The analysis of the connection between plaque morphology of asymptomatic carotid stenosis and ischemic brain lesions

Analiza povezanosti morfologije plaka asimptomatske karotidne stenoze i ishemijske moždane lezije

Djordje Milošević*, Janko Pasternak*, Vladan Popović*, Dragan Nikolić*, Pavle Milošević†, Vladimir Manojlović*

*Clinic for Vascular and Transplant Surgery, †Clinic for Abdominal, Endocrine and Transplant Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia

Abstract

Background/Aim. A certain percentage of patients with asymptomatic carotid stenosis have an unstable carotid plaque. For these patients it is possible to register the existence of lesions of the brain parenchyma – the silent brain infarction. These patients have a greater risk of ischemic stroke by modern imaging methods. The aim of this study was to analyze the connection between the morphology of atherosclerotic carotid plaque in patients with asymptomatic carotid stenosis and the manifestation of silent brain infarction, and to analyze the influence of risk factors for cardiovascular diseases on the occurrence of silent brain infarction and the morphology of carotid plaque. Methods. This retrospective study included patients who had been operated for high grade (> 70%) extracranial atherosclerotic carotid stenosis at the Clinic for Vascular and Transplantation Surgery of the Clinical Center of Vojvodina over a period of 5 years. The patients analyzed had no clinical manifestation of cerebrovascular insufficiency of the carotid artery territory up to the time of operation. The classification of carotid plaque morphology was carried out according to the Gray-Weale classification, after which all the types were subcategorized into two groups: stable and unstable. Brain lesions were verified using preoperative imaging of the brain parenchyma by magnetic resonance. We analyzed ipsilateral lesions of the size > or = 3 mm. Results. Out of 201 patients 78% had stable plaque and 22% unstable one. Unstable plaque was prevalent in the male patients (male/female ratio = 24.8% : 17.8%), but without a statistically significant difference (p > 0.05). The risk factors (hypertension, nicotine, hyperlipoproteinemia, and diabetes mellitus) showed no statistically significant impact on carotid plaque morphology and the occurrence of silent brain infarction. Silent brain infarction was detected in 30.8% of the patients. Unstable carotid plaque was found in a larger percentage of patients with silent brain infarction (36.4% : 29.3%) but without a significant statistical difference (p > 0.05). Conclusions. Even though silent brain infarction is more frequent in patients with unstable plaque of carotid bifurcation, the difference is of no statistical significance. The effects of the number and type of risk factors bear no statistical significance on the incidence of morphological asymptomatic carotid plaque.

Key words: carotid stenosis; brain ischemia; magnetic resonance imaging; risk factors.

Apstrakt


Metode. Retrospektivnom studijom obuhvaćeni su bolesnici koji su u petogodišnjem periodu operativno lečeni na Klinici za vaskularnu i transplantacionu hiruriju Kliničkog centra Vojvodine zbog visokostepene (> 70%) ekstrakranijske aterosklerotske karotidne stenoze. Analizirani su bolesnici koji do momenta operacije nisu imali kliničke manifestacije cerebrovaskularne insuficijencije karotidnog sliva. Podaci su dobijeni analizom podataka sadržanih u istorijama bolesti tih bolesnika. Klasifikacija morfologije karotidnog plaka izvedena je prema Gray-Weale klasifikaciji, a potom su svi tipovi klasifikovani u dva podtipa: stabilni i nestabilni plak. Moždane lezije su verifikovane pomoću preoperativnog snimačko-geleštanog parenhima magnetnom rezonancijom. Analizirane su ipsilateralne lezije veće od ili jednake 3 mm.

Rezultati. Istraživanjem je analiziran 201 bolesnik. Kod
78% of patients had a stable plaque, and 22% had a non-stable plaque. Non-stable plaque was found to occur in 20% of ischemic strokes. Non-stable plaques are the most frequent cause of extracranial cerebrovascular disease.

Introduction

Stroke is one of the leading health problems of modern man. It is the third most frequent cause of death in industrially developed countries, closely behind cardiac diseases and cancer, and is the leading cause of long-term disability.

The results of epidemiological research show that 88% of all strokes have ischemic etiology, whereas other causes include intracerebral hemorrhage in around 9% cases and subarachnoid hemorrhages in around 3% of cases.

Atherosclerosis of the carotid and vertebral arteries is the most frequent cause of extracranial cerebrovascular disease (ECD) which leads naturally to artery stenosis. Atherosclerotic stenosis of extracranial segment of the internal carotid artery is the cause of around 20% of ischemic strokes.

Stenosis of carotid arteries can be symptomatic and asymptomatic. The majority of extracranial carotid stenoses are asymptomatic.

The treatment of atherosclerotic ECD can be medical or surgical and its basic aim is to prevent new or recurrent ischemic event, transient ischemic attack (TIA) or stroke. With symptomatic ECD the treatment is a form of secondary prevention, whereas with the asymptomatic ECD it is a primary prevention of stroke.

Both the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) analyzed the advantages of medical and open surgical treatment of symptomatic ECD resulting with clearly defined views on medical and surgical treatment of symptomatic atherosclerotic ECD.

The Veterans Administration Centers Study (VACS), the Asymptomatic Carotid Atherosclerotic Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) analyzed the effects of medical treatment in comparison with surgical therapy in prevention of ischemic strokes in asymptomatic atherosclerotic ECD. Unlike symptomatic ECD where the benefit of surgical treatment has been proven in patients with extracranial carotid stenosis > 60% at an annual level, the studies of asymptomatic ECD showed that the benefits of surgical treatment in terms of prevention of ischemic stroke can only be observed in a five year period. According to the ACAS study, there was a decrease from 2% to 1% of the annual incidence of ischemic stroke in surgically treated asymptomatic patients; this means that there would be around 20 patients with asymptomatic ECD operated on annually in order to prevent one ischemic stroke per 5 years. According to that study there is a large number of patients operated for asymptomatic ECD with no direct benefit of the operation in terms of secondary prevention of brain lesions.

The research so far demonstrated the significance of atherosclerotic carotid plaque morphology as a factor contributing to ischemic cerebrovascular incidents in both manners: hemodynamically and as a source of thromboembolic ischemic events. Atherosclerotic plaque rupture is central for the ischemic cardiovascular incident. Plaques are usually composed of an extracellular lipid matrix, thin fibrous cap, smaller quantity of smooth muscle fibers and numerous macrophages and mastocytes in most ruptures. Thin fibrous cap of the plaque can rupture as a consequence of diminished collagen synthesis, increased matrix degradation or as a result of external mechanical and chemodynamic stress.

Plaques at the carotid artery branch point are exposed to strongest biomechanical and chemodynamic stress.

Histological researches on carotid plaque in symptomatic and asymptomatic patients show that the main features of unstable plaques found in symptomatic patients are: ulceration of the surface and rupture of the plaque, thinning of the fibrous cap and infiltration of the fibrous cap with microfags and T-lymphocytes.

Morphological assessment of carotid plaques can be determined preoperatively with the use of modern imaging methods – ultrasonography (US) and magnetic resonance imaging (MRI); or postoperatively with pathohistological analysis. Numerous researches prove the correlation of the morphological analysis of carotid plaque made by imaging methods with the pathophysiological data and thus pointing to the possibility of an adequate preoperative assessment of the morphology of carotoid plaque.

Silent brain infarction (SBI) is an ischemic change of the brain parenchyma without clinical symptomatology which can be registered by modern imaging methods – multislice computed tomography (MSCT) and MRI, and which is > or = 3 mm. The changes < 3 mm are not considered as SBI but as a consequence of perivascular space expansion. Researches show that in most cases the origin of SBI has an thromboembolic etiology – either of cardiac or arterio-arterial origin, whereas the arterio-arterial SBI are usually connected with unstable carotid plaque. It has been proven that SBI is a significant risk factor for the development of clinically manifested ischemic stroke and a contributing factor in the development of clinical...
opment of cognitive disfunction and psychiatric and neurological disturbances. There have been numerous studies on different risk factors for the development of ischemic brain lesions to detect and define a critical group of patients out of a large group with asymptomatic ECD. These would directly benefit from the operative treatment in terms of ischemic stroke prevention.

The aim of this study was to analyze the influence of atherosclerotic plaque morphology on the prevalence of SBI, as well as to analyze the impact of defined risk factors on atherosclerotic carotid plaque morphology and on the prevalence of SBI.

Methods

Medical documentation (medical history, computer data bases, operative protocols, archives and photo documentation) of the Clinic for Vascular and Transplant Surgery, Clinical Center of Vojvodina, Novi Sad, was analyzed for the period from January 1, 2005 to December 31, 2009 (5-year period). This retrospective study included the following methodological stages: stage I – selection of the material, that is medical documentation (medical history, anesthesia reports, surgery lists, intensive treatment lists, the accompanying clinical, radiological and laboratory documentation, hospital discharge, coroner’s reports) of all the patients with asymptomatic ECD; the stage II – scope of data for each patient organized according to the following parameters: age, sex, risk factors for narrowing of carotid arteries (diabetes mellitus, hypertension, hyperlipoproteinemia, nicotinism, the presence of ischemic brain changes > or = 3 mm, morphology of atherosclerotic plaque; stage III – descriptive statistics for the entire population carried out as recommended by Glantz. The parameters for the descriptive statistics were: middle value, standard deviation, median, minimum and maximum. The frequency of certain categories was examined for the nonparametric features included. In terms of comparative statistics, we used the Student’s t-test in order to define the difference in the middle values of attributes between the groups tested; the stage IV – defining the features for comparative statistics regarding sex – subjects of male and female sex were compared in terms of descriptive statistical characteristics and the existence of ischemic brain lesion and participants comparison according of the characteristics to descriptive statistics.

The statistically significant difference was set at p < 0.05.

Asymptomatic ECD is narrowing of one or both internal carotid arteries without the existence of focal or global neurological symptoms accompanying artery stenosis: TIA, amaurosis fugax (AF) and ischemic stroke. Our study included all patients with high grade (> 70%) extracranial carotid artery stenosis during a 5-year period with no previous history of cerebral vascular insufficiency at all. Symptomatic were considered the patients with their last ischemic event within the last 6 months.

Morphological classification of atherosclerotic carotid plaque was carried out according to the Gray-Weale Du-
None of the analyzed risk factors showed a statistically significant impact in the presence or absence of ischemic changes in brain parenchyma.

There was no statistically significant difference in the presence of ischemic changes between the sexes.

Table 4 shows the percentage distribution of the type of plaque in relation to the presence/absence of ischemic changes > 3 mm.

**Discussion**

Numerous epidemiological studies show that the greatest number of atherosclerotic ECD is asymptomatic. The basic aim of atherosclerotic healing ECD is the prevention of ischemic brain lesions. Studies on the treatment of asymptomatic ECD prove the preventive impact of operative treatment of carotid stenosis > 60%, but also that a treatment of a large number of asymptomatic patients would be taken to prevent a relatively small number of ischemic strokes. Taking into consideration the general operative morbidity and mortality of carotid surgery, the conclusion is that carotid surgery is not directly preventive for all the patients with asymptomatic ECD. It is estimated that around 70% of patients with asymptomatic ECD experience a massive ischemic stroke. Recent findings in relation to the treatment of asymptomatic ECD are directed towards finding the group of asymptomatic patients to benefit to a greater extent from the operative treatment. Keeping in mind the fact that coronary atherosclerotic disease has a higher incidence of ischemic lesions in case of unstable atherosclerotic plaque, the supposition was that the incidence of ischemic changes also changed in relation to the morphology and type of atherosclerotic plaque in case of carotid atherosclerotic disease. Within this study the total of 201 patients were analyzed who underwent surgery for high grade (>70%) of asymptomatic stenosis. The analysis of the carotid plaque showed a higher percentage of stable atherosclerotic plaque (78%) with asymptomatic patients, whereas a smaller number of patients...
had the unstable plaque (22%) which is in line with recent findings in the literature which state that around two thirds of atherosclerotic plaques in asymptomatic patients are stable plaques and only one third unstable. It has also been noted that stable plaques are present in a larger percentage in female patients whereas unstable ones are more prevalent in male patients, although these results had no statistically significant difference. These findings are also in line with the data from the literature where it is stated that soft unstable plaques are more frequently found in men. The literature shows that the presence of defined risk factors for cardiovascular diseases bears no statistically significant influence on the morphology and type of plaque. In this paper the risk factors were analyzed showing no significant effect on the morphology and type of plaque, and a greater percentage of unstable carotid plaques in smokers. SBI existence analysis showed their presence in 30.8% and the absence in 69.2% of patients with asymptomatic ECD, with the greater percentage of SBI registered in male patients than in female. None of these factors showed a greater influence on the incidence of SBI in patients with asymptomatic ECD.

The largest percentage of registered SBI was present in patients with unstable exulceric carotid plaque but the results did not show statistically greater incidence of SBI in unstable carotid plaque. According to the data from the literature, the number of registered SBI in asymptomatic carotid stenosis > 60% is around 34%, and tending to increase with the increase of the artery stenosis level. Around 24% of SBI is registered in the area of ipsilateral hemisphere. From the etiological point of view, SBI can be thromboembolic or nonthromboembolic. Thromboembolic SBI is a consequence of thromboembolism in silent zones of the brain parenchyma possibly of cardiogenic origin or it can be caused by artery emboli, which is the reason for the existence of unstable exulceric carotid plaque to be considered the most frequent cause of SBI in asymptomatic ECD. According to the Asymptomatic Carotid Stenosis and Risk of Stroke (ACRSRS) study, most registered SBI in asymptomatic ECD, for stenosis from 60% to 79%, are registered in male patients and is around 41%. This number is close to the results of our study. According to this study, a significant number of SBI is registered in patients with carotid stenosis > 60% and it increases with the stenosis percentage, regardless plaque morphology. Unstable atherosclerotic carotid plaque is a contributing factor in the development of SBI, whereas most registered cases of SBI have ipsilateral distribution in the brain parenchyma.

Numerous researches point to a connection between the presence of SBI and the incidence of ischemic stroke regardless the etiology. The results of the ACRSRS study show that in patients with medium or high level of asymptomatic carotid stenosis and registered ipsilateral SBI, there is an increased risk of the development of ischemic stroke. According to this study, ischemic stroke will happen in 4.6% of patients with a significant asymptomatic carotid stenosis and ipsilateral SBI, whereas in patients without SBI ischemic stroke will happen in 2.4% cases annually, which is nearly 50% less. In patients with low level carotid stenosis (< 60%) there is a small risk of ischemic stroke regardless the morphology of plaque and that it is approximately at 1.6% at an annual level. The research conducted by Cao et al. showed that ipsilateral SBI is found in 24% of patients with asymptomatic carotid stenosis > 60%. These researches point that at a 10-year level risk of ischemic stroke in patients with carotid stenosis > 60% and ipsilateral SBI is 21%, whereas in patients without SBI it is 11%, which is the level of a significant statistical importance.

Our results, regarding the incidence of SBI and asymptomatic high-grade carotid stenosis, the influence of carotid plaque morphology and defined risk factors for cardiovascular diseases, are in line with similar international researches. Analyzing these results, and those in the literature, the significance of preoperative assessment of the morphology of carotid plaque and of the brain parenchyma are stressed, thus separating a group of patients with moderated symptomatic carotid stenosis for whom the operative treatment has a considerable preventive effect on the development of ischemic brain lesions, out of a larger group of asymptomatic patients with high level carotid stenosis.

**Conclusion**

The role of (endo) surgical treatment in secondary prevention of ischemic stroke is clearly defined, whereas the primary prevention remains a moot point. Even though patients with unstable plaque of the carotid bifurcation have more frequently SBI, this difference bears no statistical importance. The effect of the number and type of risk factors of ECD is not statistically relevant for the incidence of morphological asymptomatic carotid plaques.

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**REFERENCES**


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