Cerebrovascular Events: Correlation with Plaque Type, Velocity Parameters and Multiple Risk Factors

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Purpose: Cerebrovascular events (CVE) are the third most common cause of death in Western countries and about 65-70% of CVE are due to atherosclerotic disease of carotid arteries. Color Doppler scanning is used to evaluate the presence, severity and type of atheromatous plaques as well as velocity parameters of carotid arteries. We performed this study to correlate data of morphological and velocity parameters with clinical variables in patients following CVE. Methods: We included total of 211 pts who had CVE, 118 females, 93 males, mean age 71,1± SD 12,5 years. Out of total number of pts (n=211) 93 pts had transient ischemic attacks (TIAs), 49 had recurrent TIAs (rTIAs), 44 had ischemic stroke (IS), and 25 had recurrent IS (rIS). As a control group we took 50 pts without CVE but with at least three multiple risk factor (MRF). Morphological parameters were; plaque composition and echogenecity. Velocity parameters were: peak-systolic velocity (PSV) and end-diastolic velocity (EDV). The following MRF were evaluated: age, gender, hypertension, tobacco smoking, hyperlipidemia (total cholesterol and LDL-cholesterol), obesity, and diabetes mellitus. Examination was performed on CCA/ICA segment. Results: We found significant presence of heterogeneous plaques in TIAs and rIS subgroup, p<0,014, and borderline significance for the rTIAs and IS subgroups, p<0,04. We found significant difference in PSV in TIAs and rTIAs subgroups vs. controls (PSV 103 cm/s vs. PSV in controls 87 cm/s, p<0,01). Decreased EDV, below 20 cm/s, was found in all subgroups, p<0,01, while EDV, below 16 cm/s, was found in IS and rIS subgroups. MRF score of CVE group was 4,34 vs. 3,65 in controls, p<0,012. We found significant correlation (95% CI) of tobacco smoking, obesity and arterial hypertension with presence of heterogeneous plaques, p=0,0069. Interestingly, hyperlipidemia showed no correlation with heterogeneous plaques, p=0,027. Conclusions: (i) in CVE group we found significant presence of heterogeneous plaques in TIAs and rIS subgroups, (ii) in the pts with TIAs and rTIAs events we found significant increase in PSV, (iii) EDV below 16 cm/sec was a significant single predictor of IS and rIS events, (iv) MRF score was significantly increase in the pts with CVE compared to controls, but between CVE subgroups there was no significant difference. Key words: cerebrovascular events, symptomatic carotid disease, plaque, velocity parameters, risk factors

1. INTRODUCTION

Cerebrovascular events (CVE) are the third most common cause of death in Western countries and about 65-70% of CVE are due to atherosclerotic disease of carotid arteries. Worldwide stroke is the second leading cause of death, estimated to burden up to 5 million patients per year. Approximately 60 to 65% of cerebrovascular events are due to thromboembolic complications from extracranial arteries. The anatomic distribution is as follows: carotid bifurcation 38%, intracranial 33%, arch-brachial 9% and proximal vertebral up to 20%. Data reports that in the population over the age of 65 years, and with presence of hypertension and/or tobacco smoking, and/or hyperlipidemia, nearly 20% have asymptomatic carotid disease (1,2,3). What we have in our everyday clinical practice is a number of patients who experienced cerebrovascular events, without any previous signs of carotid atherosclerotic disease (atherosclerosis or atherothrombosis, or significant changes in lumen diameter) but with some borderline changes in systolic/diastolic velocity parameters and moreover with atherosclerotic changes on common carotid and internal carotid arteries (4,5).

Asymptomatic atherosclerotic carotid disease arise as a problem since it leads to variety of complications. On the other hand, there are very few data comparing morphological changes of artery wall, velocity parameters and clinical variables in patients without significant stenotic or occlusive carotid
disease but with previous cerebrovascular events. (6,7,8) Duplex ultrasound scanning is used to evaluate the presence, severity and type of atheromatous plaques as well as velocity parameters of carotid arteries. We are aware that intimal thickening and hardening or calcification of the arteries has a number of variability or spectrum of disease. Yet, we decided that in our study defined two basic types of atheroplaques, homogeneous atheroplaque and heterogeneous atheroplaque. Detection, delineation, and measurement of atherosclerotic changes of arterial wall, homogeneous or heterogeneous plaques, is now critical in order to prevent and cerebrovascular events i.e. transient ischemic attacks or ischemic strokes and to maintenance therapy. It is of most important to identify and evaluate these patients (4,5,9,10,11,12,13).

There are very few studies correlating atherosclerotic changes of carotid arteries and their velocity parameters to multiple risk factors (MRF); age, gender, arterial hypertension, tobacco smoking, hyperlipidaemia, obesity, diabetes mellitus. In the last decade focus was on peak-systolic velocity, pulsatile index and various combination of CCA/ICA ratios, including PSV ACI/PSV ACC ratio, and PSV ACI/EDV ACC ratio. Commonly, EDV was not used in studies on grading the carotid stenosis. (14,15,16,17,18,19,20).

2. AIM
   We sought to identify risk factors in patients following CVE i.e. to identify atherosclerotic lesions and to correlate those data to velocity parameters and multiple risk factors in post-CVE patients.

3. METHODS
   We identified risk factors from medical history, baseline clinical profile and diagnostic procedures. We included total of 211 patients (pts) who had CVE, 118 females 59.9%, 93 males, mean age 71,1± SD 12.5 years. Out of total number of pts (n=211) 93 pts had transient ischemic attacks (TIAs), 49 had recurrent TIAs (rTIAs), 44 had ischemic stroke (IS), and 25 had recurrent IS (rIS). All patients were without haemodynamically significant carotid atherosclerotic disease i.e. stenosis or occlusion. As a control group we took 50 pts, all without previous CVE but with at least three multiple risk factor (MRF). (Figure 1, 2).

   Morphological parameters were: plaque composition and echogenicity. In our study we defined two basic types of atheroplaques, homogeneous atheroplaque and heterogeneous atheroplaque. Homogeneous atheroplaque we defined as hypoechogenic capped fatty deposits (also called atheromas) that extend into the lumen of the artery, causing the artery to narrow but without roughened plaque surface. Heterogeneous plaque we defined as combination of hypoechogenic and hyperechogenic changes i.e. fatty deposits and calcium deposits, with irregular roughened surface of the plaque. Subtype of this heterogeneous plaque is those with ulcerated surface. (9,10,11,12,13)

   Moore and colleagues, classified asymptomatic ulcers without associated hemodynamically significant stenosis by their two-dimensional area on lateral arteriography: type A lesion; less than 10 mm2, type B lesion; 10-40 mm2, type C lesion- more than 40 mm2. In our study we used this classification by Duplex ultrasound. (2)

   Velocity parameters were: peak-systolic velocity (PSV) and end-diastolic velocity (EDV). Examination was performed on CCA/ICA segment. We evaluate haemodynamic parameters: peak-systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI) and resistive index (RI). Color Doppler examination was performed on CCA, haemodynamic parameters were took from the distal portion of CCA, and we took the mean value of both CCA.

   The following MRF were evaluated: age, gender, hypertension, tobacco smoking, hyperlipidaemia (total cholesterol and LDL-cholesterol), obesity, and diabetes mellitus. Score of multiple risk factors was calculated as x/7 (one point for each clinical variable [x/7], which is the simplest approach to scoring a multiple risk factors.

4. RESULTS
   We had a high-risk group of patients who experience cerebrovascular events: out of the 211 patients who experience a CVE event, 91 patients had transient ischemic attacks (TIAs) (43,1%), 49 patients had recurrent TIAs (23,2%), 44 patients had ischemic stroke (IS) (20,8%), and 25 patients had recurrent IS (11,8%).

   U CVE group we found both, heterogeneous and homogeneous plaques, in 72 patients, which is 34,1% out of total group. In CVE subgroups we found significant presence of heterogeneous plaques in TIAs and rIS subgroup, p<0,014, and borderline significance for the rTIAs and IS subgroups, p<0,04. (Figure 3, 4).

   We used Moore classification in Duplex ultrasound examination, and...
found 1 patient with C lesion and 3 with B lesions in TIA subgroups, and 5 patients with B lesions in rTIA subgroups, which is of no significance.

Velocity parameters in the subgroup of patients with TIA (N=93) were as follows: PSV 105 cm/sec, and EDV 19.0 cm/sec, in the patients with rec-TIA (N=49) PSV was 102 cm/sec, and EDV 16 cm/sec, with IS (N=44) PSV was 84 cm/sec, and EDV 14 cm/sec, and in the patients with recIS (N=25) corresponding figures were 87 cm/sec, and 14 cm/sec, respectively. In Controls PSV was 91 cm/sec, and EDV 24 cm/sec, respectively. Intra-observer variability for PSV in our vascular laboratory is 5-7 cm/sec, and for EDV 3-5 cm/sec.

We found significant difference in PSV in TIA and rTIA subgroups vs. Controls (PSV 103 cm/sec vs. PSV in controls 91 cm/sec, p<0.01). Decreased EDV, below 20 cm/s, was found in all subgroups, which is comparing to Controls, p<0.01. EDV, below 16 cm/s, was found in IS and rIS subgroups (Figure 5). Clinical variables of multiple risk factors were highly positive – male gender 93 pts. (44%), age>55 yrs. 85 pts. (68.7%), with HTA 104 pts. (49.3%), tobacco smoking 101 pts. (47.9%), obesity (BMI) 87 pts. (41.2%), HLP 75 pts. (35.5%), and diabetes mellitus 59 pts. (30.3%). An average score of MRF in CVE group was 4.34, and 3.65 in Controls (Figure 6). MRF score of CVE group was 4.34 vs. 3.65 in controls, p<0.012, while MRF score in IS and rIS subgroups vs. TIA and rTIA was 4.51 vs. 4.34 vs. 4.51, NS, p=0.14. We found a significant correlation (95% CI) of tobacco smoking, obesity and arterial hypertension with presence of heterogeneous plaques, p=0.0069 (Figure 7). Statistical analysis: comparison of variables was achieved using analysis of variance ANOVA, and for paired samples Student’s t-test. Fischer exact test was used to compare differences in variables.

5. DISCUSSION

Duplex ultrasound is the first-line modality which can identify the degrees of carotid atherosclerotic disease and delineate characteristics of athero-plaque changes. Velocity analysis and spectral analysis of Doppler waveform can suggest proximal and distal narrowing of lumen or hardening the artery wall. Homogeneous athero-plaque, especially in the case of thin fibrous cap, can burden and cause athrothrombotic emboli. Heterogeneous athero-plaque, especially with roughened surface, can also lead to fibrin or platelet emboli and cause CVE events. Carotid atherosclerotic disease and several other conditions—cardiac output, arterial (hyper)tension, central regulation, and vasospasm are preconditions to cerebrovascular events in more than 75-80% of all cases. However, each of these conditions alone, or in coexistence, can lead to cerebrovascular events (21,22). We found a high percentage of atheroplques in our group of patients, out of N=211 there were 72 (34,1%) those with both, homogeneous and heterogeneous, atheroplaques on carotid arteries and there is a clear prevalence of heterogeneous plaques. Analysing CVE subgroups we found that TIA and IS subgroups has significantly higher percentage and probability value of heterogeneous vs. homogeneous athero-plaque. We also tried to identify ulcerated plaques but Duplex ultrasound method has some limitations because natural history of asymptomatic ulcerated carotid lesions is not easy to define. Carotid ulceration is difficult to detect with duplex ultrasound and is usually large when seen with this modality. This imaging technique can define plaque morphology homogeneous vs. heterogeneous, but this characteristics in some of the cases do not correlate with surface of the plaque. However, duplex ultrasound despite of its limitation seems to be more accurate in defining plaque surface than arteriography. Ulceration may vary from a slight nonstenotic changes to complicated ulcerated stenosis. Moore and colleagues classified asymptomatic ulcers without associated hemodynamically significant stenosis by their two-dimensional area on lateral arteriography: Type A; less than 10 mm2, Type B; 10-40 mm2, type C-
more than 40 mm². A and B type of lesions has a yearly risk of stroke from 0.5% to 4.5%. C ulcers has yearly risk more than 7.5% and it’s recommended for CEA. We used Moore classification in Duplex ultrasound examination, and found 1 C lesion, and 8 B lesions, and none of A lesions (2,3,7,8). Commonly used parameter in ultrasound studies is value of peak-systolic velocity. The fact that diastolic velocity, expressed as an end-diastolic velocity on common carotid or internal carotid artery was not in focus of haemodynamic studies, or some authors use it only as a marker for ICA stenosis. Thus, we have very few studies investigating this haemodynamic variable (2,11,16). The results of this study showed the association between PSV and cerebrovascular events including their severity. There is also association of low EDV, below 20 cm/sec, with the degree of cerebrovascular events i.e. the degree of low EDV was related to the CVE subgroups TIA’s, recurrent TIA’s, IS, recurrent IS. These results correspond to those of Bai CH et al. (16), as they found that low end-diastolic velocity, high resistance index and increased diameter of carotid arteries was a better predictor of ischemic stroke than of the extracranial carotid atherosclerosis (16). In Sarajevo Vascular Study, performed on a larger sample (n-275), we found strong correlation of CCA IMT and cerebrovascular events. This corresponds to the number of studies (12). Other authors found, however, significant correlation between IMT CCA and resistive index of ICA (16,20,22). Decreased EDV (below 20 cm/sec) revealed to be significant for CVE events compared to controls, and IS. In our patients with cerebrovascular events, age, hypertension, smoking, obesity, were the most potent predictors of CVE. While the obesity and CVE risk is well understood, the relationship between arterial hypertension and tobacco smoking appear to be value related, is generally a consequence of significant arterial hypertensin degree and significant daily consumption of cigarettes. In conclusion, we found significance for the following variables: age, hypertension, smoking, hyperlipidemia, obesity (23,24,25).

This study, however, has certain limitations, first cardiogenic embolism as well as blood pressure may play a significant role in the development of cerebrovascular events. Second, the diagnosis of cardiogenic embolism is based on a variety of tests, which were not performed on our patients. Third, although all patients had a CT or MRI diagnostics, intracranial angiography was not performed for all of them. However, we performed TCD. Fourth, intra-observer variability for PSV was 5-7 cm/sec, but it is still approx. 8% of PSV values in, for example, patients with rec.TIAs. (26)

Clinical implications: this analysis can be useful in identifying patients with increased cerebrovascular events risk potentially leading to increase vigilance with regards to cerebrovascular events outcome. Our analysis included a diverse population of post-CVE patients, not restricted to those undergoing surgical or interventional procedures, thus providing a broader perspective of the problem and allowing a better identification of patients who might benefit for therapeutic and preventive measures. (25,26,27,28)

6. CONCLUSIONS

In our CVE group we found significant correlation of heterogeneous plaques with TIA’s and IS type of CVE events. In patients with TIA’s and IS events we found significant increase in PSV. We found that EDV below 16 cm/sec was a significant single predictor of IS and IS events. MRV score was significantly increased and correlated with CVE events compared to controls, but between CVE subgroups there was no significant difference.

REFERENCES