Inflammation of carotid plaques and risk of cerebrovascular events

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Abstract: Carotid atherosclerotic plaques represent a risk for ischemic stroke. The data indicate that the risk for distal embolization from atherosclerotic lesions in internal carotid arteries is not related only to the degree of stenosis but also to the composition of plaques. The stability of atherosclerotic plaque depends on the thickness of the fibrous cap and plaque hemorrhage. Recent research indicated that the inflammatory activity of atherosclerotic lesions is pivotal in the progression of atherosclerotic plaques. It also promotes the development of unstable atherosclerotic lesions and is related to thromboembolic cerebrovascular complications. Inflammation destabilizes atherosclerotic plaques through the degradation of their fibrotic structure. Inflammation of atherosclerotic plaques was confirmed by histopathologic findings and levels of circulating inflammatory markers which were correlated to the intensity of the inflammation in atherosclerotic lesions. Recently, new techniques like fluorodeoxyglucose positron emission tomography (18-FDG PET) were developed for the identification of inflammation of atherosclerotic lesions in the vessel wall *in vivo*. Systemic inflammatory markers, particularly interleukins, tumor necrosis factor-alpha and metalloproteinases were shown to be related to the intensity of the inflammatory process in atherosclerotic lesions and the cerebrovascular events. Identification of inflamed atherosclerotic plaques may help to identify unstable atherosclerotic lesions and subjects at high risk for cerebrovascular incidents who need intensive preventive measures including anti-inflammatory medication.

Keywords: Inflammatory markers; unstable carotid plaques; cerebrovascular events; anti-inflammatory treatment

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Introduction

The presence of atherosclerotic disease in carotid arteries represents a substantial risk of cerebrovascular events (1). Around 1/5 of ischemic stroke appears to originate from carotid plaques, mainly due to embolization (2). Previous studies showed that the risk of internal carotid artery stenosis-related stroke occurrence correlated to the degree of stenosis (3). However, recent studies indicated that also low-grade carotid stenosis may cause ischemic cerebrovascular events (4). This indicates that besides the size of atherosclerotic plaques and degree of stenosis, other characteristics of plaques, particularly plaque composition may be related to the risk of cerebrovascular events. The vulnerability of atherosclerotic plaques to rupture and to be a source of distal embolization was shown to be related to its structure such as the size of the lipid core and intraplaque hemorrhage (5). Higher content of intraplaque lipids, particularly LDL cholesterol which is associated with its plasma level most probably represents the most important risk factors for atherosclerotic plaque instability (2). Serum LDL and total cholesterol levels were associated with acutely symptomatic carotid plaques, shown by fluorodeoxyglucose uptake, indicating that lipids

promote plaque inflammation and mediate rupture (6). Another important indicator of plaque instability is a thin fibrous cap (7). Recent research indicated that plaque structure rather than the degree of carotid stenosis was closely related to cerebrovascular thromboembolic events (8). Further, in addition to the morphological characteristics of atherosclerotic lesions in the last decade, investigations were focused on the physiological processes, particularly the inflammation of atherosclerotic lesions. Determination of the inflammatory process helps in identifying unstable atherosclerotic lesions, which are the source of thromboembolic cerebrovascular complications. The migration of circulating monocytes into the vessel wall is a key event in the initiation of atherosclerotic plaque formation. This process is mediated by the adhesion molecules expression in response to endothelial stimulation or damage, caused by arterial hypertension, turbulent blood flow, and smoking. Retention of LDL cholesterol in the extracellular space of the arterial wall is followed by the transformation of monocytes into lipid-laden foamy macrophages. Transformation of macrophages results in a local expression of pro-inflammatory cytokines and tumor necrosis factor-alpha (TNF-α). Cytokines including platelet-derived growth factor promote recruitment and proliferation of smooth muscle cells into the vessel wall which stimulates expression of matrix proteins, such as collagen and elastin (9). Expression of cytokines and collagenolytic enzymes such as metalloproteinases are involved in erosion and rupture of the plaques. Circulating platelets adhere to the damaged vessel wall surface and together with coagulation factors promote the prothrombotic state.

Therefore, inflammation promotes the rupture of atherosclerotic plaques by enzymatic degradation of their fibrotic structure (10,11).

Indicators of atherosclerotic plaques inflammation

Pathohistological findings confirmed local vessel wall inflammation at a site of plaque formation. Macrophages and other inflammatory cells are present in atherosclerotic plaques in all stages of the atherosclerotic process (12). Further, histology of advanced lesion reveals an accumulation of macrophages in arterial walls. The Oxford plaque study found marked inflammation in the resected plaques of the ipsilateral carotid artery. The presence and extent of macrophage infiltration were independently associated with plaque rupture (13). Non-invasive imaging techniques visualize the plaque, its structure, intraplaque hemorrhage, calcifications, and plaque remodeling thus providing some information regarding plaque vulnerability (14). Computer tomography (CT) provides a spatial and temporal resolution that detects detailed anatomical structure. However, CT does not provide information on metabolic activity and inflammation of atherosclerotic lesions. Magnetic resonance imaging is an accurate and non-invasive imaging technique used for early detection of atherosclerotic lesions, their morphology including lipid core, fibrous cap, intraplaque hemorrhage and gives some information on vascular wall inflammation (15). Intravascular ultrasound and optical coherence tomography are intravascular invasive imaging modalities with the ability to present different plaque components including macrophage infiltration and plaque rupture (16). Recently, new techniques, like 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET)-CT enabled non-invasive detection of atherosclerotic plaque inflammation *in vivo* (17). In the study of Jezovnik *et al.*, it was shown that FDG uptake significantly correlated with the density of inflammatory cells in specimens obtained during the endarterectomy of atherosclerotic lesions of carotid and femoral arteries. This finding suggests that FDG uptake is correlated to the severity of vessel wall inflammation (18). It was shown that inflammation of carotid plaques identified by 18-FDG PET-CT uptake and the severity of stenosis represent the risk of recurrent stroke (19).

Inflammation of atherosclerotic plaques and inflammatory blood markers

Inflammation mediates all stages of atherosclerotic disease and is involved in the progression of atherosclerotic lesions (20). Therefore, recently blood markers that indicate the presence of inflamed-unstable atherosclerotic lesions have been sought. Features of plaque instability as evaluated by magnetic resonance imaging were shown to correlate with upregulation of several pro-inflammatory markers such as cytokines—interleukin-6 (IL-6) and TNF-α, the endothelial activation markers, like high sensitivity C reactive protein (hs-CRP) and long pentraxin-3 (21). Also, in patients with stable coronary artery disease levels of neopterin, synthesized in macrophages correlated with the presence of complex—vulnerable atherosclerotic plaques (22). A meta-analysis of prospective studies showed a linear relationship between levels of circulating hs-CRP and the risk of ischemic stroke. The correlation persisted after an

adjustment for classical risk factors for atherosclerosis (23). Further, hs-CPR was shown to be an independent risk factor of recurrent stroke and other vascular events in patients after recent lacunar stroke. Baseline hs-CPR was associated with a 2.23-fold increased risk of recurrent stroke (24). In a population-based study, the Oxford Vascular Study, hs-CRP was an independent predictor of a 90-day stroke recurrence in the early period after a transient ischemic attack or ischemic stroke (25). Willems and co-workers failed to show an association of serum concentration between IL-1 receptor family and vulnerable plaque phenotype as determined histologically (26). However, Pelisek and co-workers established an association between histological features of plaque instability and serum levels of circulating matrix metalloproteinase (MMP), tissue inhibitor of matrix proteins (TIMP-1), and IL-8 (27). In one of our studies, inflammation of atherosclerotic lesions was investigated using 18-FDG PET, and 18-FDG uptake calculated by the target to background ratio (TBR) was correlated with levels of inflammatory markers (IL-6, TNF-α and hs-CRP) (28). Duivenvoorden and co-workers also found a positive correlation between IL-6 and 18-FDG TBR in the most diseased carotid segments (29). Recently, new technologies such as polychromatic flow cytometry have enabled the identification of different leukocyte subgroups. It was shown that proven circulating blood cells may serve as biomarkers. In patients with atherosclerosis, mononuclear cells, lymphocytes, and monocyte subpopulation were associated with plaque progression and vulnerability (30). The studies also demonstrated the association between the presence of plaques and total white cell (31) and monocyte counts (20). Neutrophil count was also correlated with the presence of microemboli detected by transcranial Doppler ultrasound in recently symptomatic patients (32). Further, patients with carotid plaques had higher activation of T- and B-lymphocytes and higher levels of MMP-9 expression in peripheral blood mononuclear cells (33). Leukocyte telomere shortening, an indicator of leucocyte activity and replicative capacity, was associated with an increased progression of intima-media thickness which indicates subclinical vascular damage (34).

Makers of inflammation and subsequent cardiovascular events

Circulating blood markers of inflammation have been related to cardiovascular events (35). Levels of cytokines such as TNF-α, IL-6, cell adhesion molecules, and E-selectin have been associated with future cardiovascular events (36). Also, increased levels of hs-CRP represent risk even when other risk factors are absent (36). The levels of pro-inflammatory cytokines are significantly increased in the blood of patients of symptomatic and asymptomatic carotid advanced stenosis compared to patients with modest carotid stenosis (37). Hs-CRP has been related to the risk of cerebrovascular events among healthy adults and patients with asymptomatic carotid stenosis (38). A meta-analysis of studies dedicated to the importance of hs-CRP showed that the risk of stroke in healthy individuals with the highest level of hs-CRP concentration increased by 70% compared with those with the lowest quartile of hs-CRP (39). Most of the studies included in this meta-analysis indicated that hs-CRP can predict future ischemic stroke independently of traditional cardiovascular risk factors. Fibrinogen is another risk factor of cerebrovascular events and it independently predicts future ischemic stroke (40). Preoperative levels of hs-CRP and fibrinogen are independent determinants of perioperative cerebrovascular ischemic events caused by embolization in patients undergoing carotid endarterectomy (41). The presence of rupture-prone atherosclerotic plaques is associated with increased levels of metalloproteinases. MMP-9 levels were shown to predict stroke and cardiovascular death in patients with carotid stenosis (42). Further, inflammatory markers expressed in the soluble form of CD36 were shown to correlate with the ultrasound characteristics of plaque which increase the risk of CV events (43). Further, increased levels of serum markers soon after a cerebrovascular event of carotid origin are related to a higher risk of recurrence (31).

Evidence of inflammation of atherosclerotic plaques and therapeutic interventions

The best medical treatment which includes lifestyle modification, smoking cessation, moderate exercise, blood pressure and diabetes control, antiplatelet and lipid-lowering treatment, represents the cornerstone of the management of patients with either symptomatic or asymptomatic carotid artery stenosis (44). Evidence of an independent association between inflammation of atherosclerotic lesions manifested by circulating inflammatory markers and cerebrovascular events stimulated the interest towards new therapeutic—anti-inflammatory targets. Continuous research tries to distinguish therapeutic strategies that specifically target the inflammatory mediators (10). No studies are focusing on the effect of anti-inflammatory

drugs alone on cardiovascular risk. However, some drugs used in the prevention of atherosclerosis, like antiplatelets have also anti-inflammatory effects. Aspirin which has recently been used as an antiplatelet drug was initially accepted as an anti-inflammatory drug, inhibits cyclo-oxygenase and pro-inflammatory signaling pathways, including nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB) (45). Also, clopidogrel inhibits inflammation. Prolonged treatment with clopidogrel after percutaneous coronary intervention reduced inflammation in the porcine model (46). Particularly, high dosages of clopidogrel are associated with stronger platelet inhibition and reduction of inflammation (47). Further, statins have besides their cholesterol-lowering also anti-inflammatory effects. Atherosclerosis prevention study (AFCAPS/TexCAPS) utilizing lovastatin in primary prevention proposed that statin treatment may prevent coronary events among subjects with relatively low lipid levels but with elevated levels of hs-CRP (48). Similarly, the JUPITER trial (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) in the subjects with normal lipid levels showed that reducing vascular inflammation indicated by a decrease in hs-CRP and reducing LDL cholesterol leads to lower incidence of cardiovascular events (49). Statin therapy was related to a favorable rise inechogenicity of carotid plaques. This effect was dependent on hs-CRP reduction from the baseline and independent on changes in LDL and HDL cholesterol (50). Similarly, also the study of Koutouzis and co-workers found a decrease of the hs-CRP level in patients treated with statins. However, the accumulation of macrophages in carotid plaques was not significantly lower in patients taking statins (51). Intensive lipid-lowering therapy, utilizing statin medication was more effective in the prevention of cardiovascular events in patients after a transient ischemic attack (TIA) and ischemic stroke than a moderate lowering of lipids. The composite primary endpoint including stroke, myocardial infarction, urgent coronary and carotid revascularization or death from cardiovascular causes occurred less frequently in patients with lower target LDL levels (65 mg/dL) than in a higher target group (96 mg/dL) (52). It could be the consequence of more intensive inhibition of inflammation with high dosages of statins.

Recently, novel anti-inflammatory treatment strategies of atherosclerosis were introduced. Tocilizumab, a monoclonal antibody that blocks IL-6 receptors, is widely used in patients with rheumatoid arthritis. In small randomized placebo-controlled trials tocilizumab reduced myocardial damage and systemic inflammation. However, there was a major safety concern for tocilizumab because of a significant increase in LDL cholesterol levels soon after treatment start (53).

Also, canakinumab, a human monoclonal antibody targeted at interleukin-1β which has anti-inflammatory effects, has been approved for clinical use in rheumatologic diseases. In the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) canakinumab prescribed every three months at a dose of 150 mg significantly lowered recurrent cardiovascular events compared with placebo in patients with a history of myocardial infarction and elevated hs-CRP. This effect was independent of lipid level lowering (54). Recently, colchicine which was used for centuries for the treatment of goat has been shown to have multiple anti-inflammatory properties including inhibition of caspase-1 proteolysis and IL-β secretion in macrophages. One of the studies included patients with stable coronary artery disease which were treated with a low dose of colchicine. Over a 36-months follow-up, the risk of major cardiovascular events, including stroke was reduced by 67% in patients treated with low dose colchicine (55). Besides the side effects of tocilizumab and canakinumab, the main limitation in their use in the everyday clinical practice for the prevention of cardiovascular events is high cost. In the study of Sehested and co-workers, canakinumab was not cost-effective to prevent recurrent cardiovascular events after myocardial infarction (56). The model was based on the data of the CANTOS trial and the annual price of canakinumab used in this study was $73,000. Life expectancy increased only 11.31 to 11.36 years and the quality-adjusted life years (QALY) increased from 9.37 to 9.50, with the cost increase from $242,000 to $1,074,000.

TNF-α is a mediator of systemic inflammation through the release of the acute phase reactants in immune diseases. In patients with atherosclerosis, TNF-α neutralizing antibody infliximab improved endothelial function and reduced adhesion molecules. Therefore, it could have a potential anti-atherosclerotic effect (57).

Identification of high-risk unstable inflamed atherosclerotic plaques may help in the selection of patients with asymptomatic carotid stenosis who could benefit from endarterectomy or stenting of carotid arteries or who need intensive anti-inflammatory treatment. Based only on the degree of carotid stenosis, only 10–15% of patients with asymptomatic carotid stenosis may benefit

from an intervention (58). Other indicators of high risk in asymptomatic individuals are microemboli detected on transcranial Doppler, plaque echolucency, silent embolic infarcts on brain CT, increased size of juxtaluminal hypoechoic area, and most probably the intensity of inflammation of atherosclerotic plaques represent a risk for distal embolization. These patients need intensive medical therapy and/or intervention.

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