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Short Review

Clinical Significance the Inflammatory Biomarkers of Atherosclerosis in Carotid Disease

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Abstract

Atherosclerotic disease of the carotid arteries is major cause of ischemic stroke.The degree of carotid stenosis is the main marker for assessing the risk of stroke in "carotid disease", however, the degree of stenosis alone cannot accurately predict future stroke. Asymptomatic carotid artery stenosis is a well-recognized risk factor for ischemic stroke. Non-stenotic atherosclerotic carotid artery plaques can also cause atheroembolism in the presence of ulceration and rupture of the plaque. Atherosclerosis is a dynamic process involving inflammatory and thrombotic mechanisms with progressive degree of stenosis. The ability to predict the progression of atherosclerotic stenosis can be useful for clinical practice in assessing the risk of stroke development and its prevention.To identify subgroup of patients at higher risk for ipsilateral stroke is important aim.Inflammatory activity is an integral indicator of the development of atherosclerosis and its complications and plays a key role in the pathogenesis, progression, rupture of atherosclerotic plaque and the development of clinical manifestations in patients with atherosclerotic carotid stenosis. Several serum inflammatory markers such as C-reactive protein, interleukin-6, pentraxin 3, lipoprotein-associated phospholipase A2, adhesion molecules ICAM-1and selectins and matrix metalloproteinases proposed as tool for risk assessment in patients with carotid atherosclerosis. Even though there are some cardiovascular biomarkers identified, they have only modest predictive value. Some well-established biomarkers for coronary disease are not relevant to carotid atherosclerosis. Future research may clarify the clinical significanceof serum inflammatory biomarker in carotid atherosclerosis.

Keywords: Atherosclerotic carotid stenosis; Inflammatory biomarkers; Ischemic stroke

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Introduction

About 20-25% of ischemic strokes develop as a result of atherosclerosis of large arteries, among which extracranial carotid stenosis have a significant proportion, the frequency of which increases with age [1]. The degree of carotid stenosis is the main marker for assessing the risk of stroke in "carotid disease". After two multicenter studies NASCET and ECST, the management of patients with carotid atherosclerosis is based on the degree of stenosis [2]. It is well recognized that the presence of atherosclerotic disease in the carotid arteries increases a substantial risk of ipsilateral cerebrovascular events, with reported annual ischemic stroke rates ranging from 0.35% to 1.3% in asymptomatic patients with moderate stenosis to approximately 5% for severe asymptomatic carotid artery stenosis [3,4]. Asymptomatic carotid artery stenosis is a well-recognized risk factor for ischemic stroke and its prevalence increases with severity of degree of stenosis [5]. The extent of internal carotid artery narrowing is traditionally use to stratify stroke risk and is still one of the key factors in clinical decision making regarding surgical intervention to prevent strokes. However, the degree of stenosis alone cannot accurately predict future stroke in asymptomatic patients. With risk of stroke associated also ultrasound plaque features but best treatment for asymptomatic carotid artery stenosis and prophylactic revascularization still controversial. To identify subgroup of patients at higher risk for ipsilateral stroke is important aim [6]. Current guidelines recommended surgical or endovascular revascularization in patients with symptomatic severe carotid stenosis [7], however, after revascularization operations on the carotid arteries, the development of restenosis is not uncommon [8].

Diagnostic criteria make it possible to establish atherothrombotic ishemic stroke subtype in the presence of atherosclerotic stenosis of a large artery ≥50% of the lumen [9]. Non-stenotic (<50% diameter stenosis) atherosclerotic carotid artery plaques are common in the eldery population and carry a low absolute risk of stroke [10]. Ischemic stroke in patients with non-occlusive atherosclerotic plaques and absence other stroke source defined as cryptogenic [11]. However, non-stenotic plaques in the carotid, subclavian and vertebral arteries can also cause atheroembolism in the presence of ulceration and rupture of the plaque.Thus, in 32 patients with cryptogenic stroke and non-stenosing carotid plaques, 38% had complicated plaques on the ipsilateral side, and were absent on the contralateral side [12]. Also atherosclesosisis a dynamic process involving inflammatory and thrombotic mechanisms with progressive degree of stenosis. The ability to predict the progression of atherosclerotic stenosis can be useful for clinical practice in assessing the risk of stroke development and its prevention.

Clinical, biochemical, and ultrasound markers, neuroimagine plaque characteristics or transcranial cerebral Doppler signals have been proposed as indicators of a high-risk plaque. The measurement of serum biomarkers is a promising method to assist in decision making, but the lack of reliable evidence of their potential as a standard of care in the carotid disease. A large number of different biomarkers

have been studied to assess the risk of atherosclerosis progression and cardiovascular events, including Myocardial Infarction (MI) or death, but association between biomarkers and carotid atherosclerosis is less established [13]. Some well-established biomarkers for coronary disease are not relevant to carotid atherosclerosis. Most research is focuses on measurement of Carotid Intima-Media Thickness (CIMT) is a surrogate marker of early atherosclerosis.

Furthermore, atherosclerosis is now recognized as manifestations of vascular inflammation and atherosclerotic plaque destabilization and rupture and successive clinical complications depend on several inflammatory molecules involved in the atherosclerosis pathogenesis [14]. Inflammatory activity is an integral indicator of the development of atherosclerosis and its complications. Inflammatory activity plays a key role in the pathogenesis, progression, rupture of atherosclerotic plaque and the development of clinical manifestations in patients with atherosclerotic carotid stenosis [15]. Several serum inflammatory markers have been proposed as tool for risk assessment in patients with carotid atherosclerosis [16]. Serum biomarkers reflecting the activity of biological processes involved in growth and destabilization atherosclerotic plaque and may help to predict acute cerebrovascular event occurrence.

Modification of primary serum lipid biomarkers such as Low-Density Lipoprotein Cholesterol (LDL-C) is a important component in the secondary stroke risk reduction strategy [17]. However, although epidemiological data point to a modest link between high serum LDL-C and greater risk of ischemic stroke [18,19].

It is well accepted that circulating biomarkers, including C-Reactive Protein (CRP) and interleukin-6 (IL-6), reliably predict major cardiovascular events, including Myocardial Infarction (MI) or death [20]. The first described atherosclerosis biomarker, CRP is one of the most representative acute phase proteins of the pentraxin superfamily. High sensitivity (hs)-CRP measures accurately levels of CRP to identify low but persistent levels of inflammation. This association with carotid disease, however, is also controversial. Some studies suggest that high serum hs-CRP levels can predict the presence of carotid plaque [21]. A large series including more than 1600 patients with asymptomatic carotid atherosclerosis prospectively followed for a median of 11.81 years, found that the risk of all-cause and cardiovascular mortality significantly increased in patients with elevated serum levels of hs-CRP. That risk was level response associated and patients with carotid narrowing of greater than 50% and hs-CRP levels of greater than 0.29 mg/dL had nearly twice as high a risk of cardiovascular mortality compared with patients with carotid stenosis of less than 50% and hs-CRP levels of less than 0.29 mg/dL [15]. Although other studies could not establish that association or any correlation with the degree of stenosis, plaque type relation to hs-CRP levels is also diverse [22]. Chronic elevation of serum IL-6 was association with progression of atherosclerosis in patients with vascular risk factors. CIMT progression significantly associated only with IL-6 level, but not with CRP [23].

Recently pentraxin 3 (PTX3), have been examined as potential early biomarkers of the atherosclerotic process [24]. PTX3 belongs to the pentraxin protein family, which has been divided into two groups on the basis of the primary structure of the subunit. CRP and Serum Amyloid P (SAP) belong to the short pentraxins, whereas PTX3 is classified as the long one having pentameric cyclic structure. On the contrary to CRP, mainly produced by hepatocytes, PTX3 is produced by the peripheral tissues (e.g. endothelium, monocytes, macrophages, adipocytes, and smooth muscles cells), where the inflammation takes place [25]. Elevated levels of PTX3 were also found in patients with plaque instability undergoing carotid stenting and authors concluded that PTX3 may thus be a potential predictive marker of plaque vulnerability [26]. Nevertheless, the association with the presence and severity of carotid stenosis is questioned in other studies and a population-based study involving more than 2400 subjects, showed that PTX3 is not a predictor of incident cardiovascular events [27].

One of the markers of inflammatory activity in atherosclerosis is lipoprotein-associated phospholipase A2 (Lp-PLA2), which may be involved in the process of destabilizing atherosclerotic plaques by increasing inflammatory activity in atherosclerotic foci [28,29]. Lp-PLA2 is also known as platelet-activating factor acetylhydrolase, an enzyme synthesized in macrophages and activating platelets that is transporting in a binding state with circulating low-density lipoprotein and is abundantly expresses on atherosclerotic plaque. Lp-PLA2 hydrolyzes oxidized low-density lipoprotein to form lysophosphatidylcholine, which increases monocyte adhesion, enhances the inflammatory response, and impairs endothelial function. The level of Lp-PLA2 is increased in atherosclerotic plaques; in addition, it is intensely expressed in macrophages located in the fibrous capsule at the site of rupture [30]. A meta-analysis of 32 prospective studies involving 79,036 participants showed that the level and activity of Lp-PLA is significantly associated with the risk of developing coronary disease and is an independent predictor of cardiovascular events and ischemic stroke [31]. An increased level of circulating Lp-PLA2 was found in patients with high-grade carotid stenosis and unstable plaques who underwent carotid endarterectomy [32]. In other study was showed that Lp-PLA_2 expression was significantly higher in plaques of symptomatic patients than asymptomatic patients [33]. High Lp-PLA levels have been associated with a high risk of cardiovascular events in healthy older adults [34]. However, the pharmacological reduce in Lp-PLA activity did not lead to a significant decrease in the risk of cardiovascular events in patients with stable coronary disease [35]. It has been shown that statins reduce the level of Lp-PLA2 by 35% and this reduction is associated not only with a decrease in LDL cholesterol [36]. In the study Ch. Wang et al. elevated Lp-PLA2 level in the older adults was associated with an increased risk of carotid atherosclerosis, MI and CVD mortality, however no association was found with stroke [37].

With the development of atherosclerosis, adhesion of monocytes on the surface of the endothelium is activated by adhesion molecules E-selectin and ICAM-1. E-selectin recruits leukocytes into the endothelium by binding ligands on their cell surfaces. Elevated concentrations of E-selectin have also been known to occur in high CVD risk disorders such as smoking, obesity, diabetes, hypertension and hyper-cholesterolaemia [38]. In study S. Sakurai et al. demonstrated that serum levels of sE-selectin could be biomarkers for atherosclerosis in general populations and correlated with CIMT and heterogeneous plaque [39]. Was shown that in atherosclerotic plaque in patients after carotid endarterectomy to observe endothelian expression of molecules adhesion VCAM and E-selectin that reflect the macrophage burden within plaque lesion and inflammatory activity of atherosclerosis [40]. In another study examined the relationship between E-selectin concentrations, CIMT

and cardio-metabolic traits in normo- and hyperglycaemic mixed ancestry South Africans. E-selectin concentrations in this study were associated with hyperglycaemia, possibly reflecting early endothelial damage. However, E-selectin was not useful to assess CIMT, a marker of subclinical atherosclerosis, which appeared to be determined by ageing and male gender [41].

P-selectin belongs to the family of adhesion molecules and plays a role in modulating the interaction between blood cells and vascular endothelium. P-selectin is a component of platelet membranes; it is involved in platelet aggregation, platelet-fibrinogen interaction and has procoagulant activity. P-selectin is a sensitive marker of platelet activation. In animal models, it is shown that P-selectin plays a role in the processes of atherogenesis and its expression affect the activation of atherosclerotic plaques. There is also evidence that it may be a plasma predictor of cardiovascular events, its increase is associated with coronary artery disease and hypertension [42].

Matrix Metalloproteinase's (MMPs) are a class of proteases that are involved in the degradation of the extracellular matrix, leading to destabilization and erosion of atherosclerotic plaques [43]. Many studies have suggested that MMP-9 increased levels play a role in atherosclerosis and implicated in lipid metabolism [44]. Increased expression and activity of several MMPs, mainly MMP-1,-2,-3, and -9, were observed from data related in diseased human arteries and in arterial experimental models of atherosclerosis and restenosis [45]. Elevated MMP-9 was observed in patients with active carotid plaques and symptomatic patients who underwent carotid endarterectomy [46].

Conclusion

Biomarkers are one such tool that can augment clinical risk assessment.The detection of the inflammatory biomarkers may improve to risk stratification in patients with asymptomatic carotid disease, non-stenotic carotid atherosclerosis and restenosis after CEA. Despite the extensive evidence base for the participation of inflammatory biomarkers in the process of atherogenesis, there are still no reliable biomarkers to predict the progression of atherosclerotic carotid stenosis and the development of associated ischemic strokes in clinical practice.Even though there are some cardiovascular biomarkers identified, they have only modest predictive value and therefore there is a need to identify ones from new biological pathways. Future research may clarify the clinical significance of serum inflammatory biomarkers as surrogate that reflect carotid atherosclerotic disease progression and risk of acute cerebrovascular events.

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