The relationship between structural change of neck vessels and cognitive functions in patients with metabolic syndrome

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Abstract

Background. Carotid atherosclerosis is closely connected with the development of stroke, cognitive deficits and dementia. The impact of the localization of carotid atherosclerosis on the development of cognitive deficits remains unclear. **Objective.** To analyze the relationship between the indicators of cognitive functions and structural changes of the carotid arteries in patients with metabolic syndrome (MS). **Design and methods.** The study included 178 patients divided into 2 groups. The first group included 80 patients (44,94 %) with MS without cognitive impairment. The second group consisted of 98 patients (55,06 %) with MS and cognitive disorders. All patients underwent neuropsychological testing, cognitive evoked potential (EP) for the assessment of cognitive functions, and the thickness of intima-media (TIM) of the carotid arteries was determined. **Results.** There was an increase in TIM of the internal carotid artery ($p < 0,01$) and bifurcations ($p < 0,01$) in the group of patients with MS and cognitive deficit compared to the group without cognitive disorders. The correlation was established between the TIM of the internal carotid artery and bifurcations and the results of Mini-Mental State Examination test ($p < 0,01$), as well as responsiveness and concentration ($p<0.01$), an indicator of memory, storage and display of information ($p < 0,01$). We also have found a significant relationship between TIM of the internal carotid artery, bifurcation and the cognitive EP latency period ($p < 0,01$). **Conclusions.** According to the neuropsychological testing and cognitive evoked potentials the increase of TIM in the internal carotid artery and bifurcations is associated with the development of cognitive impairment.

Key words: cognitive dysfunction, intima-media thickness, metabolic syndrome, cognitive evoked potential.

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Взаимосвязь между структурными изменениями сосудов шеи и когнитивными функциями у пациентов с метаболическим синдромом

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Резюме

Актуальность. Атеросклероз в сонных артериях тесно связан с развитием инсульта, когнитивного дефицита и деменции. Остается неясным влияние локализации изменений в сонных артериях на развитие когнитивного дефицита. **Цель исследования** — проанализировать взаимосвязь показателей когнитивных функций и структурных изменений сонных артерий у пациентов с метаболическим синдромом (МС). **Материалы и методы.** В исследование были включены 178 пациентов. Были сформированы 2 группы. В первую группу вошли 80 пациентов (44,94 %) с МС без когнитивных нарушений при проведении скринингового исследования. Вторую группу составили 98 пациентов (55,06 %) с МС и когнитивными расстройствами. Всем пациентам выполнялось нейропсихологическое тестирование, когнитивный вызванный потенциал (КВП) для оценки когнитивных функций, определялась толщина комплекса «интима-медиа» (ТИМ) сонных артерий. **Результаты.** В группе пациентов с МС и когнитивным дефицитом, по сравнению с группой без когнитивных расстройств, отмечалось увеличение ТИМ внутренней сонной артерии ($p < 0,01$) и бифуркации ($p < 0,01$). Выявлена корреляция между ТИМ внутренней сонной артерии и бифуркации и результатом тестирования Mini-Mental State Examination ($p < 0,01$), быстротой реакции и способностью концентрировать внимание ($p < 0,01$), показателем запоминания, хранения и воспроизведения информации ($p < 0,01$). Выявлена взаимосвязь между ТИМ внутренней сонной артерии и бифуркации и латентным периодом КВП ($p < 0,01$). **Выводы.** Увеличение ТИМ в зоне внутренних сонных артерий и бифуркации связаны с развитием когнитивных нарушений как по данным нейропсихологического тестирования, так и когнитивного вызванного потенциала.

Ключевые слова: когнитивные нарушения, толщина комплекса «интима-медиа», метаболический синдром, когнитивный вызванный потенциал.

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Introduction

Carotid atherosclerosis underlies cerebrovascular disease and is closely associated with the development of stroke, cognitive impairment and dementia [1–4]. Most studies evaluated the relation between atherosclerotic changes in carotid arteries and cognitive function in patients with cerebrovascular disease. Predominantly patients with severe stenosis in carotid arteries were included [5, 6]. Several studies demonstrated that a mild atherosclerotic asymptomatic stenosis of the carotid arteries was associated with the decrease of neuropsychological testing results [7, 8]. In 2011, in a study involving 2,794 people aged 21–84 years old atherosclerotic changes were assessed by the intima-media thickness (IMT) and the presence of plaques in carotid arteries. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). A significant correlation between changes in the carotid arteries and cognitive functions was found [8].

Traditional cardiovascular risk factors are associated with both atherosclerotic lesions in carotid arteries and cognitive deficits. The combination of abdominal obesity with two or three components of metabolic syndrome (MS) is associated with the thicker carotid IMT [9–13]. The pathophysiology of these processes remains unclear [9, 10, 14]. Stenosis and carotid IMT shows different stages and severity atherosclerotic lesion. IMT is considered a marker of subclinical atherosclerosis. The relation between hypertension (HTN), atherosclerosis and IMT complex and may reflect their interaction. On the one hand, carotid artery stenosis is associated with greater atherosclerotic lesion. On the other hand, IMT and carotid stenosis are associated with cardiovascular events, i. e. stroke and myocardial infarction [15–17]. Magnetic resonance imaging studies demonstrated that IMT is linked to the changes in the brain in elderly patients [18]. There are no such data in young and middle-aged patients. Evaluation of the atherosclerotic process in different parts of carotid arteries may play an important role in cerebrovascular disease and cognitive impairment [19]. Several studies showed that, depending on the cardiovascular risk factors localization of carotid arteries lesions may be different [20]. The impact of carotid arteries lesions localization on the cognitive impairment is still disputable.

The purpose of this study was to analyze the interrelation between cognitive dysfunction and structural changes of the carotid arteries in patients with MS.

Design and methods

The study included 178 patients (Table 1), and 2 groups were formed. The first group included 80 patients (44.94 %) with MS without cognitive impairment according to the results of screening study. The second group consisted of 98 patients (55.06 %) with MS and cognitive impairment.

The groups were matched by age and sex. Duration of HTN, obesity, and «office» blood pressure (BP) were comparable in the study groups.

Anthropometric indicators were measured in all patients, including waist and hip circumferences, body mass index (BMI). Three BP measurements at 2-minute- intervals in the sitting position after 5 minutes of rest were taken according to standard procedure.

Plasma glucose, lipid profile, C-reactive protein (CRP) were assessed with the use of the biochemical analyzer (production ARCHITECT C8000, Germany) and standard reagents («Abbott», Germany). Plasma insulin levels was assessed by Microparticle Enzyme Immunoassay (MEIA)-AxSymInsulin.

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS). Cognitive function was assessed by neuropsychological scales: Mini-Mental State Examination (Mini-Mental State Examination, MMSE), a Frontal lobe dysfunction battery, clock drawing test, and test «10 words by Luria». Schulte test was used for reaction speed and memory concentration assessment.

Subjective complaints of memory and attention impairment were assessed using a CFQ questionnaire (Cognitive Failures Questionnaire). The result CFQ < 1 point was considered an indicator of a non-significant complaints, CFQ > 1 point — an indicator of negative self-assessment of cognitive functions. Wechsler Memory Scale (WMS) was used to estimate memory.

Quantitative assessment of cognitive function was determined by cognitive evoked potential (CEP) (P300) using EMG/EP Nicolet Viking Select. The technique of P300 examination is based on the paradigm of «odd ball», when a subject has to count «non-significant» (frequent) and «significant» (rare) stimuli given randomly at series of two stimuli. To register CEP we used stimulation by auditory stimuli as a click with a different tone to the significant stimulus, with the duration 50 msec, significant stimuli were

Table 1

CHARACTERISTICS OF THE GROUPS

Parameter	MS without CI n = 80 (1st group)	MS with CI n = 98 (2nd group)
age	47.49 ± 6.49	47.76 ± 5.17
sex. male/female (%)	48 (60 %) / 32 (40 %)	46 (46.93 %) / 52 (53.07 %)
IMT, kg/m²	30.92 ± 3.30	32.70 ± 4.74 *
WC, cm	99.40 ± 9.93	103.33 ± 11.32 *
HC, cm	111.94 ± 7.66	113.54 ± 12.54 *
SBP, mmHg	144.06 ± 13.05	146.18 ± 14.30
DBP, mmHg	89.14 ± 8.55	90.85 ± 10.21

Note: MS — metabolic syndrome; CI — cognitive impairment; BMI — body mass index; WC — waist circumference; HC — hip circumference; SBP — "office" systolic blood pressure; DBP — "office" diastolic blood pressure; * — $p < 0.05$ compared to the group of patients without cognitive impairment.

given at the rate of 2000 Hz and the probability of 20–30 %; non-significant stimuli were applied at the rate 1000 Hz and the probability of 70–80 %. The intensity of the stimuli was 80 dB, and the interval between stimuli was 1 second. We used binaural stimulation. For analysis we applied the following parameters: an analysis epoch of 750–1000 msec, number of averaging — 30–70, separately for significant and non-significant stimuli; frequency band — 0.5–30 Hz. Only responses to significant stimuli were considered.

Duplex scan of brachiocephalic arteries with color Doppler mapping was carried out (Vivid 7Pro, HP, USA) according to standard procedures and with the use of 10 MHz linear transducer. IMT was measured by the P. Pignoli's method as the distance between the echo area between the surfaces of the lumen-intima media and the adventitia, at cross-section [22]. According to the updated guidelines by European Society of HTN and the European Society of Cardiology in 2007, the wall thickness < 0.9 mm is considered normal, IMT 0.9–1.3 mm should be assessed as thickening, and the plaque is verified at TIM of 1.3 mm.

Statistical analysis was performed using Statistica 6.0 software by parametric and nonparametric methods depending on the data distribution. Indicators are presented as M ± SD. Differences between parameters were considered significant at $p < 0.05$.

Results

There was an increase in IMT in the group of patients with MS and cognitive impairment compared to the control group (Table 2). Patients with MS and cognitive impairment had an increased IMT of the right internal carotid artery (ICA) (0.095 ± 0.017 and 0.087 ± 0.015 cm, respectively, $p < 0.01$), of the left ICA (0.097 ± 0.015 and 0.091 ± 0.014 cm, respectively, $p < 0.05$), at the right bifurcation level (0.098 ± 0.016 and 0.092 ± 0.015 cm, respectively, $p < 0.01$), and at the left bifurcation level (0.095 ± 0.014 and 0.090 ± 0.013 cm, respectively, $p < 0.01$).

Table 2

CAROTID STRUCTURE IN THE EXAMINED GROUPS

Parameter	MS without CI n = 80	MS with CI n = 98
ICA IMT on the right side, cm	0.087 ± 0.015	0.095 ± 0.017*
ICA IMT on the left side, cm	0.091 ± 0.014	0.097 ± 0.015*
Bifurcation IMT on the right side, cm	0.092 ± 0.015	0.098 ± 0.016*
Bifurcation IMT on the left side, cm	0.090 ± 0.013	0.095 ± 0.014*

Note: MS — metabolic syndrome; CI — cognitive impairment; IMT — intima-media thickness; ICA — internal carotid artery; * — $p < 0.01$ compared to the group of patients without cognitive impairment.

Table 3

RELATION OF THE INTIMA-MEDIA THICKNESS AND COGNITIVE IMPAIRMENT IN THE EXAMINED GROUPS

Parameter	MMSE	CFQ	Clock drawing	Shulte test	Wechslers scale	10 words
ICA IMT on the right side	r = –0.54	r = 0.36	r = –0.42	r = 0.46	r = –0.38	r = –0.40
ICA IMT on the left side	r = –0.57	r = 0.36	r = –0.51	r = 0.51	r = –0.51	r = –0.48
Bifurcation IMT on the right side	r = –0.48	r = 0.25	r = –0.35	r = 0.42	r = –0.41	r = –0.43
Bifurcation IMT on the left side	r = –0.49	r = 0.28	r = –0.37	r = 0.45	r = –0.48	r = –0.38

Note: MMSE (Mini-Mental State Examination) — scale evaluation of cognitive function; CFQ (Cognitive Failures Questionnaire) — self-assessment of cognitive errors; Clock drawing test; Schulte test — test for the assessment of reaction speed and attention focusing; Wechsler Scale — memory assessment; 10 words — test "10 words by Luria"; IMT — intima-media thickness; ICA — internal carotid artery; for all values $p < 0.01$.

Correlation analysis showed a relation between BMI and ICA IMT ($r = 0.39$, $p < 0.01$), and bifurcation IMT ($r = 0.36$, $p < 0.01$). There was a correlation between IMT and lipids, fasting plasma glucose, insulin and CRP. Also the relation between total cholesterol level and ICA IMT ($r = 0.65$, $p < 0.01$), and bifurcation IMT ($r = 0.68$, $p < 0.01$).

There was a positive a correlation between ICA IMT ($r = 0.39$, $p < 0.01$), bifurcation IMT ($r = 0.41$, $p < 0.01$) and low-density lipoprotein (LDL) cholesterol, as well as negative association between ICA IMT ($r = –0.39$, $p < 0.01$), bifurcation IMT ($r = –0.41$, $p < 0.01$) and the level of high-density lipoprotein cholesterol. There was a correlation between ICA IMT ($r = 0.34$, $p < 0.01$), bifurcation IMT ($r = 0.29$, $p < 0.01$) and glucose level.

We also found a correlation between insulin level and ICA IMT ($r = 0.23$, $p < 0.01$), bifurcation IMT ($r = 0.27$, $p < 0.01$); a positive correlation between ICA IMT ($r = 0.36$, $p < 0.01$), bifurcation IMT ($r = 0.28$, $p < 0.01$) and CRP. However, there were no association between triglyceride levels and IMT at any carotid level.

Correlation analysis also showed a significant relation between IMT at different carotid levels and cognitive function (Table 3): a negative association between MMSE results and left ICA IMT ($r = –0.57$, $p < 0.01$), right ICA IMT ($r = –0.54$, $p < 0.01$), bifurcation IMT on the right side ($r = –0.48$, $p < 0.01$) and on the left side ($r = –0.49$, $p < 0.01$).

There was a correlation between reaction speed and attention focusing and left ICA IMT ($r = 0.51$, $p < 0.01$), right ICA IMT ($r = 0.46$, $p < 0.01$), IMT bifurcation on the right side ($r = 0.42$, $p < 0.01$) and on the left side ($r = 0.45$, $p < 0.01$).

There was a negative association between memorization, information storage and reproduction and left ICA IMT ($r = –0.48$, $p < 0.01$), right ICA IMT ($r = –0.40$, $p < 0.01$), IMT bifurcation on the right side ($r = –0.43$, $p < 0.01$) and on the left side ($r = –0.38$, $p < 0.01$). A negative relation was also found between Wechsler memory test result and left ICA IMT ($r = –0.51$, $p < 0.01$), right ICA IMT ($r = –0.38$, $p < 0.01$), IMT bifurcation on the right side ($r = –041$, $p < 0.01$) and on the left side ($r = –0.48$, $p < 0.01$).

Latent period and amplitude of CEP were associated with IMT in patients with MS and cognitive impairment compared to the patients without cognitive dysfunction.

Latent period of CEP was correlated with left ICA IMT ($r = 0.48$, $p < 0.01$) and the bifurcation of the left IMT ($r = 0.44$, $p < 0.01$), while amplitude of CEP was associated with IMT bifurcation on the right side ($r = –0.48$, $p < 0.01$).

Discussion

The association of cognitive disorders and structural carotid changes, as well as the pathophysiology of these processes are still controversial. Macrovascular changes can largely contribute to the development of cognitive dysfunction. Stroke, and cardiovascular diseases are the predictors of cognitive impairment and dementia [23, 24]. Cognitive dysfunction and brain white matter lesions are associated with subclinical atherosclerosis and IMT [4].

Decreased regional cerebral blood flow might be one of the mechanisms of cognitive decline in patients with thickened ICA IMT [25]. As opposed to some of the other studies, we used detailed neuropsychological testing along with screening tests (MMSE, FAB, «clock drawing») [8–10]. Our results suggest that an increase in ICA and bifurcation IMT is associated with the reduced memorization, information storage and reproduction, logical memory, time and space orientation, visual-motor speed, and ability to focus attention. Some authors have shown that an increase in IMT is associated with the decrease in regional cerebral blood flow in the posterior occipital and anterior temporal cerebral region. These areas are associated with memory function [26, 27]. Apparently, the decrease in cerebral blood flow in the occipital region may be associated with the development of cognitive dysfunction in patients with increased carotid IMT [28].

Two studies suggested various localization of carotid lesions depending on the cardiovascular risk factors. In 1989, G. S. Tell et al. showed no association between the carotid lesion localization and cardiovascular risk factors such as smoking and HTN. However, ANOVA analysis did not include LDL cholesterol. In 1990, M. Espeland et al. evaluated BMI in patients with coronary heart disease (CHD) and without CHD. There was a relation between smoking and the localization of atherosclerotic plaques in the area of the bifurcation in the subgroup without CHD, however, no association was found for the lesions in common carotid arteries. In 2011, P. Rubba and colleagues obtained similar results and found equal association with other traditional risk factors (HTN, LDL-cholesterol). The injury mechanisms might be associated with the relation between different risk factors and atherosclerotic lesions localized at various levels of carotid arteries, which differ in geometry and structure. LDL may contribute to early atherosclerosis at bifurcation level, due to the higher number of macrophages [30]. HTN-associated hyperplasia develops in common carotid arteries [20]. In our study, the localization of atherosclerotic lesions was similar in patients with MS and cognitive impairment and those without cognitive dysfunction. Lack of relation between the localization of atherosclerotic lesions and cardiovascular risk factors may be due to the fact that the examined subjects had a combination of risk factors (HTN, plasma glucose, insulin, LDL, CRP), which were not included in other studies. It should be noted that cognitive decline was associated with increased bifurcation IMT and ICA IMT, which were significantly higher than in patients without cognitive dysfunction. Neuropsychological tests demonstrated an association between ICA IMT and bifurcation IMT with cognitive decline in general, as well as with single cognitive functions. A connection of IMT at the bifurcation level and ICA IMT with cognitive decline has been shown previously [8, 28]. We have shown a close association between both localizations and the results of neuropsychological testing.

Frontal cortex, hypothalamus, and thalamus are considered as the areas of CEP generation [31]. These structures play an important role for learning and memory [32]. Increased latency and reduced amplitude of CEP are associated with cognitive decline in patients with Alzheimer's disease, Parkinson's disease, cerebrovascular dementia [33, 34].

Patients with significant stenoses of carotid arteries have been shown to have an increased latent period of CEP [35]. Based on the results of neuropsychological testing and CEP, we have demonstrated a cognitive decline in patients with MS and subclinical atherosclerosis. We found an association between increased IMT at different locations (internal carotid artery, bifurcation) and quantitative measures of cognitive functions.

Conclusions

1. Cognitive disorders are associated with the increase in ICA IMT and bifurcation IMT.

2. There is a correlation between ICA and bifurcation IMT and cognitive function in general, as well as separate cognitive functions, including responsiveness speed and attention focusing, memorizing, information storage and reproduction, and logical memory.

3. Increased IMT in ICA and bifurcation is associated with the decrease in CEP amplitude and increase in CEP latency.

Conflict of interest

Authors declare no conflict of interest.

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