest level of IL-6 in plasma, with the GC genotype- intermediate and with the genotype GG – the lowest [32]. There are also many studies that do not reveal any correlation between the gene *IL6* polymorphism −174G> C and the concentration of this cytokine [33,34]. Probably this is due to a different response to the NF-1 transcription factor in the different cell types that produce interleukin-6. Elevated level of IL-6 in plasma promote the growth of atherosclerotic plaque and increase the possibility of its breaking by stimulating the expression of several fundamental genes for atherosclerosis. However, the C allele may be associated with elevated level of C-reactive protein [34].

Research on the group of Polish patients with ischemic heart disease revealed that men who are homozygous for CC have higher risk of disease than compared to men with the GG genotype [35]. These results were previously confirmed on a group of 3052 healthy men aged 51-60 [36]. It was found that men with the C allele have higher risk of coronary heart disease compared to men who are homozygous GG. This risk increases for smokers compared to non-smokers. There was no correlation between *IL6* gene polymorphism −174G> C and ischemic heart disease in the group of women [35]. It is probably caused by the influence of estrogens on *IL6* gene expression, which is bottom-up regulated by 17-β-estradiol in estrogen-sensitive tissues. Women may have a negative feedback affecting the level of interleukin-6 [37]. There is no correlation between the *IL6* gene polymorphism −174G> C and the phenotypic features of ischemic heart disease. In the research of Nauck et al. [33], there were no differences in the frequencies of genotypes and alleles of this polymorphism among patients with changes in 1-, 2- or 3-vessels in the group of people with documented ischemic heart disease. However, the results of the meta-analysis by Hou et al. [38] showed that the presence of the -174C allele in the *IL6* gene may increase the susceptibility to coronary heart disease depending on the race – there is a greater susceptibility of the Caucasians. In opposite, another polymorphic variant in the *IL6* gene, i.e. −572C – reduces the risk of ischemic heart disease in the Chinese population [38].

IL-6 in ischemic stroke

Ischemic stroke activates the inflammatory response by increased production of inflammatory cytokines, including IL-6, both in the brain and in the blood [39]. The expression of this cytokine can be neurotoxic and neuroprotective by inhibiting TNF-α and IL-1synthesis. However, literature reports in this case contradictory information [40,41]. In the acute phase of ischemic stroke, the levels of proinflammatory cytokines (TNF-α, IL-1 and IL-6) increase both in the blood and in the cerebrospinal fluid. Research on animal experimental models of ischemic stroke have shown that the source of these proteins are microglial cells, intrathecal macrophages and monocytes, and in

the case of IL-6 also neurons [42]. However, it is not clear whether microglial cells or damaged neurons are the main source of IL-6 in human ischemic stroke [43]. The role of IL-6 and other cytokines within 4-6 hours of ischemic stroke remains unclear and the majority of data comes from research on animal models, mainly conducted as transient Middle Cerebral Artery Occlusion (tMCAO). It is interesting, that the final volume of ischemia is established much earlier than the concentration of these cytokines reaches its maximum. It has been found that after intraventricular application, IL-6 causes a reduction of the brain damage caused by the closure of the middle cerebral artery [44]. High levels of IL-6 are without correlation with age, sex and severity of stroke, a risk factor of worse prognosis the functional status of patients after ischemic stroke compared to patients, who have lower IL-6 levels [45]. These conclusions, based on the examination of over 4,700 patients, confirm the previously published data on smaller groups of patients [46]. Concentration of IL-6 and other proinflammatory cytokines and acute phase proteins is also high in the blood of patients with post-stroke cognitive impairment compared to patients whose cognitive functions, despite their previous stroke, were maintained [47, 48]. Previous studies have shown that IL-6 levels increases in the cerebrospinal fluid in the acute phase of ischemic stroke and up to 90 days after the stroke remains elevated [49]. There is also a connection between IL-6 level and stroke volume [50]. In turn, Vila et al. showed a correlation between the concentration of IL-6, body temperature, glucose and fibrinogen levels in blood [51]. Research by Brazilian authors showed a higher levels of IL-6 in patients with cardioembolic infarction and in the large vessels with atherosclerosis, which probably results from damage to the larger area of the brain compared to lacunar infarction [52]. In childhood stroke and most likely also in perinatal stroke, cerebral ischemia induces an inflammatory response. It was observed that the levels of IL-6, IL-8 and CRP in children with stroke were higher compared to controls [53]. The significance of the −174G> C and −572C> G polymorphisms localized in the *IL6* gene has been proven both in the etiology of ischemic stroke in young adults as well as in the development of hypertension and obesity [54]. The results of the meta-analysis conducted in a group of over 30,000 patients indicate that the −174 G> C *IL6* polymorphism is associated with the predisposition to atherosclerosis, especially in the group of non-Caucasian patients and related to vascular events [55]. In addition, elevated level of IL-6, especially in elderly patients, is a significant biomarker of infection (usually pneumonia) in the first days of stroke, and it is an unfavorable prognostic factor in the extent of stroke, severity and mortality associated with the stroke during hospitalization and in the early post-stroke period [56,57]. This concerns particularly patients with the GC genotype of *IL6* polymorphism [58,59]. The results of a research conducted by Norwegian authors, a long-term (mean follow-up period of 7 years, range from 1 to 43 years) observation of 187 patients after ischemic stroke, further indicate that the persistence of high levels of IL-6 is an independent risk factor for subsequent mortality in this group of patients [60]. On the other hand no correlation between −174G>C *IL6* polymorphism and ischemic stroke was observed in the group of pediatric patients. However, more frequent occurrence of the G allele was found in children with post-stroke epilepsy [61]. Previous data indicate that IL-6 levels are higher in children with epileptic status without disabilities compared to children with disabilities and are correlated with TNF-α concentration [62].

There is also a connection between the presence of the homozygous CC genotype and the occurrence of lacunar stroke, which suggests the particular susceptibility of small brain vessels to inflammatory damage, which is mediated by IL-6 [63,64]. Polish authors' research confirms the correlation of high concentration of IL-6 with the progression of radiographic changes in patients with small cerebrovascular disease, such as lacunar stroke, but also vascular dementia and parkinsonism; it is also an exponent of endothelial damage [65].

Conclusions

Interleukin-6 belongs to cytokines involved in inflammatory mechanisms, including the development of atherosclerotic process and is a marker of vascular endothelial damage. IL-6 concentration is genetically

determined but modified by environmental factors such as obesity, sex hormone levels and inflammation. IL-6 can also be considered as a biomarker important for prognosis in patients with ischemic stroke, both in the acute phase and in long-term observation.

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