



Original article

ACTA FAC. MED. NAISS. 2005; 22 (3): 149-155

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IS SCREENING OF ASYMPTOMATIC CAROTID DISEASE IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE EFFECTIVE?

SUMMARY

The aim of the paper is to determine the frequency of asymptomatic carotid stenosis in patients with atherosclerosis of lower extremities' arteries and to answer the question whether early screening of asymptomatic disease in certain subgroups of patients is effective. The study included 109 patients with obliterated atherosclerosis of lower extremities. On the basis of ACAS criteria, we conducted color Doppler screening in all the patients. In 36.69% of patients, we discovered hemodynamic significant stenosis $\geq 60\%$ or occlusion; in 29% of patients we discovered stenosis $\geq 70\%$. Morphologic characteristics of the plaque were analyzed on 43 patients' arteries with carotid artery stenosis ranging from 50-99%. In the majority of patients fibrolipid (44.18%) and fibrous plaque (23.26%) were present. In 58.14% of the plaques, the surface was irregular, and in 23.26% it was ulcerated. Additional examinations aimed at determining whether there was any correlation between asymptomatic carotid stenosis $\geq 60\%$ and occlusion, and certain characteristics of patients with obliterated atherosclerosis of lower extremities. Univariate analysis showed the association of hemodynamic significant stenosis of carotid arteries and previous vascular operations, age over 60, arterial hypertension, pedobrachial index (ABI) < 0.5 and carotid serum. By the application of multivariate logistic regression analysis, we found that this association refers only to carotid sum ($t = 0.50$; $p = 0.01$), whereby the sensitivity was 67%, and specificity 56%. Therefore, the conclusion is that limited early screening of carotid stenosis in neurological asymptomatic patients with symptomatic atherosclerosis of lower extremities, regarding certain subgroups of patients, is ineffective and unjustified.

Key words: asymptomatic carotid stenosis, prevalence of carotid stenosis, obliterated atherosclerosis of lower extremities

INTRODUCTION

Arterial occlusive disease is a systemic phenomenon involving more than one arterial system (1, 2). In one arterial bed the disease is presented with symptoms, in another it is asymptomatic.

There are many reports concerning the association between coronary and carotid occlusive disease (3). In 5-18% of patients, where coronary by pass grafting was indicated, coronary occlusive disease was connected with haemodynamically significant carotid occlusive disease (4, 5).

On the other hand, there are only several reports indicating the prevalence of carotid stenosis in patients with peripheral vascular disease (6), relative to atherosclerotic occlusive disease of the lower extremities, the most frequent cause of peripheral vascular disease (7-11).

Asymptomatic carotid stenosis is defined as the presence of internal carotid/carotid bifurcation stenotic or occlusive lesions in patients with no signs or symptoms of cerebrovascular disease (12). Two factors are particularly important: severity of diameter stenosis (in percentage) and morphologic characteristics of stenotic plaque (13).

Natural history of asymptomatic carotid stenosis was unknown for a long time. Now it is accepted that asymptomatic carotid stenosis will not progress to symptomatic lesions nor change in any manner, or will be presented as TIA, or completed stroke, or will progress to total occlusion, but stay asymptomatic, or total occlusion will be presented as TIA or frank stroke (14, 15). The course of natural history is determined by characteristics of vessels and lesions (stenosis or occlusion, homogen or heterogen plaques, smooth, irregular or ulcerated plaque surface) and collateral pathways (15). Asymptomatic carotid stenosis will progress to symptomatic within the mean time from 3 to 4 years. The frequency of completed stroke in asymptomatic patients with haemodynamically significant carotid stenosis is the same as in the patients with total occlusion: 2-5% (16, 17).

Two large multicentric prospective studies dealt with benefits of surgical treatment of asymptomatic carotid stenosis by carotid endarterectomy related to best medical treatment: Department of Veterans Affairs Hospital Carotid Trial (completed in 1991) and ACAS – Asymptomatic Carotid Atherosclerosis Study (1995) (17,18). ACAS study showed that surgical treatment of asymptomatic carotid stenosis 60% compared with best medical treatment, reduces relative risk of completed stroke for 53%, and absolute 5-year risk from 11 % to 5.1 % (under the condition that carotid endarterectomy is performed with perioperative mortality and morbidity less than 3 %, and that it is supplemented with risk factors aggressive treatment which can be managed) (18). At this moment, there is underway a prospective, randomized study ACST which will try to answer the question: which soft or heterogen plaque with more than 25 % echolucent material indicates carotid endarterectomy (19).

Taking into account results of all these studies, the need for successful and efficient early detection of atherosclerotic carotid stenosis has been imposed. The significance of early detection is reflected through the fact that both doctor and patient are

aware of the presence of the disease. Risk factors modification which can be managed is possible (arterial hypertension, diabetes mellitus, smoking, hypercoagulable states). Then, medical treatment can start (antithrombotic agents, hypolipemic drugs, antioxidants).

Early detection of carotid artery disease in general population is ineffective and very expensive. It is well-known that in the randomized prevalence of severe carotid stenosis is infrequent; significant carotid artery stenosis in the atherosclerosis risk factors patients is very frequent (20). Other groups (older than 65 or previous cerebrovascular disease) with higher frequency of carotid occlusive disease risk have been identified (2, 4, 9).

Identification of patients with asymptomatic carotid stenosis appears as accidental findings during the routine auscultation of carotid arteries, or within the framework of the screening program in search of carotid stenosis in high-risk patients.

The aim of the study

1. To find out the prevalence of asymptomatic carotid stenosis in patients with atherosclerotic occlusive disease of the lower extremities.
2. To find out, whether the limiting screening of carotid stenosis to the specific subgroup of patients (risk factors, presence of carotid bruit, and severity of peripheral vascular disease) can be justified.

METHODS

Patients

We analyzed 109 patients treated for atherosclerotic occlusive disease of the lower extremities. Mean age was 63.25 years. Male to female ratio was 88 to 21. Indication for hospitalization, related to severity of the clinical stage of the atherosclerotic occlusive disease of the lower extremities was: 19 patients with claudication, 64 with rest pain, and 26 with ulcer or gangrene. The following patients have not been evaluated:

1. Patients with symptomatic carotid artery disease,
2. Patients with no atherosclerotic carotid disease,
3. Patients with previously carried out carotid arteriography or endarterectomy,
4. Patients immediately operated for acute peripheral vascular disease (e.g. emboli, acute thrombosis).

In all the patients angiologic and angio - neurologic examinations were performed.

The primary examination was carried out with the aim of detecting the prevalence of carotid artery stenosis in patients with atherosclerotic occlusive disease of the lower extremities. Color Doppler duplex scans reveal:

1. Severity of stenosis in percentage (Doppler signal and spectral analysis based on ACAS criterion), and

2. Plaque morphology characteristics (using B-mode): plaque structure and plaque surface characteristics.

According to Gray Weale classification there are four different carotid plaque types: I. lipid (echo lucent with thin echogenic cap), II. lipofibrous (substantially echo lucent), III. fibrolipid (dominantly echogenic) and type IV. fibrous (homogenous echogenic) (21).

Following primary and before secondary examination two groups of patients were defined: the examined with carotid artery stenosis $\geq 60\%$ (40 patients), and the controlled ones with carotid artery stenosis $< 60\%$ (69 patients). These two groups were compared in terms of atherosclerosis risk factors, carotid bruit, peripheral vascular disease severity (previous vascular operation, ASPI value, and clinical stage of the disease).

Statistical analyses consist of the Student t-test, χ^2 test. Probability that different factors independently influenced the presence of carotid artery stenosis was estimated with multivariate logistic regression analysis. The results were considered significant if $p < 0.05$.

RESULTS

Haemodynamic characteristics of the carotid artery stenosis were examined by means of duplex scan (Doppler signal and spectral analysis) in patients with atherosclerotic occlusive disease of the lower extremities. Diameter stenosis of the dominant affected carotid artery is shown in table 1.

Table 1. Diameter stenosis of the dominant affected carotid artery in the examined 109 patients with atherosclerotic occlusive disease of the lower extremities

Diameter stenosis (%)	Number of patients (%)
≤ 49	57 (53)
50-59	12 (11)
60-69	8 (7)
70-79	11 (10)
80-99	12 (11)
Occlusion	9 (8)

In 40 patients (36.69%) there was a haemodynamically significant carotid artery stenosis $\geq 60\%$ or occlusion, and in 32 patients (29%) stenosis $\geq 70\%$ or occlusion.

By means of B mode morphologic characteristics of the plaque, which led to stenosis of 50 - 99% of the dominant affected carotid artery, were examined: 1. structure of the plaque and 2. surface of the plaque. The majority of the plaque belonged to the fibrolipid 19 plaques (44.18%), followed by the equal number of lipofibrous and fibrous in 10 (23.26%), whereas the least frequent was lipid plaque in 4 (9.30%) patients. Plaque surface was irregular in 25 patients (58.14 %), ulcerated in 10 (23.26 %) and smooth in 8 (18.60 %). As the frequency of asymptomatic carotid stenosis in patients with atherosclerotic occlusive disease of the lower extremities is high, secondary analysis is performed in order to answer the following question: if the limited screening of the asymptomatic carotid artery stenosis to the specific subgroups of patients is worthwhile. The relation of atherosclerosis risk factors and asymptomatic carotid stenosis $\geq 60\%$ in 40 patients is depicted in the table 2.

Table 2. Coexistent medical risk factors and their association with carotid stenosis of $\geq 60\%$ in 40 patients (N=40)

Risk factor	No (%) of patients	P value
Male	31 (78)	0.514
Arterial hypertension	36 (90)	<0.01
Smoking	25 (62)	0.07
Diabetes mellitus	13 (32)	0.202
Hiper/dislipidemia	17 (42)	0.42
Age over 60 years	35 (88)	<0.01

Asymptomatic carotid artery stenosis $\geq 60\%$ in patients with atherosclerotic occlusive disease of the lower extremities is accompanied with the age over 60, arterial hypertension, whereas this relation is not present in the following subgroups: male, lipid abnormality, smoking, and diabetes mellitus. Multivariate logistic regression analysis did not reveal significant correlation with asymptomatic carotid stenosis $\geq 60\%$, either in patients older than the age of 60, or with arterial hypertension.

Out of 40 patients with asymptomatic carotid stenosis $\geq 60\%$ carotid bruit was presented in 35, which was statistically significant ($p < 0.001$). Multivariate logistic regression analysis confirmed this correlation ($t = 0.50$; $p = 0.01$).

The severity of peripheral vascular disease was examined through previous vascular operations, ASPI, and clinical stages of the disease. Out of 40 patients with asymptomatic carotid artery stenosis $\geq 60\%$, 25 (62.5%) underwent some surgical intervention

related to arterial disease of the lower extremities, which is statistically significant; 28 patients (70%) had ASPI lower than 0.50, which is statistically significant as well ($p < 0,001$). Asymptomatic carotid artery stenosis 2: 60 % was present in 5 patients with claudication, in 28 with rest pain, and in 7 with ulcer or gangrene which is not statistically significant.

DISCUSSION

It is a well-known fact that annual rate risk for TIA, RIND, or frank stroke in patients with asymptomatic carotid artery stenosis depending on stenosis severity and plaque characteristics is 5 – 18% (22, 23). On the other hand, vascular surgeons perform carotid endarterectomy for asymptomatic stenosis with low mortality and morbidity rate (0 – 3 %) (24, 25). Two large multicentric prospective studies (Department of Veterans Affairs Hospital Carotid Trial and ACAS) revealed the advantages of surgical treatment of carotid artery stenosis in comparison with the best medical treatment (17, 18). Taking this into account it is indispensable to define a rational approach to early detection of asymptomatic carotid stenosis. General population examination aimed at early detection is ineffective and very expensive (20). Therefore, it is worthwhile to define the subgroups of patients with high risk for significant asymptomatic carotid artery stenosis (2, 4, 20). This fact is emphasized in countries with low health budget, especially in those in transition.

The frequency of asymptomatic carotid artery stenosis. It is well-known that one in four patients with the lower extremity ischaemia has carotid artery stenosis ≥ 70 %. Ahn and associates from UCLA analyzing 91 duplex scan of carotid arteries in 78 patients with the lower extremity arterial disease found out carotid artery stenosis ≥ 50 % in 15 patients (19%). This analysis did not include patients with carotid bruit, abnormal carotid artery pulses, or focal neurologic symptoms (10). Klop and coworkers detected significant carotid artery stenosis ≥ 75 % in 64 patients (15 %) out of 416 examined with peripheral arterial disease (26). Gentile and coworkers reported carotid artery stenosis equal or greater than 50% or occlusion in 28.4% of 225 patients surgically treated for lower limb ischaemia (11).

The frequency of 36.69% of patients with carotid artery stenosis greater than 60% in our group of patients is rather high, but could be explained by several facts. 83% of patients were with critical limb ischaemia. The aforementioned studies included patients with aneurysmatic disease, as well as patients with functional ischaemia (10), or in more than one third of patients with functional ischaemia (11).

The presence of risk factors in our patients was extremely high: smoking cigarettes in 81 % of patients, arterial hypertension in 76%, and diabetes mellitus in 40%, hyper/dyslipidemia in 31%. More than one half of patients were previously treated for peripheral arterial occlusive disease with some surgical procedure (by pass, sympathectomy or amputation), in 35% of patients surgical procedure or PTA was performed.

Carotid artery diameter stenosis. The "golden standards" in diagnosing carotid artery occlusive disease (arteriography, DSA), due to its being invasive, are not easily applicable (27). Due to good characteristics of examination: high sensitivity, the fact that it can frequently be repeated (and also being inexpensive), duplex scan ultrasound examination is considered just as good as angiography (26, 28). Moreover, the level of stenosis is precisely defined: in 28.4% of 109 patients internal carotid artery stenosis greater or equal than 70% is present within 2 cm of its origin. In 16% of patients the same degree of carotid bifurcation stenosis is present. High frequency of significant carotid artery stenosis in patients with atherosclerotic occlusive disease of the lower extremities imposes the necessity for routine carotid artery ultrasound examination.

Morphological characteristics of carotid artery stenotic lesions. B-mode of duplex scan ultrasound examination reveals morphologic characteristics of carotid artery plaques. The study, which compared morphological characteristics of 252 symptomatic and 260 asymptomatic neurologic patients with carotid artery stenosis, showed a greater number of lipid (echolucent) plaques in symptomatic patients, whereas the plaque surface was not very much different (29,30).

In our analysis of 43 plaques in neurologic asymptomatic patients with carotid artery stenosis from 50 to 99%, we found that the majority of them were fibrolipid (44.18%) and fibrous (23.26%). This is in accordance with the widespread opinion that dominantly lipid plaque structure (type II and I) makes the plaque instable, leads to complicated plaque (fissure, thrombosis, or intraplaque hemorrhage) and the appearance of symptoms (28-30).

The plaque surface examination showed that the greater number of plaques had irregular (58.14% of patients), or ulcerated (23.26%) surface. It is highly significant that one half of ulcerated plaque was present in patients with diameter of carotid artery stenosis from 50 to 60%, which was a permanent danger for thrombosis and embolic events developments. This fact additionally puts the stress on the necessity of early carotid artery stenosis detection with a specific emphasis on plaque surface examination.

Risk factors. Risk factors identification enables their modification (cigarette smoking, arterial hypertension, hyperlipidemia). Furthermore, identification is of great importance because of: 1. the influence of risk factors as a determining factor for development of asymptomatic carotid stenosis in patients with atherosclerotic occlusive disease of the lower extremities, and 2. limiting screening of asymptomatic carotid artery stenosis in patients with atherosclerotic occlusive disease of the lower extremities could be obtained in the subgroup of patients with specific risk factor.

There were a lot of risk factors in patients with atherosclerotic occlusive disease of the lower extremities and asymptomatic carotid artery stenosis. Our results showed that asymptomatic carotid artery stenosis equal or greater than 60% in patients with atherosclerotic occlusive disease of the lower extremities is significantly associated with patients over 60 years of age, and arterial hypertension. Neither of the two factors is independent of asymptomatic carotid artery stenosis (assessed through multivariate logistic regression analysis). Furthermore, there were 12.5% of patients under 60 years of age with carotid artery stenosis equal or greater than 60%, which points to the fact that carotid artery stenosis could be identified in patients under 60 years of age. That is the reason why limiting screening of asymptomatic carotid artery stenosis in the subgroup of patients with specific risk factor is not effective (6, 11, 31).

Asymptomatic carotid bruit. Results of the Framingham study showed that mortality caused by stroke in patients with asymptomatic carotid bruit was 1.9% (32). Various authors, depending on peripheral vascular disease characteristics, indicated different frequencies of asymptomatic carotid artery bruit from 25-45% (7, 11).

In our study of 109 patients with atherosclerotic occlusive disease of the lower extremities asymptomatic carotid bruit was present in 57 subjects (52.29%). Almost in 70% of patients moderate or rough bruit was detected on both sides. Asymptomatic carotid bruit is significantly associated with atherosclerotic occlusive disease of the lower extremities estimated by univariate and multivariate analysis. However, sensitivity (to reveal the existing disease) was 67%, and specificity (neither disease was present, nor bruit was detected) was 56%. According to this limiting screening of asymptomatic carotid artery stenosis in the subgroup of patients with asymptomatic carotid bruit is unreliable and ineffective. In that way, nearly one third of patients would be excluded from the early detection of asymptomatic carotid artery stenosis.

The severity of atherosclerotic occlusive disease of the lower extremities. The severity of the lower extremity arterial occlusive disease was estimated through; 1. previous vascular procedures on arteries of

the lower extremities, 2. ASPI (ankle-systolic pressure index) and 3. clinical stage of disease (Fountain classification).

The presence of previous operations confirms the evolutive course of atherosclerosis, which results in new hospitalization. Different authors state the frequency of previously peripheral vascular operation ranging from 15 do 41 % (7,11). 62% of patients with carotid artery stenosis equal or greater than 60% underwent previous peripheral vascular operation, which is statistically significant. This significance is not confirmed with multivariate logistic regression analysis. In other words, early detection of asymptomatic carotid artery stenosis in the subgroup of patients with previous vascular operation is not effective.

ASPI values were in accordance with clinical stage of the lower extremity arterial occlusive disease (33). Limiting screening of carotid artery stenosis to the subgroup of patients with ASPI less than 0.5 showed 71 % of sensitivity, 14% of specificity, 27% positive predictive value, and 53% negative predictive value. In other words, the probability that carotid artery stenosis in 50% of patients with ASPI less than 0.5 does not exist. Limiting screening of asymptomatic carotid artery stenosis to the subgroup of patients with ASPI less than 50% is not effective.

The estimation of clinical stage is the most available method in determining severity of peripheral vascular disease. Neither univariate nor multivariate analysis revealed association between asymptomatic carotid artery stenosis and the stage of peripheral vascular disease. Limiting screening of carotid artery stenosis for the subgroup of patients with rest pain, or ulcer, or gangrene is not effective (7,9-11,26).

CONCLUSION

1. The frequency of asymptomatic carotid artery stenosis equal or greater than 60% in patients with atherosclerotic occlusive disease of the lower extremities is 37%; whereas carotid artery stenosis is equal or greater than 70% is 29%.

2. Limiting screening of significant carotid artery stenosis in neurological asymptomatic patients with symptomatic atherosclerotic occlusive disease of the lower extremities to the subgroup of patients with risk factors (male, over 60 years of age, arterial hypertension, diabetes mellitus, cigarette smoking, dyslipidemia), carotid bruit, ASPI values less than 0.5, previous vascular operation is not effective.

3. Screening of asymptomatic carotid artery stenosis is indicated in all patients with atherosclerotic occlusive disease of the lower extremities, except in those where prophylactic carotid endarterectomy is not recommended due to comorbid diseases or very old patients.

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DA LI JE RANO OTKRIVANJE ASIMPTOMATSKE KAROTIDNE STENOZE KOD BOLESNIKA SA PERIFERNOM VASKULARNOM BOLESTI EFIKASNO?

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SAŽETAK

Cilj rada je da se utvrdi učestalost asimptomatske karotidne stenozе kod bolesnika sa aterosklerozom arterija donjih ekstremiteta i da se odgovori na pitanje da li je ograničeno rano otkrivanje asimptomatske bolesti na pojedine podgrupe bolesnika efikasno. Ispitivanje je obuhvatilo grupu od 109 bolesnika sa obliterantnom aterosklerozom donjih ekstremiteta. Kod svih bolesnika je na osnovu kriterijuma ACAS studije sprovedeno skeniranje kolor Dopplerom. Kod 36.69% bolesnika otkrivena je hemodinamski značajna stenozа $\geq 60\%$ ili okluzija, a kod 29% bolesnika stenozа $\geq 70\%$. Morfološke karakteristike plaka sagledane su na arterijama 43 bolesnika sa stenozom karotidne arterije od 50 do 99%. Kod najvećeg broja bolesnika bio je prisutan fibrolipidni (kod 44.18% bolesnika) i fibrozni plak (23.26%). Kod 58.14% plakova površina je bila iregularna, kod 23.26% ulcerisana. Naknadno ispitivanje imalo je za cilj da utvdi da li postoji povezanost asimptomatske karotidne stenozе $\geq 60\%$ ili okluzije, i pojedinih karakteristika bolesnika sa obliterantnom aterosklerozom donjih ekstremiteta. Univarijantnom analizom pokazana je udruženost hemodinamski značajne stenozе karotidnih arterija i prethodnih vaskularnih operacija, starosti preko 60 godina, arterijske hipertenzije, pedobrahijalnog indeksa (ABI) manjeg od 0.5 i karotidnog šuma. Primenom multivarijantne logističke regresione analize ova udruženost se održava samo za karotidni šum ($t = 0.50$; $p = 0.01$), pri čemu je senzitivnost 67%, a specifičnost 56%. Stoga se može zaključiti da ograničenje ranog otkrivanja karotidne stenozе kod neurološki asimptomatskih bolesnika sa simptomatskom aterosklerozom donjih ekstremiteta na pojedine podgrupe bolesnika nije efikasno i nema opravdanja.

Ključne reči: asimptomatska karotidna stenozа, prevalenca karotidne stenozе, obliterantna ateroskleroza donjih ekstremiteta