”Ovidius” University of Constanta
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PhD Thesis

Clinical, ultrasonographic and imagistic correlations between the atheromatosis of cervical vessels and ischemic strokes

ABSTRACT

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ABSTRACT

Atherosclerosis represents a systemic disease of the arteries, multi focal, insidious, affecting medium and large arteries by depositing lipid, fibrous and mineral material in the arterial wall. This process is a dynamic one, which may know acceleration or stagnation, being influenced by certain factors of risk and it may even be improved by specific medication.

In industrialized countries, atherosclerosis and its complications are the major cause of mortality and disability by myocardial infarction, and due to the stroke they produce. Atherosclerosis accounts for approximately 35-40% of deaths in these countries. It is very important that atherosclerosis does not cause significant events, the plaques' disruption being the one leading to pathological events with impact on health.

Atherothrombosis is progressive and diffuse, characterized by atherosclerotic plaque rupture leading to thrombus formation and platelet activation with significant consequences (myocardial infarction, stroke or vascular death).

This paper aims at providing prognostic factors of stroke up occurrence (imagistically confirmed) in patients with cervical vessels atheromatosis, identified by ultrasonography examination.

The thesis is structured on the classical model, having a general part and a specific one of personal research, to which, a chapter of conclusions is added.

The general part comprises three chapters and several subchapters. The first part deals with atherosclerosis (definition, history, risk factors, pathogenesis, endothelial dysfunction, atherosclerotic plaque).

The second chapter is reserved to stroke, epidemiology and mortality as reference.

The third chapter of the general part covers the anatomy, including vertebral and carotid artery hemodynamics as well as the cervical ultrasonography of the cerebral arteries according to well established criteria.

The special part includes personal research, motivation and research objectives, work material and method. A final chapter is devoted to the results and conclusions. The purpose of this paper is the identification and the role of carotid and vertebral atherosclerotic changes in the occurrence of spinal ischemic stroke. The ischemic cerebral-vascular disease is a constant challenge for the clinician. Ultrasound carotid-vertebral brings valuable information in determining the aetiology and therapeutic conduct regarding the patient with increased

cardiovascular risk. Of the many patients with carotid atheromatosis of varying degrees of damage, only some make strokes at a certain time.

Carotid atherosclerosis is a condition with an increasing spreading and whose many aspects are difficult to follow by an ordinary clinician. The existence of certain identifying and tracking criteria are necessary to establish clinical relevance.

Stroke remains a continuing debate and a significant public health problem, with consequences for the patient but with different major global risks for disability and death. Last but not least, the work aimed at identifying the carotid and vertebral atheromatosis model the most vulnerable for stroke developing, or lacunar ictus.

The objectives of this paper are as follows:

1. correlation between the presence of carotid atheroma and the first ischemic stroke;
2. determining the predictive model for stroke occurrence and carotid atheroma;
3. correlation between stroke and spinal atheroma;
4. identifying other predictive factors for carotid atheroma association with ischemic stroke ;
5. presence of carotid atheroma association with lacunar ictus.

Material and method

Atherosclerosis of cervical vessels, particularly the carotid one, a major factor for cerebral ischemia, is the research subject of my PhD. thesis.

The overall objective of my work was to determine the correlation between paternal carotid atherosclerosis revealed by the cervical – cerebral ultrasonography and the vascular ischemic stroke and lacunar ictus. We note that the primary endpoint was referring in our study at the occurrence of the first stroke.

The objectives pursued have been as follows:

1. identification of patients with constituted ischemic stroke, and those with lacunar ictus,
2. calculating the intimate - average index,
3. identifying and stabilizing atherosclerotic plaques,
4. counting of atherosclerotic plaques,
5. identifying carotid stenosis,
6. correlation between intimate - average index and the appearance of plaques,
7. correlation between intimate - average index and the degree of stenosis,

identifying other imaging markers (leukoaraiosis, cerebral abiotrophy calcifications of intracranial arteries) which might arise in the first prediction stroke.

The main criteria for study inclusion was the presence of neurological symptoms or suspicion of stroke.

Exclusion criteria have been:

a. another type of vascular disease identifiable by ultrasonography - Takayasu vasculitis, fibro-muscular dysplasia, carotid artery or vertebral artery dissection;
b. the existence of atrial fibrillation, both the paroxysmal and permanent one;
c. the existence of another type of stroke as well as the haemorrhagic one;
d. cerebral tumours, arteriovenous cerebral or cavernous malformations;
e. other possible causes of stroke - atrial tumours;
f. any type of known neoplasia;
g. lack of atheromatosis changes specified in the ultrasonography ;
h. a history of transient ischemic stroke – I have considered that it is a quite heterogeneous entity, clinically speaking and most often medically undocumented.

The study carried out was an observational and analytic study and during the period July 2013 - June 2014, it comprised 159 patients from specialized outpatient units. These patients were examined under cervical-cerebral extra-cranial ultrasonography by an independent examiner, using a Philips HD 15 ultrasound, equipped with a 7.5 MHz transducer.

The patients underwent a demographic questionnaire and they were referred to a cranial-cerebral CT examination, native examination with a multislice spiral device.

According to demographics, verifying the exclusion criteria, patients were examined by means of ultrasonography in a standardized manner by a single examiner.

Both carotid arteries axes, common carotid, internal and external and vertebral arteries have been examined.

Patients were examined according to the same protocol of examination, namely:

- intimate average index calculation, at the level of the common carotid artery, with manual method and complying to the Mannheim criteria;
- examining the carotid, common internal and external arteries in the longitudinal and cross-section;
- identifying atherosclerotic plaques, counting them, their location, and classification according to the same Mannheim criteria.

As for the examiner, plaques identification according to the Gray Weale classification is cumbersome being thus possible only in research laboratories, therefore I have limited the category of atherosclerotic plaques in three categories: hypoechogenyc

or fibre lipid plaques, mixed plaques (of heterogeneous appearance, including hypoechoic and hyperechoic areas in random proportions) and calcified plaques, hyper-echogenic.

The extent and volume of plaques, although validated as a risk factor for stroke, were not the subject of my research.

Although many studies and even ultrasonography labs consider external carotid artery insignificant, we have examined these branches of the carotid axis with the same accuracy:

- carotid stenosis identification and quantification by using the Duplex method and internationally validated velocimetry criteria;
- identifying stenosis or occlusion of vertebral artery.

Upon CT examination, we have excluded other cerebral pathologies compared to the primary endpoint, thus defining stroke as a super sub sub-tentorial, more than 1.5 cm in diameter, cortical, subcortical, or to the border

Lacunar stroke defined as being hypo-density of up to 15 mm in size with unilateral or bilateral location.

Also, at the CT examination, the presence of calcifications of the intracranial arterial wall have been recorded (make of atherosclerotic disease in the intra-cerebral vessels), the presence of leukoaraiosis and the presence of cerebral abiotrophy with inactive ex-vacuo hydrocephalus.

Identifying risk factors, highly debated in other works, was not the subject of this paper.

Statistical processing

Data obtained have been gathered in table format by using the Microsoft Excel application. Subsequently, they have been transferred to the IBM SPSS version 23 for the processing of the information obtained.

To highlight the main features we have used descriptive statistical analysis methods. Since the compared groups were not of equal size, we have reported the results as a percentage in order to provide a better picture of the distributions analysed.

For the analysis of the association between variables, we have used the chi-square test. If the conditions for the application of this test have not been met, we have used the plausibility test or, for the 2x2 contingency tables, the Fisher test. In this case, the actual size was assessed by the ratio rates (odds ratio).

In the case of continuous variables we have used descriptive statistical analysis methods. To compare the data we used parametric tests such as the t test or ANOVA test, and in cases where conditions for applying these tests have not been met, we have used nonparametric tests such as Mann-Whitney U and Kruskal-Wallis.

The threshold for the statistical significance that I have used is $p \leq 0.05$.

RESULTS AND CONCLUSIONS:

1. Carotid atheromatosis is an important ethiopathogenetic factor for ischemic cerebrovascular disease. Of the 159 patients enrolled in the study, 30 of whom representing 18,87% were diagnosed with ischemic stroke, imagistically confirmed.
2. Carotid atherosclerotic disease is of systemic nature, the affecting being in the entire artery of the carotid axis, atherosclerosis having as favourite location precisely this vascular axis compared to the vertebral one, the most likely explanations being of hemodynamic nature.
3. The existence of spinal atheroma could not be correlated to ischemic stroke, due to the small number of identified cases of the total of 159 patients. In fact, we have identified three vertebral artery occlusions, two located on the right side and one on the left, and only two vertebral artery stenosis less than 50%, located on the left. In this case, I failed to emphasize the link with the stroke in the posterior circulation. It must be noted that atherosclerotic disease is associated with vertebral and carotid disease and I have not identified isolated vertebral atherosclerosis without carotid damage.
4. The presence of atherosclerotic plaques in the carotid axis is associated with increased risk of ischemic stroke constituted of about 5 times compared to those without atherosclerotic plaque identified.
5. The study involved 159 patients, gender distribution is almost equal (49.49% women and 50.31% men). Risk of men with carotid atheroma is 3 and a half times more likely to develop ischemic stroke, the risk being maintained also after adjusting age and the intimate -average index.
6. The presence of atherosclerotic plaques in the carotid axis is associated with the increased risk of ischemic stroke, about 5 times more than those without atherosclerotic plaques identified by ultrasonography. In patients without atherosclerotic plaques a percentage of 5.7% developed a stroke, while in patients with present atherosclerotic plaques, a percentage of 22.6% developed a stroke. Although the appearance of plaques which was correlated with ischemic stroke was of mixed type, heterogeneous, this result was not statistically very significant. Male patients had a predilection for the type of mixed, heterogeneous plaques and this was highly statistically significant.
7. The position of the atherosclerotic plaques in the arterial anterior/ posterior/ bilateral wall is not associated with the risk of stroke and nor with the gender of the patients investigated.
8. Most patients of our study, patients with both ischemic stroke and those not belonging to the age group of 60-65 years old with a rate of 22.64%. There are no statistically

significant differences in terms of age and risk of ischemic stroke. Differences are observed for the age group 60-65 years old type, where the proportion of patients for males is 11.39% while for females this percentage is almost twice higher (21.25%). Significant differences in the distribution are also observed in patients less than 55 years old. If the percentage of males is 20.26%, for females is of 11.25%.

9. Atherosclerotic plaques are correlated with their age, appearance and the type of fibrocalculous plaque being the prerogative of the older age. It is noted that in patients with fiberlipid plaque, their average age is the lowest, of 61.82 years old, (S. D 7.33 years). Patients with mixed plaques have higher average age of 65.23 years old (S.D. 8.56 years), and patients with fibercalculous plaque, the mean age being the highest, reaching a value of 69.11 years old (S. D. 9,54 ani)
10. Although a quarter of the atheromatosis and stroke patients had increased intimate - average index, it was not statistically significantly associated with the occurrence of stroke. It is noted that within the group of stroke patients, the percentage of those with normal intimate-average index is of 56.67%, while in the group of patients without stroke, their percentage is 65.89%. The increased intimate – average index does not correlate with age ($r = 0.05$, $p = 0.529$), but it correlates with male gender. The average IMT value in male patients was of 1.44 mm (0.56 S.D.), while for females this was lower, 1.16 mm (S. D. 0,296).
11. Increased medium – intimate index is strongly associated with the presence of plaques, this combination is predictive for developing ischemic stroke. In the group of patients presenting atherosclerotic plaques, the average of IMT is 1.39 mm (0.72 mm S.D.), and in the group of patients with atherosclerotic plaques the average value is 0.983 mm (S. D. 0,28 mm).
12. The intimate average index is also associated to the type of plaque. The increased IMT predominates in patients with mixed plaques (62.3%), while in patients with a normal IMT value, the prevailing plaques are fibrocalculous. Increased IMT meets less than 2% of patients who have plaques of fibrocalculous appearance compared to those with a normal IMT value where the fibrocalculous plaques percentage is higher than 15%.
13. The presence of plaques in the common carotid artery, pre-bulbar, or their number is not correlated with acute ischemic stroke. There were no significant differences between the right and left. It is noted, however, that in the case of patients who developed stroke, the percentage of atherosclerotic plaques at the level of the pre-bulbar segment was of 40%, while in patients who have not developed a stroke, their rate was of 25.6%.
14. Locating the plaques at the carotid bulb level and number of plaques is being correlated with stroke, the risk increasing up to 4 times. It should be noted that 90% of patients diagnosed with stroke show such plaques, while in the case of patients undiagnosed with stroke, the atherosclerotic plaques percentage at bulbar level is significantly lower, 69%. Left carotid bulb plaques are often symptomatic compared to the right and are associated with stroke. The proportion of patients who develop atherosclerotic plaques in carotid bulb located just to the right is 12.6%, while that of patients who have atherosclerotic plaques in carotid to the left is only 11.3%. Almost half of patients (49.1%) have localized bilateral atherosclerotic plaques. The location is therefore quite the same on the left and on the right, confirming that atherosclerosis is systemic and symmetrical. The difference between

the left vulnerable plaques could be explained hemodynamically because at this level, the emergence of the common carotid artery is directly from the aorta level to the right, where the brachiocephalic trunk is located.

15. Plaques from the internal carotid artery are statistically significantly associated with stroke, the risk increasing of 3 times for right ACI and 4 times to the left. For patients diagnosed with stroke in my study, the proportion of those who have atherosclerotic plaques at ACI is 86.7% higher compared to the group who have not been diagnosed with stroke and the proportion of those with atherosclerotic plaques is of 55%. Regarding the presence of atherosclerotic plaques at right ACI, the proportion of the stroke patients group is of 66.7%, while in the group of patients without stroke is of 40.3%. Of all patients diagnosed with stroke, 80% present atherosclerotic plaques present at left ACI, the proportion being nearly two times higher compared to patients who were not diagnosed with stroke, 48.8%.
16. Bilateral location of carotid plaques is associated with the occurrence of ischemic stroke. The result of the study shows a 60% proportion of patients with atherosclerotic plaques bilaterally located in the case of those diagnosed with stroke. This result is significantly higher than that in patients without stroke.
17. The number of atherosclerotic plaques presented at the carotid arteries level is significantly associated with the occurrence of stroke. The more plaques there are, the higher risk it is. In the case of patients diagnosed with stroke, more than 63% have more than three atherosclerotic plaques, while in the group without stroke, patients with less than 3 atherosclerotic plaques reach 38.8%
18. Common carotid artery stenosis is associated with ischemic stroke. As far as right ACC stenosis is concerned, 36.6% of patients with stroke had stenosis, of which 3.3% stenosis above 50%. As for left ACC stenosis, we have obtained the same results. In patients without stroke, the percentage of stenosis is about two times lower (21.7%)
19. Carotid bulb stenosis, especially the left one, correlates with ischemic stroke. On the right carotid bulb, out of all patients with stroke, 43.4% had no stenosis, while in patients who have been diagnosed with AVC their percentage is 30%. Most of the stenosis is lower than 50%, less than 2% of patients without stroke, respectively 3.3% of patients with stroke having a degree of stenosis greater than 50%. The proportion of patients presenting stenosis of the left carotid bulb is 73.3%, significantly greater than the one recorded in patients without stroke, where their share is 51.9%. Most patients had stenosis lower than 50%, about 2% of patients without stroke and 7% of stroke patients having higher stenosis than 50%.
20. Internal carotid artery stenosis is significantly associated with the risk of ischemic stroke, and it increases with the degree of stenosis. On right ACI level, only 34.6% of patients diagnosed with stroke do not show a degree of stenosis, while in the group of patients without stroke their percentage is 60.5%. 50% of stroke patients present stenosis less than 50%, a rate of about 15% with stenosis higher than 50%. In patients without stroke, about 28% have stenosis lower than 50% and about 11% of them present stenosis higher than 50%. It is noted that the proportion of patients with stenosis <50% is approximately two times higher in patients diagnosed with stroke. This difference remains roughly constant with increasing degree of stenosis. The result is highly statistically significant between the

presence of stenosis in the right ACI and stroke occurrence. In the case of the left ACI stenosis recorded in the proportion of patients with stenosis in the group of patients with stroke it is of 76.3% compared to 48.8% in patients who have been diagnosed with stroke. More than 26% of stroke patients have shown a degree of stenosis higher than 50%, while in the case of AVC, a rate of 8.6% was recorded. The risk of stroke is associated with increased stenosis. Analysing this aspect only from the presence of stenosis, patients with stenosis have significantly higher risk of developing stroke.

21. Male gender is statistically significantly correlated with left carotid stenosis. On left ACI, the proportion of male patients presenting stenosis is significantly higher ($p = 0.026$). The presence of stenosis in male patients is two times higher compared to the risk of the presence of stenosis in female patients.
22. ACI occlusion, is not associated with ischemic stroke in this study, probably due to the small number of patients. Patients with ACI occlusion, but most of them, accounting for 80% (4 out of 5 patients) were diagnosed with stroke. Occlusions were identified as the location on the internal carotid artery on the left.
23. External carotid artery stenosis is significantly associated with stroke, regardless of the left and right location. The association between ACE stenosis on the right side and the risk of stroke is almost twice higher than in patients without stroke (53.3% and 26.4%). ACE risk patients with stenosis on the left to be diagnosed with stroke is almost three times higher, with a special statistical significance. (Odds Ratio = 2.952, 95% CI 1.308 to 6.663)
24. The presence of plaques on the carotid bulb, internal carotid artery and external carotid artery is correlated with the presence of lacunar stroke, regardless of the plaques type. The existence of atherosclerotic plaques in carotid arteries is correlated to the extent of more than 95% in patients with lacunar ictus imagistically confirmed. The risk of lacunar ictus in patients with atherosclerotic plaques in the carotid arteries is over 6.5 times higher than in patients without atherosclerotic plaques.
25. Intracranial vascular calcifications, mark of intracranial atherosclerosis does not correlate with stroke, but with lacunar ictus. About two thirds of patients with intracranial vascular calcification shows lacunar ictus, while those with lacunar ictus, represent more than a third.
26. THE PRESENCE OF PLAQUES IN THE EXTERNAL CAROTID ARTERY REPRESENTS AN INDEPENDENT FACTOR OF PREDICTION FOR THE OCCURRENCE OF STROKE. THIS DEMONSTRATES THAT OUR ATTENTION SHOULD BE DRAWN ALSO TO THE EXTERNAL CARAOTID ARTERY, THE EXPLANATION BEING LIKELY TO BE GIVEN BY THE IMPORTANCE OF COLLATERAL CIRCULATION. Out of the four predictor variables used in this model, namely the presence of atherosclerotic plaques at pre-bulbar, bulbar, ACI and ACE, one is statistically significant. It is the presence of atherosclerotic plaques at the level of the external carotid artery, the risk of stroke occurrence for the presence of atheromatosis in this level is of 2,457 or higher. Patients of the stroke group presenting atherosclerotic plaques in arteries external carotid is of 63.3%, about two times higher than in patients with atherosclerotic plaques at the same level in the group without stroke.

ORIGINAL CONTRIBUTION

The original contribution of this paper is given by the practical approach of the clinician in terms of finding a predictive model of the atheromatosis cervical and cerebral-carotid pattern, especially for the occurrence of a constituted stroke. The sample size studied has proven reliability of the cervical-cerebral ultrasonography and the importance of rigorous review criteria validated, raising new hypotheses which probably require further validation in larger series. The originality of the approach is that most of the works of this kind in Romania and abroad have approached the association of ischemic stroke and cerebral cervical atherosclerosis in the sense of first finding a stroke and subsequently linking them.