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PATHOGENIC PECULIARITIES OF ISCHEMIC STROKE IN PATIENTS WITH METABOLIC SYNDROME

321.05 –CLINICAL NEUROLOGY

Summary of Ph.D. Thesis in Medical Sciences

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The Ph.D thesis has been elaborated within the Department of Neurology nr. 2 at ”Nicolae Testemitanu” State University of Medicine and Pharmacy

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The Ph.D thesis and the summery can be consulted at the library of "Nicolae Testemitanu" State University of Medicine and Pharmacy and on the ANACEC website.

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CONTENTS

CONCEPTUAL LANDMARKS OF THE RESEARCH

Introduction. Stroke are one of the most important public health problems, with a strong socio-economic impact worldwide, being also a major cause of disability in highly developed countries. Stroke is the second leading cause of death and disability in the world [1, 2]. The share of stroke in the structure of cerebrovascular diseases in the Republic of Moldova constitutes in average 25.0%. The average incidence of stroke, in the period 2004-2014, was equal to 9.5 cases per 10,000 inhabitants. The average mortality from stroke, entirely in the republic is 201.2 cases per 100,000 inhabitants [3, 4]. The current incidence of cerebrovascular accidents and the lack of effective treatment measures have led to the need to deepen research into risk factors. The analysis of major risk factors for ischemic strokes highlights the fact that an important place among them is occupied by some defining components of the metabolic syndrome or closely related to it, such as: hypertension, hyperlipidemia, diabetes mellitus, physical inactivity, coronary heart disease, the presence of biological markers of inflammation [6-8].

Data in the field of research problem

Metabolic syndrome (MS) is a constellation of closely related risk factors for cardiovascular disease in general and cerebrovascular disease in particular. Currently, the recommended name is "metabolic syndrome" and the definition proposed in 2009 by the American Cardiology Association, the International Diabetes Federation and the National Heart, Lung, and Blood Institute is used [6, 9 - 14].

The association between metabolic syndrome and ischemic stroke is less than in the case of coronary heart disease. In guidelines for the primary prophylaxis of vascular events, conducted by the American Cardiology Association and the American Stroke Association, MS is framed as a less documented risk factor [15, 16]. The high prevalence of metabolic syndrome in the population suggests that its link to stroke is certainly relevant to have a better etiological understanding and to identify individuals at high risk for stroke [17 - 19].

The research purpose: to assess the particularities of the complex of metabolic disorders in patients with ischemic strokes in relation to markers of ischemic brain damage, biological and ultrasonographic markers of carotid atherosclerotic vascular disease and development of criteria for predicting the evolution of cerebrovascular events in the effort to develop early therapeutic methods of primary and secondary prevention.

Research's objectives:

1. Highlighting the clinical features and spectrum of risk factors in patients with ischemic stroke with and without metabolic syndrome.

2. Identification of carotid phenotypes and their association with atherosclerotic plaques in patients with ischemic stroke with or without metabolic syndrome.
3. Determination of the correlation between the level of proinflammatory markers, indicators of lipid and carbohydrate metabolism, anthropometric parameters and markers of atherosclerotic disease of the carotid vessels in patients with stroke.
4. Research on the dynamics of markers of ischemic brain damage, oxidative stress and glucotoxicity in the acute phase of vascular event in patients with and without metabolic syndrome and their correlation with the dynamics of neurological deficit with the highlighting of their role in predicting functional recovery of patients with stroke.
5. Elaboration of criteria for predicting the evolution of cerebral vascular events in the effort to develop early therapeutic methods of primary and secondary prevention.

Materials and methods: To achieve the purpose and objectives of the research, a cohort study was performed that included 2 groups of patients with ischemic stroke: one with MS that included 102 patients and the second without MS, consisting of 108 participants. **Statistical analysis of data** was made using EXCEL programs and the XLSTAT application. The t-Student criterion was used to estimate significant differences in the means of two groups. Statistically significant in all methods of analysis was considered the value of $p < 0.05$. The study of the interaction between the quantitative parameters was performed by calculating the Pearson correlation coefficient (r). To determine the predictive values of biological markers−ROC curves were analyzed, the area under the curve was calculated using the XLSTAT application. The relative risk (RR) and standard error, 95% confidence interval (CI) are calculated according to the recommendations of Altman, 1991.

Scientific novelty and originality: A study of the complex of metabolic disorders in patients with ischemic stroke was performed for the first time in the Republic of Moldova, establishing the relationships between the risk factors that make up MS, biological and ultrasonographic markers of carotid atherosclerotic vascular disease. The correlation between the presence of risk factors, anthropometric parameters, biological markers of inflammation, indicators of lipid and carbohydrate metabolism with markers of atherosclerotic disease of the carotids were highlighted. The relative risk of carotid vessel disease in patients with diabetes mellitus (DM) and MS has been calculated. The biomarkers of ischemic brain damage in the acute phase and their role in predicting functional recovery were investigated. The values of hsCRP, S-100β protein were elucidated and MMP-9 in predicting the evolution of ischemic stroke. It was calculated the relative risk of development of DM during the lifetime, depending on the presence of DM in first-degree relatives.

The scientific problem solved consists in establishing a complex relationship between the risk factors that constitute MS with the biomarkers of ischemic brain damage and the markers of atherosclerotic disease of the carotids in patients with ischemic stroke. The identification of these risk factors will contribute to the optimization of risk stratification, the early initiation of prophylaxis and treatment measures, which will reduce the number of patients with MS and ischemic stroke, respectively, pathologies that are currently on an upward trend.

Theoretical importance

The research results demonstrated the role of a spectrum of risk factors for ischemic stroke, such as high BP present in 98.04% of patients, overweight/obesity – in 84.3% and dyslipidemia in 66.7%. The role of metabolic risk factors on the structure of the carotid vascular wall has been shown.

The major genetic role of DM inheritance was highlighted, demonstrating a 7.79 times higher risk of developing diabetes in people with first-degree diabetic relatives.

New objective data were obtained regarding the dynamics of markers of oxidative stress, inflammation, endothelial dysfunction, markers of ischemic brain damage in the first 48 hours after the onset of ischemic stroke and the evolution of biomarkers during 7 days of treatment. There were identified close correlations between the biomarkers of ischemic brain damage and the degree of neurological deficit that allowed the subsequent development of criteria for predicting the evolution of neurological deficit and complications, that will, in the future, dictate treatment tactics. It has been shown that patients with MS have a higher degree of expression of inflammation, manifested by statistically significant elevated values of IL–6 and hsCRP, a positive correlation was observed between these indicators and intima-media thickness (IMT) values (r=0.45, respectively r=0.38), atheromatous plaques in the extracranial segment of the carotid arteries were with a frequency 2 times higher compared to the control group.

The applicative value of the research

The high rate of constituent risk factors of MS in patients with ischemic stroke found in this study, requires the need for mandatory screening for this syndrome in all patients with or without ischemic stroke, the results of the study confirming the significance of hypertension, obesity/overweight, dyslipidemia and insulin resistance as components of MS, according to the consensus of the American Cardiology Association, the International Diabetes Federation, and the National Heart, Lung, and Blood Institute (2009).

This research demonstrates the statistically significantly higher degree of expression of systemic inflammation and oxidative stress in patients with MS, also in this category of patients

with a frequency 2 times higher than–atheromatous plaques were found in the carotid arteries, while atrial fibrillation and tabagism were present in the control group with a higher frequency.

Thanks to this cohort study, new data were obtained regarding the opportunity and usefulness of assessing specific biomarkers such as: catalase, ceruloplasmin, AGE, AOPP, hsCRP, IL-1β, MMP–9, the S-100 protein, which would play a predictive role in the evolution of major vascular events in patients with or without MS.

Main scientific results submitted for support:

1. The share of dysmetabolic risk factors in the general study group was as follows: a single dysmetabolic risk factor was identified in 17% of patients, 2 risk factors in 34.3%, 3 risk factors 25, 2%, 4 risk factors 19.5%, and 5 risk factors 3.8%. In the control group the most common combination of risk factors was hypertension and abdominal obesity found in 62%, and in the MS group the same combination of risk factors was found in 95% of cases.
2. The values of hsCRP and IL-6, AOPP and AGE were statistically significantly elevated in the group of patients with ischemic stroke and MS, while antioxidant factors such as ceruloplasmin and catalase were decreased, which would demonstrate the level of expression of systemic inflammation and higher oxidative stress in this category of patients.
3. Proinflammatory cytokine concentrations (IL-1β, IL-6, IL-10) correlated with neurological deficit, but vigorous studies are needed to demonstrate their role in the prognosis of functional recovery in stroke victims.
4. Concentrations of hsCRP, MMP–9 and S-100β protein may be considered in patients with acute ischemic stroke in order to predict the evolution of the vascular event and IL-1 and MMP-9 concentrations could be considered in patients with acute ischemic stroke in order to predict hemorrhagic transformation of the ischemic area.
5. In the present study it was shown that patients with metabolic syndrome have significantly higher values of IMT and internal diameter of the common carotid artery than subjects without metabolic syndrome. Carotid artery stenosis ≥50% was found to be almost 2 times higher in patients with MS.
6. Carotid phenotype 3 was recorded in more than half of patients with MS (59.8%), this phenotype linking plaques with severe stenosis in 57.4% of cases, and phenotype 1 predominated in patients without MS (62.9%), the frequency of plaques with stenosis ≥50%, occurring in 20.5% of patients.
7. Proper diagnosis and management of MS is an important part of stroke prophylaxis. The obtained results suggest that the cluster of risk factors constituting MS is associated with altered

carotid artery structure, these changes explaining the relationship between MS and the high risk of cardiovascular and cerebrovascular diseases.

Implementation of scientific results was performed in the clinical activity of the neurology department no. 2 of the State University of Medicine and Pharmacy "Nicolae Testemitanu", of the Department of Strokes and of the Scientific Laboratory of Cerebrovascular Diseases and Epilepsy of the Institute of Emergency Medicine.

Approval of the results. The essential results of the study were communicated and discussed at various scientific forums: the 5th Congress of Neurologists of the Republic of Moldova with international participation (Chisinau, 2015); The 6th European Teaching Course on Neurorehabilitation (Cluj-Napoca, 2016); Annual scientific conference of scientific and teaching staff, doctoral students, students and residents of USMF "Nicolae Testemitanu" (Chisinau, 2016, 2018); The 26th European Stroke Conference (Berlin, 2017); The 3rd Congress of the European Academy of Neurology (Amsterdam, 2017); XXIII World Congress of Neurology (Kyoto, 2017); VI Congress of Neurologists and Neurosurgeons (Chisinau, 2017); The 4th Congress of the European Academy of Neurology (Lisbon, 2018); The 4th European Stroke Organization Conference (Gothenburg, 2018).

Thesis materials were discussed and approved at the joint meeting of the Department of Neurology no. 2 of IP USMF "N. Testemiteanu" of 19th of September 2018 (minutes no. 2); at the meeting Scientific profile seminar "Clinical Neurology - 321.05, Neurosurgery - 321.21, Neurosciences (including psychophysiology) - 312.02" within the IP USMF "N. Testemiteanu" of 11th of October 2018 (minutes no. 2).

Publications on the thesis

The study materials were reflected in 26 scientific papers, including 12 articles published in national journals, 3 publications as a single author, 2 articles in international journals, presentations and summary papers at 2 national scientific conferences, 7 international scientific conferences and 4 international congresses.

The volume and structure of the thesis. The thesis consists of the following sections: introduction, 5 chapters, general conclusions, practical recommendations, bibliography from 190 sources and 5 annexes. The paper consists of 110 pages of basic text and includes 37 tables, 29 figures.

Keywords: stroke, metabolic syndrome, risk factors, biomarkers, carotid arteries.

THESIS CONTENT

1. ACTUALITIES IN THE FIELD OF METABOLIC DISORDERS IN PATIENTS WITH ISCHEMIC STROKE.

This chapter contains a brief synthesis of data from the literature with reference to the achievements and issues of the field of investigative interest. The epidemiological data of stroke and MS worldwide are presented, the risk factors, the etiopathogenic hypotheses of the disease based on the contemporary scientific support, the evolution of the concepts about MS and the diagnostic criteria is elucidated. The clinical and pathogenetic correlation between the metabolic syndrome and cerebrovascular risk is described. A special subchapter is dedicated to inflammatory cytokines: their mechanism of action and their role in stroke are elucidated. Another subchapter is dedicated to Doppler-duplex investigation of carotid extracranial vessels: the usefulness of the measurement of the IMT, gradation of carotid stenosis and classification of atheromatous plaques. The literature review shows that metabolic syndrome is a constellation of closely related risk factors for cardiovascular disease in general and cerebrovascular disease in particular, and the prevalence of MS in the general population is about 24%-35% in adults and is constantly increasing [9, 10]. MS is associated with an increased risk of acute ischemic non-embolic stroke in elderly patients. Given the high prevalence of MS in the population, the assessment of its association with stroke is certainly relevant to have a better etiological understanding of stroke and to identify individuals at high risk for stroke [7].

2. RESEARCH MATERIALS AND METHODS

General characteristics of the research methodology

In this research, a cohort study was designed that included 210 patients with ischemic stroke, hospitalized in the Strokes Neurology Department of Institute of Emergency Medicine between 13th of June 2016-24th of November 2017. Patients were divided into 2 groups according to the presence / absence of MS: the first group included 102 patients with metabolic syndrome, and the second group consisted of 108 patients without metabolic syndrome, but that in turn could have one, two or no constituent risk factor for MS.

All patients have undergone the following examinations:

- **survey:** it was used the stroke risk factor estimation questionnaire developed in the Laboratory of Cerebrovascular Diseases and Epilepsy by Groppa S., Zota E., Efremova D., et al., in 2015. The information in the file included: personal data (name, surname, age, sex, occupation, residence, ethnicity), complaints at admission, history of current illness (time

elapsed from onset to referral to a physician, type of onset, type of referral), usual risk factors for an acute vascular event (physical activity, diet, smoking, alcohol consumption), personal history (stroke or transient ischemic attack in medical history, myocardial infarction, atrial fibrillation, ischemic heart disease, valvulopathy, stenosis of main vessels, obesity, dyslipidemia, migraine, sleep disorders, etc.) and significant heredocolateral history (hypertension, diabetes, stroke, myocardial infarction),

- **clinical anthropometric** (waist, body mass, abdominal circumference, body mass index), BP values,

- **neurological status** was assessed using the NIHSS scales, Rankin, Barthel index, TOAST and Bamford / Oxford Classification,

-**laboratory**: general blood analysis, lipid metabolism (total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, atherogenic index was calculated according to the formula proposed by Klimov A. N. and Niculcheva N.G. in 1999; carbohydrate metabolism: fasting blood glucose, basal insulin, advanced glycosylation end products (AGE). Several indicators characteristic for the hemostasis system were also examined**:** prothrombin index, thrombin time, partially active thromboplastin time, fibrinogen; markers of immuno-inflammatory activity were evaluated: TNF-alpha, hsCRP, IL-1β, IL-6, IL-10; oxidative stress markers: advanced oxidation end products (AOPP), ceruloplasmin, catalase; nitric oxide metabolites: NO2, NO3; markers of ischemic brain damage: metalloproteinase-9, S-100β, cytokines of inflammation. Markers of immuno-inflammatory activity, markers of oxidative stress, nitric oxide metabolites, markers of ischemic brain damage were studied in the first 48 hours after the onset of the disease and on the 7th day of treatment.

All patients underwent imaging (Doppler-duplex of the extracranial vessels with of the IMT at the level of the common carotid arteries, the presence and morphology of atheromatous plaque, the presence and degree of carotid artery stenosis. The ultrasound examination protocol of the extracranial segment of the carotid arteries developed by the Laboratory of Cerebrovascular Diseases and Epilepsy was used (Groppa S., Zota E., Efremova D., et al., 2015).

The criteria for inclusion in the research were:

- Informed written agreement of the patient.
- Patients with ischemic stroke.
- The referral time from the onset of the disease to admission up to 48 h.
- Brain CT.
- Age> 18 years.

Criteria for excluding patients from the study:

- Lack of informed agreement of the patient.
- Hemorrhagic stroke.
- Subarachnoid hemorrhage.
- Other pathologies (non-vascular) of the nervous system.
- The referral time from the onset of the disease> 48 h.
- Patients up to 18 years of age.
- Patients with insulin-dependent type 1 diabetes.
- Patients with somatic pathology in the decompensated phase, renal or hepatic impairment, advanced heart failure (NYHA grade IV), myocardial infarction and stroke sustained during the last year, oncological pathologies or other severe diseases.
- Patients undergoing vascular recanalization treatment.
- Patients with severe neurological impairment (NIHSS >14).

Statistical analysis of data was made using EXCEL programs and the XLSTAT application using the functions and modules of these programs. The t-Student criterion was used to estimate significant differences in the means of two groups. The testing of the dynamics of the group parameters was performed by the T-criterion test of coherent selections. The study of the interaction between the quantitative parameters was performed by calculating the Pearson correlation coefficient (r). Statistically significant in all methods of analysis was considered the value of $p < 0.05$. In order to determine the predictive values of the biological markers, the ROC curves were analyzed, the area under the curve was calculated using the XLSTAT application. The relative risk (RR) and standard error, 95% confidence interval (CI) are calculated according to the recommendations of Altman, 1991.

Method for calculating predictive values

Curves for assessing the ability of a diagnostic test to differentiate healthy subjects from sick subjects (Receiver-operating characteristic curves) are an excellent way to compare diagnostic tests. The area below the ROC curve is a reflection of the ability of the diagnostic test to distinguish patients with or without disease/complication. The larger is the surface, the more perfect the test results. Accuracy of the diagnostic test using the scoring system **AUROC** is as follows: 0.9-1.0 – excellent; 0.8-0.9 – good; 0.7-0.8 – fair/reasonable; 0.6-0.7 – weak; 0.5-0.6 – failed.

3. CLINICAL CHARACTERISTICS OF PATIENTS IN THE STUDIED GROUPS

This chapter presents a detailed characteristic of the general study group and compares the 2 study groups according to demographic data, lifestyle, pathological and hereditary antecedents, gives a clinical characteristic and the results of paraclinical investigations.

The mean age of the subjects studied in the general group was 66.99 ± 8.48 years. The most common age group was between 61-70 years (48%), followed by the age group 71-80 years (28%). From the total number of 210 participants, men were 104 (49.5%) with a mean age of 64.74 ± 8.51 years, and women were 106 (50.5%), with a mean age of 69.2 ± 7, 89 years, a statistically significant difference was found between the ages of women and men (p = 0.00011). Regarding the onset of focal neurological deficit that would suggest the onset of a stroke, most patients sought medical help within 1-3 hours of the onset of the disease (32.5%), but a significant number of patients referred for help in over 24 hours from the onset of clinical manifestations (21.4%).

The lifestyle in the two study groups did not differentiate in terms of physical effort and alcohol consumption, it was observed that in the control group predominated smoking patients (17.6% vs. 10.7%) and slightly ex-smokers (29.6% vs. 27.4%) and with a higher frequency there have been patients with increased consumption of animal fats (**table 3.1**). Regarding the pathological antecedents in the control group, patients with atrial fibrillation (AF) predominated (33.3% vs. 17.64%) and a history of myocardial infarction (MI) (11.1% vs. 6.8%), but in the first group with DM (60.8% vs. 0.92%) and ischemic heart disease (65.7% vs. 51.8%).

From the patients who reported having first-degree relatives with diabetes, 47 suffered from diabetes at the time of inclusion in the study, which represents 82.45% of the group of diabetic patients who have first-degree relatives with diabetes, this shows the major genetic role of DM inheritance. People with first-degree relatives with type 2 diabetes have a 7.79 higher risk of developing diabetes (RR = 7.79, 95% CI 4.1-14.5, z = 6.4). The number of normal-weight patients, estimated by using BMI values was quite small (15.7%, n = 66), the rest of the patients being either overweight or obese **(Table 3.2)**. In the first group were identified 3.9% (4 patients) normal weight, 24.5% (n = 25) overweight, 34.3% (n = 35) obese first degree, 24.5% (n = 25) obese second degree, 13.7% (n = 14) obese third degree, and in the control group 26.8% (n = 29) normal weight, 37.9% (n = 41) overweight, 19.44 % (n = 21) obese first degree, 12% (n = 13) obese second degree, 2.8% (n = 3) obese third degree. Abdominal obesity in the control group was found in 85.2% (n = 46) women and 38.8% (n = 21) men, and in the MS group 100% women (n = 52) and 91.8% (n = 45) men.

Table 3.1. The characteristic of the study groups, according to the vascular risk behavioral factors and the pathological antecedents

	Study group (102)	**Control group (108)**	**P**
Physical activity			
Light	51 (50%)	47 (43,5%)	0,07
Medium	51 (50%)	59 (54,62%)	0,14
Heavy		2 (1,85%)	
Diet			
Vegetarian	3 (2,9%)	4 (3,7%)	0,66
Increased consumption of animal fats	14 (13,72%)	22 (20,37%)	0,03
Increased consumption of animal protein	31 (30,4%)	35 (32,4%)	0,23
Balanced	54 (52,9%)	47 (43,5%)	0,09
Smoking			
smokers	11 (10,78%)	19 (17,59%)	0,023
<10 cigarettes/day	2 (1,96%)	3 (2,77%)	0,44
10-20 cigarettes/day	4 (3,92%)	11 (10,2%)	0,012
>20 cigarettes/day	5 (4,9%)	5 (4,6%)	0,61
ex- smokers	28 (27,4%)	32 (29,6%)	
Non-smokers	63 (61,76%)	57 (52,77%)	0,13
Alcohol consumption			
Does not consume	53 (51,96%)	45 (41,66%)	0,06
Consume in moderation	46 (45,09%)	61 (56,48%)	0,05
Alcohol abuse	3 (2,94%)	2 (1,85%)	0,66
Pathological history			
Transient ischemic attack in history	1 (0,98%)	2 (1,85%)	0,44
Ischemic stroke	16 (15,68%)	20 (18,51%)	0,54
Hemorrhagic stroke	0	2 (1,85%)	
Hypertension	96 (94,11%)	94 (87,03%)	0,53
Atrial Fibrillation	18 (17,64%)	36 (33,33%)	0,023
Myocardial infarction	7 (6,86%)	12 (11,11%)	0,15
Ischemic heart disease	67 (65,6%)	56 (51,85%)	0,05
Diabetes mellitus	62 (60,78%)	1 (0,92%)	<0,001

Table 3.2. The characteristic of the 2 study groups according to the morphometric data

	Study group	Control group	P value
Abdominal circumference (cm)	105,7±11,6	94,97±12,24	<0,001
Height (cm)	165±12,71	165,61±12,71	0,68
Weight (kg)	92,79±15,25	78,75±15,58	<0,001
BMI (kg/m²)	33,8±5,84	28,9±5,59	<0,001
Systolic BP (mmHg)	145,77±18,4	142,17±16,5	0,14
Diastolic BP (mmHg)	84,9±7,92	84,49±7,57	0,7

After comparing the clinical manifestations of neurological pathology in the two study groups, there was a slight predominance of damage of a hemibody expressed as hemiparesis / hemiplegia and hemisensitive syndrome in patients in the MS group, and in the control group with a frequency of almost 2 times higher was found the atactic and bulbar syndrome, possibly due to the fact that in the MS group with a slightly higher frequency the anterior circulation was affected, while in the other group with a higher frequency - the posterior circulation.

In the study, dyslipidemia was present in a large number of patients, 66.6% (144 patients) had hyperlipidemia. For the whole group of patients, the most common dyslipidemia was mixed (25.23%, 53 patients) followed by hypercholesterolemia diagnosed in 23.8% (50 participants). Isolated hypertriglyceridemia presented 10.95% (n=23) patients. Isolated high LDL cholesterol was determined in 6.7% (n=14) patients. Atherogenic index with the value that exceeded the value considered normal (> 3), was found in 19.5% (n=41). In the core group, 77 subjects (75.5%) with dyslipidemia were identified, while in the control group 63 (58.3%). Mixed dyslipidemia predominated in the core group (26.5%, n = 27), followed by hypertriglyceridemia (19.6%, n = 20) and hypercholesterolemia (18.6%, n = 19), isolated high LDL cholesterol in the SM group was found in 10.8% of cases (n = 11), while in the control group hypercholesterolemia predominated (24% of the number of patients without MS, n = 26), followed by mixed dyslipidemia (22 , 2%, n = 24) and isolated high LDL cholesterol (9.2%, n = 10).

According to the Bamford / Oxford (1991) Clinical-Imaging Classification, the most common form of ischemic stroke was partial anterior circulation stroke (131 patients; 62%), followed by total anterior circulation stroke (45 patients; 22%) and lacunar stroke (26 patients; 12.0%), the rarest form in our study being total anterior circulation stroke (8 patients; 4.0%), 3 of the 8 patients with total anterior circulation stroke presented MS, of which 2 died within 4 days of admission. Comparing the two groups according to the type of ischemic stroke, we noticed

that in the SM group predominated those with partial stroke of the anterior circulation and lacunar ones, while in the control group - partial stroke of the anterior circulation and 2 times more frequently stroke of posterior circulation (**Fig. 3.1**).

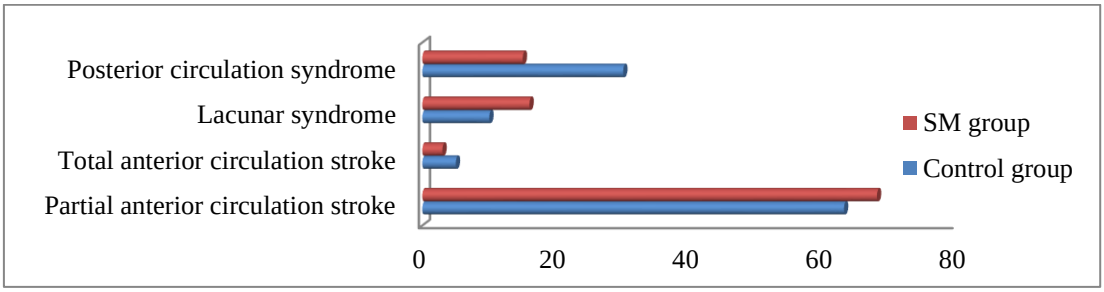

Fig. **3.1** Distribution of patients according to the type of ischemic stroke according to the Bamford / Oxford classification

According to the TOAST (1993) classification, the most common form of ischemic stroke was macroangiopathy (80 patients; 38%), followed by stroke of cardioembolic origin (56 patients; 27%) and microangiopathy (26 patients; 12%), 48 (23%) cases were of unidentified origin, and cases of ischemic stroke of other origin were not registered. Thus, in the core group, patients with stroke of atherothrombotic origin (45%), cardioembolic (21.6%) and lacunar origin (15.7%) predominated, while in the control group with a similar frequency was found stroke of cardioembolic origin (31.5%) and of microangiopathic origin (31.5%), followed by stroke of undetermined etiology (27.8%) (**Fig. 3.2**).

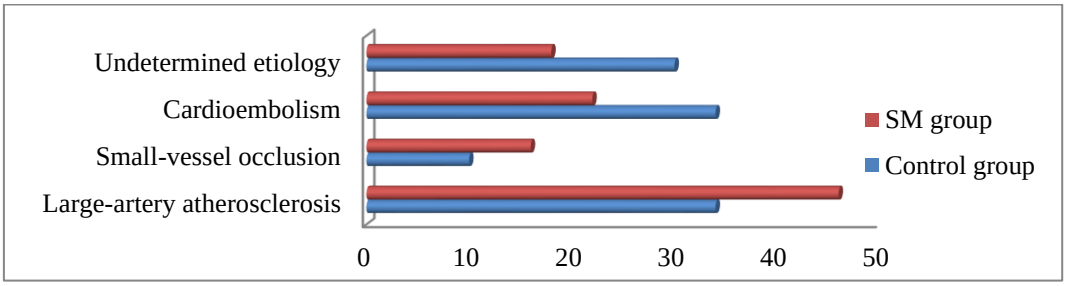

Fig. 3.2 Distribution of patients according to TOAST classification

Mean values of neurological deficit according to the NIHSS scale in patients from the SM group at admission were 8.91 ± 4.73, on the 7th day after admission – 7.36 ± 4.34, and at discharge – 6.56 ± 3.92, while in the control group was 8.07 ± 3.79 at admission, on the 7th day – 6.73 ± 3.88, and at discharge – 6.04 ± 3.81. NIHSS values were statistically insignificant higher in the SM group at admission ($p = 0.27$), on the 7th day ($p = 0.56$) and at discharge ($p = 0.42$), compared to the control group.

The share of patients with a single dismetabolic risk factor in the general study group was 17% (36 patients), with 2 risk factors 34.3% (n=72), with 3 risk factors 25.2% (n=53), with 4 risk factors 19.5% (n=41), and with 5 risk factors 3.8% (n=8). From the category of patients with

a single dismetabolic risk factor, the patients included in the study either had abdominal obesity (n=2, 5.55%), or high values of BP (n=34, 88.8%), 14 (38.9%) patients presented FA on the ECG route, and 11 (30.5%) were smokers. From the group of patients with 2 RF, visceral obesity was found in 65 (90.27%), all patients had elevated BP (100%), hypertriglyceridemia was detected in 5 (6.94%), hypo-HDL cholesterol in one patient (1.4%), type 2 diabetes was detected in one patient, 8 people reported smoking (11.11%), and 21 AF (29.2%). From the group of those with 3 RF visceral obesity was found in 48 (90.6%), all patients had elevated BP levels (100%), hypertriglyceridemia was found in 31 (58.5%), hypo-HDL cholesterol in 19 patients (35.8%), type 2 diabetes was observed in 20 patients (37.7%), 8 people reported smoking (15.1%), and 11 AF (20.75%). From the group of patients with 4 RF visceral obesity was was found in all participants (100%), 39 patients had elevated BP levels (95.12%), hypertriglyceridemia was found in 38 (92.6%), hypo-HDL cholesterol in 7 patients (17.07%), type 2 diabetes was detected in 35 patients (85.4%), 2 people reported smoking (4.8%) and 8 AF (19.5%). From the group of patients with 5 RF type 2 diabetes was detected in 7 patients (87.5%), 1 person reported smoking (12.5%), and 3 AF (37.5%).

Thus, in the control group the most common combination of risk factors was hypertension and abdominal obesity found in 67 representatives of the control group (62%), hypertension, visceral obesity and AF in 34 (31.5%), and hypertension, obesity and smoking in 11 (10.2%).

In the SM group, the most common combination of risk factors found was the association between abdominal obesity, hypertension and DM occurring in a proportion of 58.8% (n = 60) and, respectively, hypertension, abdominal obesity and hypertriglyceridemia - 67 , 6% (n = 69), and the association between high values of BP, triglycerides, CA and DM were detected in 32.35% of cases (n = 33).

4. CHARACTERISTICS OF IMMUNO-INFLAMMATORY MARKERS, OXIDATIVE STRESS AND GLUCOTOXICITY, NITRIC OXIDE METABOLITES AND INSULIN RESISTANCE IN PATIENTS WITH ISCHEMIC CEREBRAL VASCULAR ACCIDENT

Inflammation is an important component of MS that could be the link between MS and the risk of cardiovascular and cerebrovascular diseases. A low degree of systemic inflammation has been shown in several studies to be present in patients with MS.

Venous blood was collected on an empty stomach in the first 24 hours after admission and on the 7th day after admission. Fasting venous blood was also collected in 39 healthy subjects to compare data from patients with ischemic stroke with those obtained from absolutely healthy

subjects in the same age group.

It was observed that the values of inflammatory cytokines in patients with ischemic stroke were significantly elevated compared to the values determined in healthy subjects. The mean inpatient values of inflammatory cytokines were as follows: IL-6 was 15.69 ± 11.8 pg / ml, IL-1β - 8.01 ± 5.4 pg / ml, IL-10 - 6, 81 ± 2.39 pg / ml, TNF-α - 40.13 ± 17.71 pg / ml. The mean values at discharge were: IL-6 - 14.95 ± 10.83 pg / ml, IL1β - 6.11 ± 3.46 pg / ml, IL-10 - 6.75 ± 3.27 pg / ml, TNF-α - 34.02 ± 14.38 pg / ml.

The mean values of inflammatory cytokines in 2 patients with ischemic hemorrhagic transformation were: IL-1β 17.34 pg / ml, IL-6 13.88 pg / ml, IL-10 6.37 pg / ml, TNF-α 45.71 pg / ml at admission, and IL-1β 15.74 pg / ml, IL-6 25.38 pg / ml, IL-10 12.15 pg / ml, TNF-α 39.0 pg / ml at the 7th day. The mean values of inflammatory cytokines at admission in this category of patients did not exceed the mean values of the whole study group, except for IL-1β which had double value compared to the mean level of the whole group. It was also observed that IL-10 and IL-6 approximately twice exceeded the value recorded at admission, and those of TNF-α and IL-1β slightly decreased.

A positive correlation was determined between TNF–α, IL-6, and IL-10 values and NIHSS values established at admission ($r = 0.36$, $r = 0.34$ and $r = 0.21$), the best correlation being established between IL-1β values and NIHSS ($r = 0.67$). These results suggested that proinflammatory cytokine concentrations (IL-1β, IL-6, TNF-α) could be considered in patients with acute ischemic stroke in order to predict the evolution of the vascular event. HsCRP and IL-6 values were statistically significantly elevated in the group of patients with ischemic stroke and MS both in the first 24 hours ($p = 0.014$ and $p = 0.043$, respectively) from the admission, and on the seventh day ($p = 0.035$, respectively $p = 0.016$), which would demonstrate the higher degree of expression of systemic inflammation in this category of patients.

Degree of expression of protein S-100β was statistically significantly high compared to the values of healthy subjects in both the SM group ($p <0.001$) and the control group ($p<0.001$), but comparing the two study groups no statistically significant difference was observed. The average value of S-100β in the whole study group was 0.83 ± 0.47μg / L at admission (min. 0.17 μg / L, max. 2.37 μg / L), the average value at discharge was 0.55 ± 0, 43 μg / L (min. 0.11 μg / L, max. 2.48 μg / L). One patient underwent hemorrhagic transformation of the ischemic area on the second day of admission; the value of S-100β in this patient did not exceed the mean value of the entire study group (0.86 μg / L at admission, 0.49 μg / L at discharge). A positive correlation was determined between the NIHSS score and the S-100β protein values at admission ($r = 0.62$) and

at discharge (r = 0.28).

In our research, the mean values of MMP-9 activity at admission were statistically significantly high in both study groups as opposed to the degree of expression of MMP-9 activity in healthy subjects (p=0.001 and p <0.001, respectively)

The mean values of MMP-9 activity at admission were 7.44 ± 5.32 ng / dl (min 1.55 ng / dl, max 34.84 ng / dl), the maximum value was identified in the patient who was observed on the second day of admission the hemorrhagic transformation of the ischemic area, which corresponds to the data from the literature, this being proposed as a biomarker of the hemorrhagic transformation of the ischemic stroke. The mean discharge value of MMP-9 activity was 6.34 ± 4.03 ng / dl (min. 1.91 ng / dl, max. 22.74 ng / dl).

The correlations between NIHSS and MMP-9 values were as follows: at admission r = 0.42, at discharge r = 0.37, there was no statistically significant difference between the degree of expression of MMP-9 at admission and discharge (p = 0.306).

From the total number of patients with ischemic stroke, higher than normal serum insulin values (> 12.2 μU / ml) were identified in 41.02% of patients and HOMA values> 2.5 were found in the same patients with increased serum insulin levels, all these patients being part of the SM group. Basal insulin values of healthy subjects were compared with those of the SM group (p <0.001) and the control group (p <0.001).=0.03), determining that they were significantly elevated in stroke patients with or without MS**.** No relationship was found between NIHSS values at admission and basal insulin levels in the first 24 hours after admission (r = 0.08) nor with HOMA index (r = 0.16), and on the 7th day after admission a low-intensity correlation with basal insulin was found (r = 0.38).

AOPP values were elevated in patients with ischemic stroke compared to the level recorded in healthy subjects, there was also a significant difference between AOPP values in the two study groups, being higher in patients with MS both in the first 24 hours and and in the 7th day after admission (p = 0.002, p = 0.006).

The level of ceruloplasmin in the control group was statistically significantly increased compared to the SM group on the first day of admission (p = 0.003), such a difference was not–observed on the seventh day of admission (p=0.066). The catalase value was statistically significantly decreased in the total group both in the first 24 hours after admission and in the 7th day of admission compared to healthy subjects (p <0.001, respectively p = 0.009). Comparing the level of catalase, we noticed higher values in the group of patients without MS (p = 0.04) in the first 24 hours of admission and on the seventh day (p = 0.02). The values of pentosidine-like

AGE and vesperlysine-like AGE were statistically significantly higher in the general study group compared to those obtained in healthy subjects (p = 0.027, p=0.039), but when comparing the degree of expression of pentosidin-like AGE and vesperlysine-like AGE between stroke patients with and without MS we observed a statistically significant increase in the SM group (p <0.001 and p = 0.0001, respectively), both in the first hours after admission and on the 7th day of admission (p 0.001 and 0.09, respectively) (**Table 4.1**).

Table 4.1. Mean values of oxidative stress indicators in the study groups

	SM group at admission	On the 7th day	p	Conrol group at admission	On the 7th day	p
AOPP, µM/L	72,49±33,4	54,42±21,03	0,007	52,31±20,18	42,73±13,46	0,01
Catalase, µM/L	14,7±3,61	14,06±5,47	0,55	16,89±5,35	17,14±6,1	0,84
Ceruloplasmin, mg/L	217,3±68,85	251,8±115,4	0,16	301,5±155,4	273,3±133,3	0,39
AGE pentozidine-like, µg/ml	784,2±307,7	710,9±337,6	0,33	470,9±214,3	438,7±185,8	0,48
AGE vesperlyzine-like, µg/ml	687,7±245,3	585,3±188,4	0,05	499,1±166,2	516,1±160,9	0,64

We observed that the values of nitric oxide metabolites were statistically significant (NO3, NO2) decreased in stroke patients (p <0.001, p<0.001), compared to the group of subjects without stroke, the same phenomenon was observed in terms of the amount between nitric oxide metabolites (p<0.001) and NO3 / NO2 ratio (p = 0.023). Comparing the 2 study groups we found that the NO2 and NO3 values (p = 0.05, p = 0.31) were not statistically different. NO2 and NO3 values do not show a significant change on the 7th day after admission, it can demonstrate a poor response of the vascular endothelium by the synthesis of the vasodilator NO in this category of patients under the conditions of treatment.

Predictive values of ischemic stroke evolution

From **Fig. 4.1** and **Fig. 4.2** it turns out that hsCRP and Protein S−100β can be used to predict the unfavorable course of ischemic stroke. For hsCRP we established as predictive value the level of hsCRP> 13 (µg / ml), for this value we determined a sensitivity of 100% and a specificity of 69%, and for protein S−100β we established as a predictive value the level of protein S-100β> 1.0 (µg / L) having a sensitivity of 66% and a specificity of 77%.

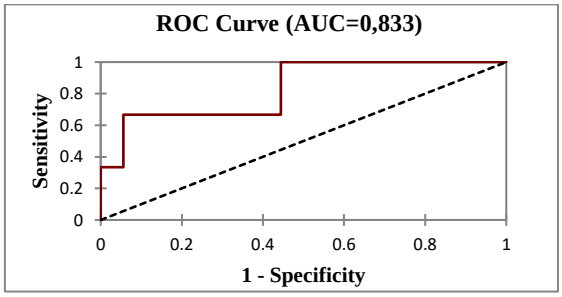

Fig. 4.1. ROC curve for assessing the possibility of prognosis of ischemic stroke depending on the degree of expression of hsCRP (µg/ml).

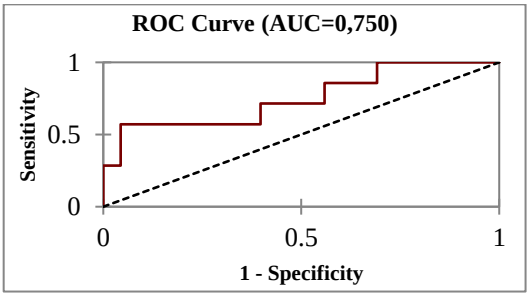

Fig. 4.2. ROC curve for assessing the possibility of predicting the evolution of ischemic stroke depending on the degree of expression of the protein S-100β (µg/L).

From **Fig. 4.3** we deduce that the MMP-9 values play a role in predicting the evolution of neurological deficit. For MMP-9 we established a predictive value> 10 ng / dl, at this value we found a sensitivity of 100% and a specificity of 86%.

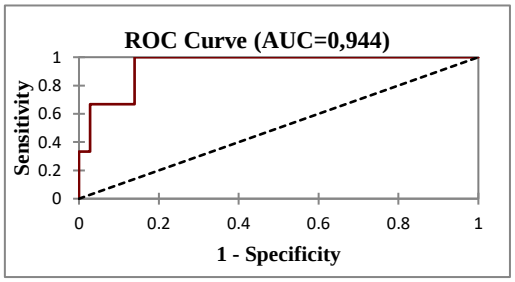

Fig. 4.3. ROC curve for assessing the possibility of predicting the evolution of ischemic stroke depending on the degree of expression of MMP-9 (ng/dl).

Analysis of ROC curves to assess the possibility of an unfavorable prognosis of ischemic stroke has shown that inflammatory cytokines can not be used to predict the evolution of functional deficit in patients who have suffered an acute cerebral vascular event.

5. ULTRASOUND EXAMINATION OF CAROTID VESSELS, EXTRACRANIAL SEGMENT.

This chapter characterizes the geometric data of the carotid arteries at the level of the extracranial segment and the presence of atheromatous involvement depending on the presence or absence of constituent risk factors of MS.

So the descriptive analysis of the arterial parameters on the whole study group highlights their average values within limits considered pathological. Thus, the mean value of the initma-mean complex (IMT) in stroke patients was 1.01 ± 0.3 mm on the right (minimum 0.5 mm, maximum 2.0 mm), 0.98 ± 0.32 mm (minimum 0.44, maximum 2.0 mm) on the left, and the

luminal diameter of the common carotid artery (CCA) was 6.92 ± 1.1 mm (minimum 4.07 mm, maximum 11.0 mm) on the right and 6.96 ± 1.22 mm (minimum 4.5 mm, maximum 11.0 mm) on the left.

The present study showed that patients with MS have significantly higher values of IMT and of the internal diameter of the common carotid artery than those without MS (**table 5.1).**

Table 5.1. IMT (mm) and CCA diameter (mm)values in the study groups

	IMT (mm)	CCA diameter (mm)
Patients with ischemic stroke and MS	1,09±0,3	7,07±1,15
Patients with ischemic stroke without MS	0,94±0,29	6,84±1,17
p	<0,001	0,04

We compared IMT values in women (0.94 ± 0.24 mm) and men (1.01 ± 0.34 mm) and found that IMT is statistically significantly higher in men (p = 0.04). We compared the IMT values in women from the MS group (1.07 ± 0.26 mm) and control group (0.89 ± 0.23 mm), noting that in the group with MS the IMT values were significantly higher (p <0.001), we observed the same phenomenon in men (mean IMT value in the MS group 1.11 ± 0.33 mm, and in the control group 0.9 ± 0.32 mm (p0.001). IMT and CCA diameter values have been shown to increase depending on the age groups. IMT is statistically significantly thickened in patients with MS, possibly due to the fact that MS and diabetes have a negative influence on IMT values. It was determined that 86.67% of insulin-resistant patients had atheromatous plaques, of which more than half had stenosis > 50%. We calculated the relative risk (RR) for high IMT values (mm) in patients with MS compared to patients without MS, so we found that RR = 1.6 (95% CI = 1.3629-1.8877, p <0.001). We determined the relative risk for stenosis over 50% in patients with MS compared to patients without MS, we obtained a risk of 2.18 times higher in this category of patients (95% CI 1.25-3.8, z = 2.77). The relative risk for plaques in patients with MS and IMT values ≥0.9 mm is 3.7 times higher than in patients with MS but with IMT <0.9 mm, and 1.9 times higher for stenosis carotid arteries more than 50%, while in patients without MS the relative risk of atheromatous plaques with IMT ≥0.9 mm was 1.2 (CI 95% 0.38–3.2, z=0.2), and for stenosis more than 50% RR = 1.11 (CI 95% 0.4–3.2, z=0.2).

From **Table 5.2** it is noted a correlation between IMT values with IL-6 expression (r = 0.45), pentosidine-like AGE (r = 0.42), basal insulin (r = 0.25) and hsCRP (r = 0.38).

Table 5.2. Correlation of the values of immunoinflammatory markers with atherogenetic markers

	IMT (mm)	CCA diameter (mm)
IL-1 beta (pg/ml)	–0,04	–0,12
IL-6 (pg/ml)	0,45	–0,10
IL-10 (pg/ml)	0,078	–0,32
TNF-alfa (pg/ml)	0,063	0,05
Basal insulin (ng/ml)	0,25	–0,17
hsPCR (µg/ml)	0,38	–0,05
HOMA index	0,19	–0,22
AGE vesperlysine-like (µg/ml)	0,17	0,06
AGE pentozidine-like (µg/ml)	0,42	–0,16

There was a correlation between the age of the study participants and the CCA diameter (r = 0.47) and between age and IMT (r = 0.2). There was no correlation between the RF number constituting MS and the CCA diameter values (r = 0.08), while between IMT and the FR number (r = 0.31) we observed a weak correlation. We determined that IMT and CCA diameter values were significantly higher in the MS group compared to the control group; these data indicate the high degree of atheromatous damage of the carotid vessels in patients with MS. So the presence of MS influences not only the dimensions of the IMT, but also of the luminal diameter.

We noticed that there is a link between the number of risk factors and the presence of atheromas with stenosis ≥50%, so 19.4% of patients with a single risk factor had stenosis over 50%, with 2 risk factors - 19.4%, with 3 risk factors - 24.5%, with 4 risk factors - 36.4%, with 5 risk factors - 37.5%.

The IMT of ex-smokers (1.02 ± 0.33 mm) and smokers (1.04 ± 0.41 mm) was found to be statistically insignificant (p = 0.74). The average duration of smoking cessation was 12.25 ± 8.78 years, the IMT values in the group of smokers and ex-smokers were statistically significantly higher compared to the IMT of non-smokers (0.97 ± 0.25 mm) (p = 0.26 and p = 0.2, respectively). It was observed that the CCA diameter in smokers is statistically significantly smaller than that of ex-smokers (p = 0.0003) and non-smokers (p = 0.0002), but no significant difference was found between ex-smokers and non-smokers (p = 0.59). The mean value of the CCA diameter in smokers was 6.46 ± 0.91 mm, in ex-smokers - 7.06 ± 1.29 mm, and in non-smokers - 6.99 ± 1.11 mm.

Carotid phenotypes were classified according to IMT values and CCA diameter, so phenotype 1 is represented by values considered normal of IMT and carotid artery diameter, phenotype 2 – high values of CCA diameter and within IMT norm, phenotype 3 – high values of IMT and within limits considered normal of the CCA diameter, phenotype 4 high values of IMT and CCA diameter. Carotid phenotype one was–recorded in 28 participants in the MS group, 10 of whom had stenosis >50% and 68 people in the control group, of which 14 had stenosis >50%. Phenotype 2 was–detected in 8 patients of which 5 were with MS and 2 had stenosis over 50%, and 3 without MS, 2 of them with severe stenosis (preocclusion), phenotype 3 was–recorded in 35 patients in the control group of which 12 had stenosis over 50%, and 61 were with MS, of which 35 with stenosis over 50%. Phenotype 4 was–observed to be present in 8 people (4 with stenosis over 50%) with MS and 2 without MS (1 with stenosis over 50%).

Respectively, we deduce that the most common phenotypes recorded in the study groups were phenotype 1 and phenotype 3, from the MS group 35.7% patients with phenotype 1 were with severe stenosis, and 20.5% from the control group, of those with phenotype 3 in the group of patients with MS 57.4% had stenosis of more than 50%, and in the group without MS – 34.3%. Phenotypes 2 and 4 were found less frequently, but in 50% of cases were associated with severe stenosis. We emphasize that the phenotype 3 was–recorded in more than half of MS patients (n=61, 59.8%), and phenotype 1 predominated in patients without MS (n=68, 62.9%) (**Fig. 5.1, fig. 5.2, fig. 5.3, fig 5.4**).

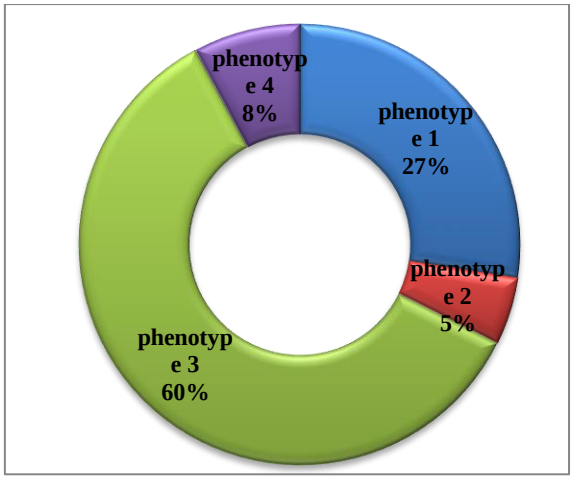

Fig. 5.1. Distribution according to carotid phenotype in patients with stroke and MS.

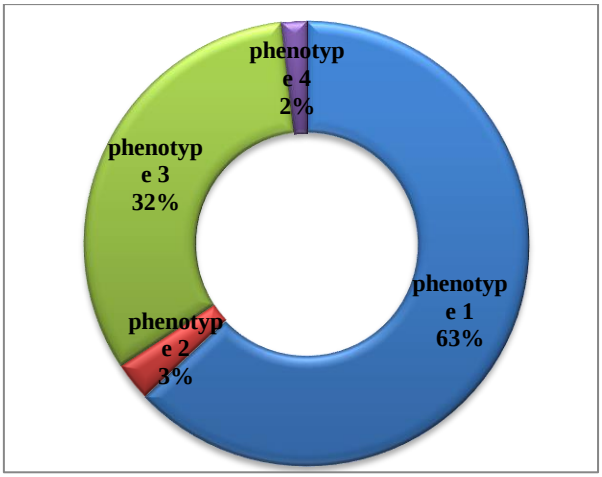

Fig. 5.2. Distribution according to carotid phenotype in patients with stroke without MS.

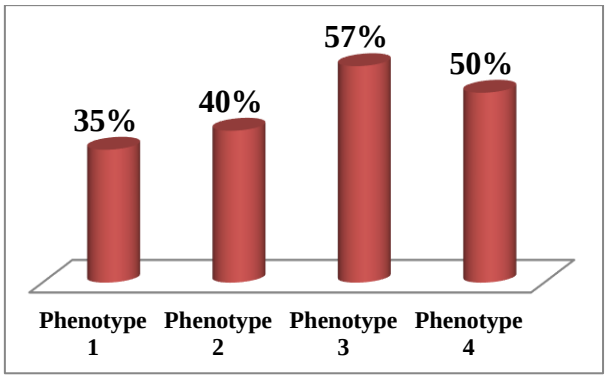

Fig. 5.3. Frequency of severe stenotic plaques in patients with ischemic stroke and MS.

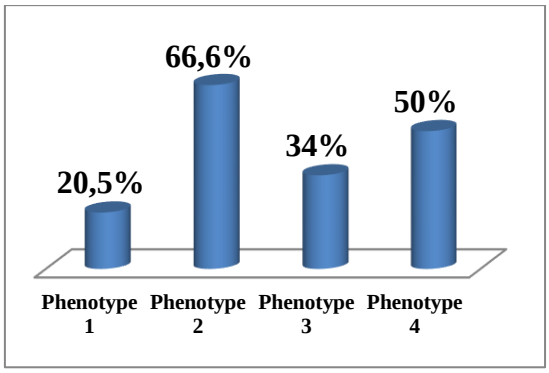

Fig. 5.4. Frequency of severe stenotic plaques in patients with ischemic stroke without MS.

By the logistic regression method we determined the possibility of predicting the development of atheromatous plaques with stenosis≥50% in case of presence of MS in patients, high values of IMT and IL–6 (**Fig. 5.5**). We found that high hsCRP values influence IMT (mm) values and the presence of atheromatous plaques. The relative risk for carotid stenosis of more than 50% for ≥6 μg / ml values of hsCRP in patients with ischemic stroke is 1.7 times higher in patients with MS compared to those without MS (CI $_{95\%}$ 1.15–2.5, z=2.6) (**Fig. 5.6**).

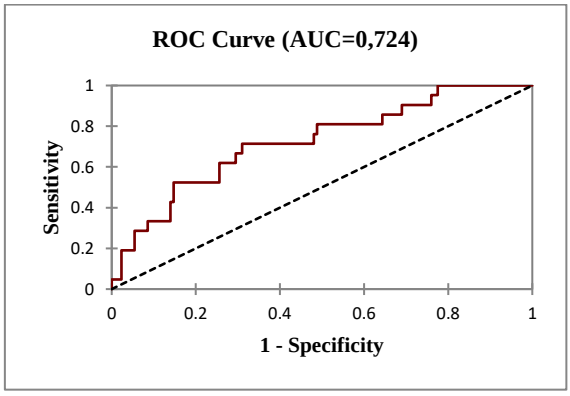

Fig. 5.5. ROC curve for predicting stenoses ≥50% in patients with ischemic stroke depending on IL-6, IMT and MS

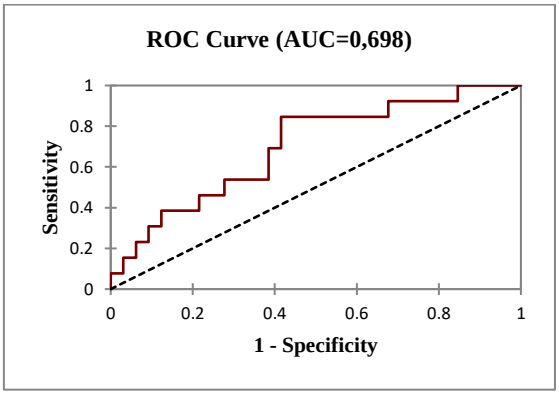

Fig 5.6. ROC stenosis prediction curve ≥50% in patients with ischemic stroke according to hsPCR values.

The obtained results suggest that the cluster of risk factors constituting MS is associated with altered carotid artery structure, these changes explaining the relationship between MS and the high risk of cardiovascular and cerebrovascular diseases. In MS, the risk of cerebrovascular disease is multifactorial, and their early detection and treatment can prevent vascular events.

6. **GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS**

GENERAL CONCLUSIONS

1. The clinical manifestations in patients with MS and stroke did not differ from those presented in the group of patients with ischemic stroke, but without MS, except that in patients of the control group 2 times more frequently the atactic syndrome was registered.
2. The most common RF presented by patients with ischemic stroke was hypertension of various degrees, its share being 98.04%, without any statistically significant difference in the 2 study groups. Number of patients with abdominal obesity and dyslipidemia was found more frequently in patients with MS (95.09% vs. 62.03% and 75.5% vs 58.3%, respectively). The most common combination of 2 risk factors was hypertension and abdominal obesity found in 62% of the control group and 95% of the MS group.
3. In the group of patients with MS, a carotid phenotype was observed manifested by increased values of IMT found in 59.8% of patients with MS and associating plaques with severe stenosis in 57.4% of cases, while in the control group the carotid phenotype with normal values of CCA and IMT predominated.
4. It was established the correlation between the number of constituent risk factors of MS (r = 0.3), the high level of basal insulin (r =0.25), pentosidine-like AGE (r=0.42) and IL−6 (r=0.45) and markers of atherosclerotic damage of carotids, such as IMT. Carotid artery stenosis ≥50% was found to be almost 2 times higher in patients with MS. It was determined that patients with MS have a 1.6 times higher risk of elevated IMT (mm) and a 2.18 times higher risk of cartotid stenosis ≥50%.
5. Despite a correlation between the degree of inflammatory cytokine expression and the degree of neurological deficit using the NIHSS scale, their usefulness for predicting functional recovery in patients with ischemic stroke is not yet sufficiently substantiated, but it is necessary to accumulate strong evidence for the elaboration of complex systems for estimating the prognosis of patients with ischemic stroke according to the values of inflammatory cytokines.
6. We established predictive values for an unfavorable prognosis of ischemic stroke for MMP-9 (> 10 ng / dl), for S-100 protein β(> 1.0 μg / l), for hsCRP (> 13 μg / l).
7. The combined use of oxidative stress markers (AOPP, AGE, catalase, ceruloplasmin) is possible in order to estimate the aggravation of neurological deficit in patients in the acute phase of ischemic stroke. AOPP and AGE values were statistically significantly elevated in patients with MS, while antioxidant factors (ceruloplasmin and catalase) were decreased.

PRACTICAL RECOMMENDATIONS

1. The research results argue the need for diagnosis at the level of the primary health care, MS based on the criteria of AHA, NHLBI, IDF (2009), in order to initiate early measures of prophylaxis of vascular complications.

We propose the following evaluation algorithm for the purpose of primary prophylaxis:

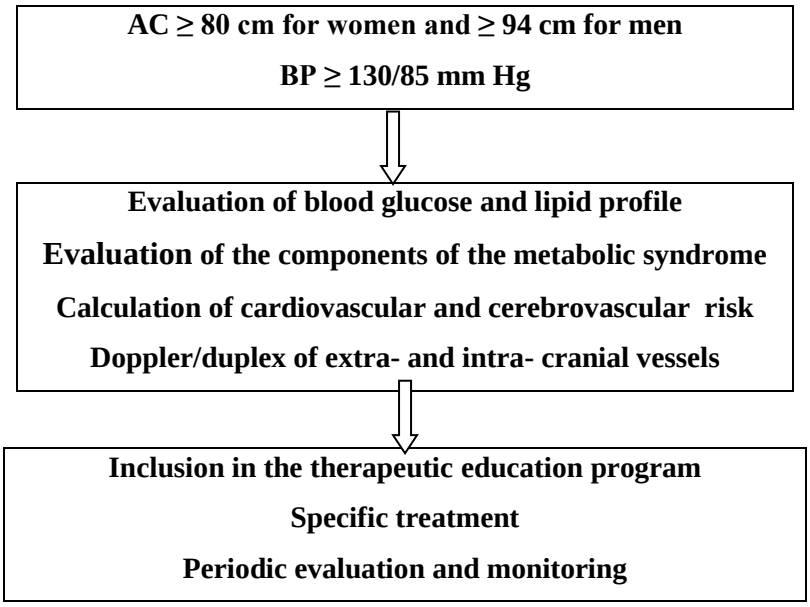

Fig. 6.1. Evaluation algorithm for primary prophylaxis.

Given that a significant proportion of patients with ischemic stroke have sought medical help outside the therapeutic window, it is argued that family physicians need to be informed and he must introduce into the patient's schooling system, especially hypertensive, diabetic and MS, the FAST score for recognizing the signs of a stroke.

2. Ultrasound examination of the extracranial segment of the carotid arteries is recommended in all patients with MS for primary prophylaxis of vascular events, and in all patients who have suffered an acute stroke regardless of the presence / absence of MS for secondary prophylaxis.

3. Implementation in practice of the determination of serum IL 6 values and hsCRP in MS patients could be useful in quantifying the individual risk for stroke.

4. MMP-9 is a reliable marker of permeability of the blood-brain barrier, it could be used for the unfavorable prognosis of ischemic stroke and the possibility of hemorrhagic transformation of the ischemic area, it is appropriate to include in the future in the selection criteria of patients eligible for vascular recanalization treatment.

5. Protein S-100β and hsCRP could be used as prognostic markers to detect early the possibility of an unfavorable evolution of stroke and help to provide early care.

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INFORMATION ON VALUATION OF RESEARCH RESULTS

- **Articles in international scientific journals (abroad):**

- articles in journals Scopus, Pubmed, And other international databases SCOPUS

1. CIOBANU, N., GROPPA, S. The relationship between vascular changes and risk of vascular events in subjects with metabolic syndrome. In: *Archives of the Balkan Medical Union.* 2017, nr. 52(1), pp. 68-74. ISSN 0041-6940.

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LIST OF ABBREVIATIONS

AC – abdomen circumference
AF – atrial fibrillation
AGE – advanced glycation endproduct
AOPP – advanced oxidation protein products
AUROC – the surface below the ROC curve "sensitivity versus"
BMI – body mass index
BP – blood pressure
CCA – common carotid artery
CI – confidence interval
CT – computed tomography
DM – diabetes mellitus
ECG – electrocardiogram
HDL-cholesterol – high density lipoproteins
HOMA – insulin resistance index
hs-CRP – highly sensitive C-reactive protein
IDF – International Diabetes Federation
IL – interleukina
IMT – intima-media thickness
LDL-cholesterol – low density lipoprotein
MI – myocardial infarction
MMP-9 – matrix metalloptroteinase–9
MS – metabolic syndrome
NO – nitric oxide
NO2 – nitrate
NO3 – nitrite
p – test of statistical significance
r – correlation index
RF – risk factor
ROC – Receiver-operating characteristic curves
RR – relative risk
TNF-α – tumor necrosis factor
TOAST – Trial of Org 10172 in Acute Stroke Treatment