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Clinical Neuroimaging Peculiarities and Functional Consequences of Ischemic Stroke in Patients with MS

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Keywords:
ischemic stroke;
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cortex atrophy;
volumetric test.

Abstract.

The objective of the research was to study the peculiarities of post-stroke period in patients with metabolic syndrome (MS), functional consequences, cognitive impairment, to identify structural brain changes on the basis of MRI results; to perform correlation analysis between the brain volumetric test results and cognitive deficit.

Materials and methods. The study involved 116 patients, aged 51 to 81, with ischemic stroke, 79 patients – main group – during the early and late recovery periods after ischemic stroke related to MS. The control group included 37 patients in the early and late recovery periods after acute cerebrovascular accident (ACVA) without MS. To determine the functional consequences of ischemic stroke after 12 weeks and 1 year after it, the examination was conducted and the results were evaluated according to modified Rankine scale (MSHR) and Barthel Index (BI). We determined patients' mortality rate within 1 year after the ischemic stroke. Their condition of cognitive functions was measured according to MMSE, MOSA and FAB scales. The volume of cortex and white matter of the cerebral hemispheres, temporal and frontal lobes were measureed (cm^3) by applying MRI scanner Toshiba Vantage Titan 1,5. Workstation Vitrea was used for images post-processing.

Results. Patients with MS had more common significant signs ($p<0.05$) of neurological status functional disorders, delayed recovery and disability. Within a year, in the main group mortality rate because of recurrent stroke was 5.06%, which was significantly higher than in the control group, where the mortality rate was 2.7%. Within a year, the process of lost functions restoring according to MSHR occurred in both groups, but in the main group, this rate was significantly lower in comparison to the control group. Patients with MS were determined to have a significant impairment of cognitive functions according to cognitive scales. However, a year later cognitive performance did not differ significantly in the main and control groups, although they declined in both groups. Volumetric parameters were determined: the volume of cortex and white matter of the cerebral hemispheres, temporal and frontal lobes (cm^3). Results obtained: reduced total volume of the brain, of the temporal and frontal lobes in patients of the main group ($p<0.05$). Patients of both study groups were determined to have cognitive functions impairment - reduced volume of the cortex in the frontal and temporal lobes according to MMSE scale. The correlation index between cortex indicators of frontal and temporal lobes volume and the results of cognitive functions according to MMSE scale was: $r = 0,62$ - temporal and $r = 0,59$ frontal lobes indicators. Modules of correlation coefficients were within the average strength.

Conclusions. Patients who have suffered from primary ischemic stroke related to MS restored their lost functions slower and the mortality rate among them was significantly higher ($p<0.05$) within the first year after stroke than in patients without MS. Patients had cognitive deficits related to cortex atrophy in the frontal and temporal lobes after the primary ischemic stroke. Atrophy in these areas of the cortex was more distinct ($p<0.05$) than in patients without MS. Positive correlation relationship was determined between cognitive performance and the degree of cortex atrophy in the frontal ($r = 0.59$) and temporal ($r = 0.62$) lobes of patients with ischemic stroke related to MS.

Problem statement and analysis of the recent research

The high morbidity, mortality and disability resulting from strokes have made this problem not only a medical but also a social one. Every year about 5.5 million people die from stroke in the world. However, the stroke morbidity and mortality vary widely depending on the economic level of the country. On average it makes up 200-220 persons per 100,000 population [1, 2]. More than one third of these cases are fatal, one third of patients tend to need care and outside assistance, becoming a burden to their families and state, and not more than 20% of the patients return to their usual daily activities they used to do before the disease [3, 4, 5]. Although in recent years the mortality rate from stroke tends to decrease in our country, but it is still almost twice higher than the rate in the developed countries in Europe and where it is 70-80 cases per 100,000 population [6,7,8]. The ischemic stroke constitutes 80-85% of all acute cerebrovascular accidents (Zozulya I.S. and co., 2012). Only for medical care of the patients' with acute ischemic stroke is spent from 4 to 6% of the funds allocated to health care in the developed countries annually.

All the above mentioned information causes interest in the stroke risk factors correction, treatment and prevention. Today, such risk factors as stroke, hypertension, physical inactivity, obesity, dyslipidemia, smoking and combination of them have increased among the population. That is why the problem of metabolic syndrome (MS) comes to prominence.

The most important argument for studying the impact of MS on the origin, course and prognosis of ischemic stroke is its atherogenic affect leading to cardiac and cerebrovascular complications of atherosclerosis. Many studies have shown that patients with MS have often early atherosclerosis signs of carotid and coronary arteries. This indicates that the causes of myocardial infarction, ischemic stroke, peripheral vascular disease have a common origin. Scientific interest encouraged by MS, determines the evolution of the views on such components of MS as hypertension, abdominal-visceral adiposity, insulin resistance and diabetes. These factors should be considered as a generalized cardiovascular-metabolic disease. [9] The MS definition of ATP classification - III National Cholesterol Education Program in the US [10] is widely used in the clinical practice.

MS can be characterized as clinical and pathogenic complex of symptoms associated with multiple disturbances of metabolic processes, of mechanisms regulating endothelial function, of blood pressure homeostasis processes which form on the background of neurologic, of immunologic and endocrine dysfunctions under the conditions of reduced tissue sensitivity to insulin - insulin resistance and systemic hyperinsulinemia associated with it. Results of Fremingham Heart Study and Parisian Prospective Project have shown that hyperinsulinemia is an independent risk factor for atherosclerosis but insulin-dependent diabetes, abdominal-visceral obesity, elevated levels of fibrinogen and of highly sensitive C-protein in the blood, along with dyslipidemia, hypertension and smoking are the main pathogenic risk factors for cardiovascular diseases [11].

Among the Finnish population, the relationship between the individual components of MS and the risk of primary stroke has been studied involving almost a thousand of people for 14 years. Abdominal obesity (waist > 102 cm in men and > 88 cm in women), regardless of the other components of MS, was associated with an increased relative risk of stroke developing, 1.52 times up (95% CI, 1.06-2.17, $p<0.05$) [12].

Numerous prospective studies indicate that MS has promoted cardiovascular morbidity and mortality RATE in recent years, and it concerns coronary heart disease and ischemic stroke in particular [Lakka H.M. et al., 2002, Ford E.S., 2004; McNeil A.M. et al., 2005; Iso H. et al., 2007]. According to S.Cronin al. [2009] MS increases the risk of ischemic stroke more than twice. With the increasing number of MS components, the risk of stroke is several times up. If there are five MS

components present - the risk increases 5 times. The most important components of MS are hypertension and hyperglycemia.

According to Boden-Albala B. et al., [2008] 3298 patients who had cerebrovascular disease combined with components of MS revealed the risk of stroke occurrence by 50% higher during 6 years of monitoring. In case of MS successful treatment, the risk of stroke occurrence reduced by 19% on average in men and by 30% in women [13].

Japanese scientists having analyzed more than 2,000 people's MRI brain results without cardiovascular and cerebrovascular pathology, found a direct, independent and linear relationship between the value of the waist index and the number of lacunar cysts in the brain [14].

The literature presents scarce results on clinical and neuroimaging peculiarities of ischemic stroke in patients with MS, on comparison of brain morphometric characteristics and its cognitive and functional consequences.

The objective of the research was to study the peculiarities of post-stroke period in patients with MS, functional consequences, cognitive impairment, to identify structural changes in the brain on the basis of MRI results; to perform correlation analysis between the brain volumetric test results and cognitive deficit.

Materials and methods of the research

To determine the significance of MS affect on the patients' early and late recovery periods after ischemic stroke, 116 patients were examined and monitored. Monitoring was conducted during their in-patient treatment in the neurological department, individual visits, by means of mail survey and telephone interview.

79 patients, aged 51 to 81, were examined during the early and late recovery periods after ischemic stroke while receiving in-patient treatment in the neurological department of Kyiv City Hospital №9. The control group included 37 patients during their early and late recovery periods after acute cerebrovascular accident (ACVA) without MS.

To determine the functional consequences of ischemic stroke, examination was conducted after 12 weeks and 1 year after it. Post-stroke consequences (degree of disability) were defined according to MSHR. The degree of activities of daily living and the degree of dependency activities of daily living were evaluated by applying Barthel Index (BI). We determined patients' mortality 1 year after ischemic stroke.

Patients were given a complete neurological examination (complaints, medical history, neurological status, examination of the cardiovascular system, blood pressure, ECG, blood glucose test, anthropometric measurements were taken). The condition of cognitive function was measured by applying MMSE, MOSA and FAB scales.

To diagnose metabolic syndrome, IDF and AHA /NHLBI criteria were used (2005, modified in 2009).

Total cholesterol level, HDL cholesterol and triglycerides were determined by means of enzymatic method, both LDL and VLDL cholesterol levels were calculated by the conventional method. To determine insulin resistance, index HOMA was used.

All patients were performed MRI of the brain and determined the extent of ischemic foci.

The brain and its liquor system of 41 patients (27 patients with MS - Group 1 and 14 patients without MS - group 2) were assessed with the help of volumetric method (measuring volume of certain brain areas) with MRI scanner Toshiba Vantage Tenitan 1,5. Workstation Vitrea was used for images post-processing. We used MRI sequences: T1 - suspended images, T2 - suspended images, Isotropic, Flair, DWI, T2 *, FSBB. We determined the volume of cortex and white matter of the cerebral hemispheres (cm^3), of temporal and frontal lobes.

Results of the research

The patients' distribution in the comparison groups, based on gender is provided in Table 1.

Table 1

The patients' distribution based on gender during early and late recovery periods after ischemic stroke

	Main group (n 79)		Control group (n 37)	
	men	women	men	women
The number of patients (n) and %	34 (40.6%)	45 (59.4%)	17 (45.5%)	20 (54.5%)

Data provided in table 1 revealed gender distribution in the main and control groups, where women are dominating. It is likely due to the facts that women are more medically conscious, they follow doctors' prescriptions more carefully and stick to schedules of the visits, and that greater number of women participated in the study.

Post-stroke functional consequences in the study groups according to modified Rankine scale (MSHR) are provided in Table 2.

Table 2

Post-stroke functional consequences 12 weeks after CVA

	Evaluation according to MSHR, points			
	1 point	2 points	3 points	4 points and more
Main group(n 79)	16 (20.3%)	23 (29.1%)	28*(35.4%)	12*(15.1%)
Control group (n 37)	11 (29.7%)	19(51.35%)	5 (13.5%)	2 (5.5%)

*$p<0.05$ – in comparison to the control group.

Data provided in table 2 prove that the patients with MS had more functional disturbances of neurological status, delayed recovery and signs of disability.

The main group included the greatest number of patients with medium degree of capacity loss (3 points) 3 months after the disease onset, when the patients could walk independently but needed a physical, psychological or intellectual assistance.

A large number of patients with mild capacity loss (2 points) composed the main group as well, the condition when patients could serve themselves, but not as properly as before the disease. In addition, among patients with a mild capacity loss (1 point) there was defined the difference between the main and control group with the reduced number of patients with MS. We observed a delayed recovery in the early period after stroke in patients with MS in the groups where evaluation of patients' condition corresponded 3 and 4 points according MSHR.

To evaluate recovery process after ischemic stroke objectively 1 year after it, the patients with MS of both groups were examined and their condition was assessed according to MSHR. At the same time the analysis of patients' mortality was made during 1 year of recovery after ischemic stroke. The results of the study are provided in Tables 3 and 4.

Data provided in Table 4 reveal that mortality rate was 5.06% in the main group, which is significantly higher than in the control group, where the rate of mortality was 2.7%. All patients died because of recurrent stroke (data about patients' injuries, poisoning and other possible causes of death have not been received).

Table 3

Post-stroke functional consequences 1 year after CVA

	Evaluation according to MSHR, points			
	1 point	2 points	3 points	4 points and more
Main group(n 75[1])	26 (34.7%)*	24 (32%)	21*(28%)	4 (5.33%)
Control group (n 36[1])	21 (56.75%)	10 (27.0%)	5 (13.5%)	

*P<0.05 – in comparison to the control group

[1]During 1st year of recovery after ischemic stroke, the number of patients decreased in comparison to their original number due to mortality.

Table 4

Patients' mortality during 1st year of recovery after ischemic stroke

	The number of patients (per cent)
Main group	4 (5.06%) *
Control group	1 (2.7%)

*P<0.05 – in comparison to the control group

Thus, the data provided Table 3 indicate that the process of lost functions restoring according MSHR occurred in both groups within the previous year. The number of patients with a mild capacity loss (1 point) increased, but their number was significantly lower in the main group than in the control group. The number of patients with MS, who had medium degree of capacity loss, slightly increased due to their improved condition. The number of this category of patients decreased in the control group as well due to their reduced neurological deficit and due to considering them to be patients with a mild capacity loss. The number of patients who had medium degree of capacity loss reduced significantly in the control group (3 points). Almost all the patients were considered to have mild capacity loss.

We determined the dynamics of activities of daily living according to BI in both main and control groups 12 weeks and 1 year after ischemic stroke. The data are provided in Table №5.

Table 5

Dynamics of activities of daily living according to BI

	Barthel Index (points)	
	12 weeks after CVA *Me [Q1,Q3]*	1 year after CVA *Me [Q1,Q3]*
Main group	75[50;70]	85[65;75]
Control group	85[60;85]	90[75;95]

*P<0.05

There were more patients requiring assistance in the main group. A year after the disease onset there was determined a decline of dependency on the outside assistance while using the toilet and taking personal care in both groups. During the primary examination, the median of differences between the main and control groups was 10 points, and after 1 year the difference was 5 points.

In addition to motor and sensory disturbances that occurred in patients due to ischemic stroke, there was a significant number of cognitive functions disturbances that appeared to be an independent causative factor affecting patients' social adaptation and quality of life during the early and late recovery periods.

To determine the impact of MS on the development of patients' cognitive and non cognitive disorders during their early and late recovery periods, we performed of those patients' neuropsychological testing who were able to come to visit with their care givers and do tests.

Table 6 provides neuropsychological test results according to MMSE, MOCA and FAB scales 12 weeks after the stroke.

Table 6

Neuropsychological test results according to MMSE, MOCA and FAB scales 12 weeks after the stroke

	Main group					Control group				
	Min	*Max*	*Me*	Q1	Q3	*Min*	*Max*	*Me*	Q1	Q3
MOCA	16	25	21.00*	22.5	23,5	19	27	23.00*	21.50	24.00
MMSE	18	25	22.00*	23.25	24,75	19	28	23.00*	21.50	25.00
FAB	11	17	14.00	12.5	15,5	12	18	16	13.50	17.50

*p<0.05

Table 7 provides neuropsychological test results according to MMSE, MOCA and FAB scales 1 year after the stroke.

Table 7

Neuropsychological test results according to MMSE, MOCA and FAB scales 1 year after the stroke

	Main group					Control group				
	Min	*Max*	*Me*	Q1	Q3	*Min*	*Max*	*Me*	Q1	Q3
MOCa	16	25	21.50	22.5	23.5	19	27	22.00	21.50	24.00
MMSE	18	25	22.00	23.25	24.75	19	28	22.00	21.50	25.00
FAB	11	16	12.00	12.5	15.5	12	18	15	13.50	17.50

*p<0.05

Results provided in Tables 6 and 7 suggest that the patients with MS were identified to demonstrate significantly worse cognitive performance than those without MS. The results according to all the three scales without exception prove it. But a year later, cognitive parameters in the main and control groups did not significantly differ, although they declined in both groups.

Taking into account disputable test results obtained after a year of the disease onset, we analyzed some indicators of the brain structures and, above all, the volume of white and gray cortex substances of the brain hemispheres, of the frontal and temporal brain lobes, of the right and left hippocampus (cm^3).

The brain and its liquor system of 38 patients (24 patients with MS – main group and 14 patients without MS – control group) were assessed with the help of volumetric method (measuring volume of certain brain areas) with MRI scanner Toshiba Vantage Tenitan 1,5. Workstation Vitrea was used for images post-processing. We used MRI sequences: T1 - suspended images, T2 - suspended images, Isotropic, Flair, DWI, T2 *, FSBB.

The greatest changes occurred in the frontal and temporal brain lobes. In this regard, we held volumetric measurements of the temporal and frontal brain lobes. The data are presented in Table 8.

Table 8

The volume of white and gray (cortex) substance of the temporal brain lobe (см³).

Measurement area	Main group (n=24) Me (Q1,Q3)	Control group (n=14) Me (Q1,Q3)	P
The volume of gray (cortex) substance of the temporal brain lobe (см³)	94.5 [82;107] *cm^3	137.5 [115;160] cm^3	0.05
The volume of white (cortex) substance of the temporal brain lobe	99 [82;110] *	135[125;145]	0.05

*P <0.05 – in comparison to the control group

Table 9

The volume of white and gray (cortex) substance of the frontal brain lobe (см³).

Measurement area	Main group (n=24) Me (Q1,Q3)	Control group (n=14)Me (Q1,Q3)	P
The volume of gray (cortex) substance of the frontal brain lobe (см³)	94.5 [82;107] *cm^3	137.5 [115;160] cm^3	0.05
The volume of white (cortex) substance of the frontal brain lobe	99 [82;110] *	135[125;145]	0.05

*P <0.05 – in comparison to the control group

Figures 1, 2, 3 demonstrate volumetric measurements of brain structures.

The cortex volume of frontal and temporal lobes as well as cognitive impairments were analyzed according to MMSE scale. The results are presented in Table 10.

Table 10

Relationship between cognitive performance and the cortex volume of frontal and temporal lobes

	Main group (n=24) Me (Q1,Q3)	Control group (n=14) Me (Q1,Q3)
Volume of gray matter(cortex) of frontal lobe (cm^3) Me [Q1Q3]	126 [82;147] *cm^3	197.5 [112;240] cm^3
Volume of gray matter(cortex) of temporal lobe (cm^3)	94.5 [82;107] *cm^3	137.5 [115;160] cm^3
MMSE (points) Me [Q1Q3]	23.0*[22.0; 25.0]	24.5 [23.5; 26.0]

*p<0.05- the significant difference in comparison to control group

Data provided in Table 10 show that the patients of both study groups were determined to have the impairment of cognitive performance according to MMSE scale with reduced cortex volume in the frontal and temporal lobes. The correlation between the cortex volume of frontal and temporal lobes and the results of cognitive performance according to MMSE scale was determined. The correlation index was r = 0.62 – of temporal lobe and r = 0.59 of frontal lobe. Modules correlation coefficients were within the average strength.

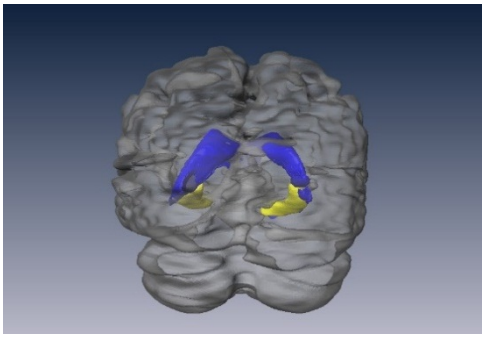

Fig. 1. Volume measurements of the cerebral cortex, of the hippocampi and of the lateral ventricles(lateral ventricles of brain hemispheres are marked with a blue colour, hippocampi are marked with a yellow colour)

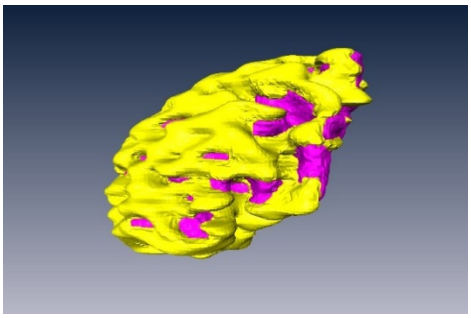

Fig. 2. Volume measurements of the cerebral cortex and of white matter of the frontal brain lobe (cerebral cortex of white matter of the frontal brain lobe is marked with a yellow colour, white matter of the frontal brain lobe is marked with a pink colour).Patient Sh., 67 years old, main group, partial atrophy of cerebral cortex of the frontal brain lobe.

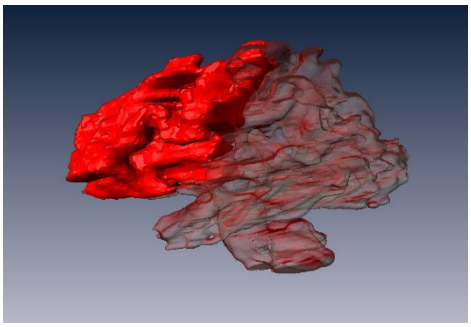

Fig. 3. Volume measurements of the frontal brain lobe. Patient S., 65 years old, control group.

Discussion of the results

Patients with MS had more significant signs of neurological status functional disorders, delayed recovery and disability12 weeks and a year after ischemic stroke according to MMSE scale. The obtained results prove that patients' with MS early recovery was delayed after ischemic stroke. A year after ischemic stroke, mortality rate was significantly higher among patients with MS than in patients' group without MS.

According to the information provided in the literature, more than 80% of patients are diagnosed with cognitive disorders, and in one third of cases they have certain degree of dementia after ischemic stroke [15]. In addition, a stroke may be complicated by the development of other

neuropsychiatric disorders of emotional-affective and behavioral characteristics - depression, anxiety, apathy. The cause of post-stroke cognitive impairment may be multiple infarction brain damage, separate infarction of 'strategic' areas or a combination of cerebral infarction with diffuse affection of cerebral matter of different origin.

Patients with MS were determined to have a significant cognitive impairment in comparison to the patients without MS according to cognitive measurements scales. But 1 year later, the cognitive parameters both in the main and control groups did not differ greatly though they declined in both of them. It could be connected, on the one hand, with changing comorbide factors and cofactors of underlying condition. For example, except possible increase in waist (3 patients did not have that abnormality when they were included into the control group), patients had heterotonia, hypertriglytceridaemia, ischemic coronary heart disease, anxiety and depressive disorders. On the other hand, ischemic stroke foci developing in the 'strategic' areas of the brain could provoke cognitive impairments. In addition, the neurodegenerative process that had heterogeneous genesis, after acute ischemic stroke was associated with vascular, dismetabolic and other changes in the brain, and it was not related to MS cluster.

The correlation of cognitive functions (according to MMSE scale) and changes of cortex matter volume proved that after primary ischemic stroke related to MS with a reduced cortex volume in the frontal and temporal lobes, patients had significant cognitive deficit. The correlation index was: r = 0.62 – temporal lobe volume reduction and r = 0.59 – frontal lobe volume reduction. Modules of correlation coefficients were within the average strength.

Obviously, increased apoptosis in the frontal and temporal lobes contributed to the atrophic processes in the cortex of these brain areas and to cognitive functions impairment.

Conclusions

1. Patients who have suffered from primary ischemic stroke related to MS, restored their lost functions slower and the mortality rate among them was significantly higher ($p<0.05$) within the first year after stroke than in patients without MS.
2. Patients had cognitive deficits related to cortex atrophy in the frontal and temporal lobes after the primary ischemic stroke. Atrophy in these areas of the cortex was more distinct ($p<0.05$) than in patients without MS.
3. Positive correlation relationship was determined between cognitive performance and the degree of cortex atrophy in the frontal ($r = 0.59$) and temporal ($r = 0.62$) lobes of patients with ischemic stroke related to MS.

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