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Membrane characteristics and vascular cognitive impairment

Objective: *to study the clinical phenomenology of vascular cognitive impairment (VCI) in individuals with different rates of passive transmembrane ion transport.*

Patients and methods. *Cognitive functions were evaluated in 372 patients with different clinical variants of moderate VCI after 1, 5, and 10 years of follow-up. Quantile analysis was used to group patients into quartiles according to the ranges in the rate of passive transmembrane ion transport reflecting the genetically determined properties of cell membranes and identified by the study of Na^+—Li^+ countertransport (NLC) in the erythrocyte membrane.*

Results. *There was initially a monofunctional non-amnestic type in 11.0% of the patients, a monofunctional amnestic type in 16.1%, a multifunctional non-amnestic type in 34.9%, and a multifunctional amnestic type in 37.9%. At the same time, in the patients with high-speed NLC, the number of amnestic VCI types statistically dominated: 77.1% of the patients belonging to quartile IV. After 1 year and 5 years of follow-up, there was an increase in the number of patients with severe cognitive impairment, reaching the degree of dementia (33.2% of all the examinees following 1 year). The patients with high-speed NLC showed a significant predominance of not only the total number of dementias (86.7% of the patients in quartile IV; $p<0.001$), but also a more unfavorable mixed (disregulatory + Alzheimer's disease) type of dementia (74.7% of the patients in IV quartile; $p<0.001$). The dysregulatory type of dementia was more common in patients with low- and moderate-speed NLC. 70% of all dementias developed from the multifunctional amnestic type of mild cognitive impairment (MCI). Different types of MCI were found to be transformed to the prognostically unfavorable multifunctional amnestic type of MCI. The study conducted 10 years later noted the same trends.*

Conclusion. *The NLC speed has been shown to be associated with the VCI profile, which makes this indicator promising for predicting the course of VCI in the early stage of the disease and for choosing a treatment policy.*

Keywords: *vascular cognitive disorders; passive transmembrane ion transport.*

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Introduction. Cognitive impairments (CI) are the most unfavorable predictor in cerebrovascular diseases. Mild cognitive impairment occurs in the early stages and as a rule progresses to dementia that disables patients. For many years overdiagnosis of vascular CI (VCI) has been observed in our country. However, degenerative disorders manifested as CI have been revealed only occasionally. [1, 2]. Despite the clear criteria and recently acknowledged theory of mixed dementia [3], it is often difficult to differentiate between VCI and Alzheimer's disease at the earliest stages. VCI associated with Alzheimer's disease significantly worsens the prognosis and prevails in elderly population [4]. However, even among elderly people with CVI there can be considerable differences in neuropsychological profile of cognitive deficit, its progression rate and association with other neurological symptoms. Age and associated pathology are apparently strong but not exclusive risk factors for neurodegenerative process manifestation. At the same time, the importance of early detection of CI for choosing correct therapeutic strategy and determining prognosis is well known. Many recent studies have been focused on searching for clinical, laboratory and instrumental markers which can help make a nosological diagnosis of cognitive impairment as early as possible [5—7]. Nevertheless, search for predictors of different clinical variants of VCI development convenient for wide use (inexpensive, minimally invasive) is continuing.

The strongest hypothesis of pathological aging and Alzheimer's disease development is the theory of structural and functional mitochondrial abnormality. [8]. According to this theory age-specific changes in mitochondrial signaling pathways promote cell membrane depolarization and affect Ca^{2+} signaling. Ineffective Ca^+ dynamics disrupts release of neurotransmitters and, as a result, causes the following changes: neurotransmitter imbalance, cellular energy deficiency and oxidative stress, activation of β-amyloid cascade, synaptic loss and apoptosis. However, the mechanism determining the initiation of neurodegenerative process is still unclear and appears to be multimodal. In this regard genetically determined ion transport characteristics of cell membrane can be interesting.

It is known that structural and functional state of cell membrane refers to such fundamental characteristics as transport of monovalent ions and process of excitation and transmission related to modification of Ca^{2+} metabolism [9]. Multiple experiments proved that the rate of passive ion transport across cell membrane is constant and concerns all types of cells (both excitable and non-excitable) [9]. Today there is considerable evidence concerning the relationship between structural and functional abnormalities of the membranes of both excitable and non-excitable cells and various diseases. Specifically, a correlation was found between a high rate of passive transmembrane ion transport and

primary arterial hypertension, lipid metabolism disorders and atherosclerosis, severity of ischemic brain damage in stroke along with response to antihypertensive therapy [10—12]. Taking into consideration the hypothesis of mitochondrial abnormality, it will be interesting to study the role of membrane characteristics in the progress of VCI.

The purpose of the study is to investigate clinical phenomenology of VCI in individuals with different rates of passive transmembrane ion transport.

Patients and methods. 372 patients (228 male and 144 female, aged 73,0±6,2) with cerebrovascular disease (CVD) and mild cognitive impairment (MCI) detected by neuropsycological tests and based on NIA-AA (the National Institute on Aging and Alzheimer's Association criteria) [13] were enrolled in the study. A battery of neuropsychological tests to assess cognition included the following tests: Mini-Mental State Examination (MMSE), Frontal assessment battery (FAB), Free and Cued Selective Reminding Test Immediate Recall (FCSRT-IR), clock drawing test, Schulte tables. Functional capacity was evaluated according to the Activity of Daily Living Scale by M. Lawton and E. Brody (1969) with the assistance of a responsible informant (a relative or a person who could provide medical history).

CVD was diagnosed on the basis of current vascular disease with minimum 5 years of clear clinical presentation (arterial hypertension, atherosclerosis) and multiple vascular lesions of brain tissue revealed by neuroimaging. To evaluate structural alterations of the brain, all patients underwent MRI (1.5T) including T1, T2, FLAIR, DWI and magnetic resonance angiography. White matter lesion was rated by Fazekas scale and ARWMC (Age-Related White Matter Changes) [14,15]. Atherosclerosis of cerebral vessels was evaluated by both extracranial and transcranial Doppler ultrasonography.

The rate of passive transmembrane ion transport was assessed in all patients. The approach suggested by Canessa M. et al. was applied to measure erythrocyte Na^+/Li^+countertransport (NLC) activity [16]. Easy accessibility and structure of erythrocytes allow to study functional characteristics of plasmolemma without complexities caused by intracellular organelles and contractive activity. To study monovalent cations exchange Na^+/Na^+, sodium was replaced by lithium in the incubation medium and active transport involving Na^+/K^+-ATPase was inhibited by ouabain. Na^+/Li^+ exchange rate was estimated by kinetics of lithium efflux. According to previous studies the most preferable approach was the investigation of various diseases and symptoms in association with NLC rate ranges in quartiles. Population-based studies revealed the following ranges: males: 1st quartile 0 — 206 cell /hours; 2nd quartile 207 — 276 cell /hours; 3rd 277 — 347 cell /hours; 4th quartile 348 — 660 cell/hours; females: 1st quartile 0 — 165 cell/hours; 2nd quartile 166 — 208 cell/hours; 3rd 209 — 267 cell/hours; 4th quartile 268 — 361 cell/hours [17].

According to the risk factors for CVD, the patients included in the study were divided into the following groups: 46% of patients with arterial hypertension (25% with uncontrolled hypertention and 75% with controlled hypertention) (In this article, "uncontrolled\controlled hypertension" signifies blood pressure that is inadequately\adequately treated rather than blood pressure that is resistant to treatment); 36% of patients with combination of arterial hypertension and atherosclerotic disease of the extracranial carotid and vertebral arteries; 18% of patients with atherosclerotic disease of the extracranial carotid and vertebral arteries but without hypertension. Patients with atherosclerotic stenosis of brachiocephalic artery had hemodynamically insignificant stenosis.

Exclusion criteria: patients under 65 years of age and older than 80, patients with diabetes mellitus, and those suffering from clinically significant depression (7 points and over by Hamilton Depression Rating Scale).

The follow-up period for all patients was 10 years. Cognitive assessment was conducted initially after 1, 5 and 10 years. Standard criteria were used to diagnose dementia, including necessity of physical assistance, cognitive deficit causing significant impairment of complex activity, social or occupational functioning.

Statistical analysis of the results was performed with SPSS (v.18.0) software, χ^2 (Pearson's chi-squared test) and Fisher exact test (for a 2×2 table). The difference was considered to be statistically significant at p-value less than 0.05.

Results. MCI neurophysiological profile evaluation conducted in the screening phase revealed the following clinical types: monofunctional non-amnestic type — 41 patients (11% of the examined patients), monofuctional amnestic type — 60 patients (16.1%), multifunctional non-amnestic type — 130 patients, multifunctional amnestic type — 141 patients (37.9%) (see Table 1). Generally, multifunctional type of MCI involving different cognitive domains prevailed. The difference in the number of patients with initially revealed hippocampal amnestic impairment and disregulatory non-amnestic type was not significant (P>0.05). However, comparative evaluation of clinical phenomenology after distribution of patients into quartiles according to NLC rates appeared to be different. The number of patients with multifunctional amnestic type of MCI significantly prevailed in the 4th quartile (see Table 1). Percentage of

Table 1. *Initial distribution of patients into quartiles based on NCL rate according to the type of MCI n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
Monofunctional:					
non-amnestic type	20 (27,0)	20 (18,2)	1 (1,0)	0 (0)	41 (11)
amnestic type	15 (20,3)	21 (19,1)	18 (17,1)	6 (7,2)	60 (16,1)
Multifunctional:					
non-amnestic type	26 (35,1)	50 (45,5)	41 (39,0)	13 (15,7)	130 (34,9)
amnestic type	13 (17,6)	19 (17,3)	45 (42,9)	64 (77,1)	141 (37,9)
Total	74 (100)	110 (100)	105 (100)	83 (100)	372 (100)

Table 2. *Distribution of patients into quartiles based on NCL rate according to cognitive impairment type after one- year follow-up, n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
Monofunctional:					
non-amnestic type	9 (12,2)	12 (11,1)	0 (0)	0 (0)	21 (5,7)
amnestic type	7 (9,5)	11 (10,2)	4 (3,8)	0 (0)	22 (5,9)
Multifunctional:					
non-amnestic type	20 (27,0)	42 (38,9)	41 (3,8)	0 (0)	66 (17,8)
amnestic type	30 (40,5)	37 (34,3)	60 (57,1)	11 (13,3)	138 (37,3)
Dementia:					
disregulatory dementia	2 (2,7)	3 (2,8)	16 (15,2)	10 (12,0)	31 (8,4)
mixed dementia	6 (8,1)	3 (2,8)	21 (20,0)	62 (74,7)	92 (24,9)
Total	74 (100)	108 (100)	105 (100)	83 (100)	370 (100)

Table 3. *The quartile distribution of cognitive impairments according to the severity of the process after five-year follow-up, n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
MCI	25 (37,9)	65 (62,5)	6 (8,2)	0 (0)	96 (36,6)
Demetia	41 (62,1)	39 (37,5)	67 (91,8)	19 (100)	166 (63,4)
Total	66 (100)	104 (100)	73 (100)	19 (100)	262 (100)

Table 4. *Distribution of patients into quartiles based on NCL rate according to cognitive impairment type after five-year follow-up, n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
Monofunctional:					
non-amnestic type	3 (4,5)	3 (2,9)	0 (0)	0 (0)	6 (2,3)
amnestic type	3 (4,5)	1 (1,0)	0 (0)	0 (0)	4 (1,5)
Multifunctional:					
non-amnestic type	13 (19,7)	29 (27,9)	0 (0)	0 (0)	42 (16,0)
amnestic type	6 (9,1)	32 (30,8)	6 (8,2)	0 (0)	44 (16,8)
Dementia:					
disregulatory dementia	10 (15,2)	18 (17,3)	3 (4,1)	0 (0)	31 (11,8)
mixed dementia	31 (47,0)	21 (20,2)	64 (87,7)	19 (100)	135 (51,5)
Total	66 (100)	104 (100)	73 (100)	19 (100)	262 (100)

patients with multifunctional non-amnestic and amnestic types was almost equal — 39% and 42.9% respectively (of all patients of the 3rd quartile). Multifunctional non-amnestic type of MCI prevailed in patients with low NLC rate assigned to the 1st and 2nd quartiles (35.1% and 45.5% of the total number of patients of the corresponding quartile) (see Table 1).

After one year of observation dementia progressed in 33.2% of all patients in the study, with the prevalence of mixed dementia (disregulatory+amnestic) (24.9% of all participants) over the single disregulatory type (8.4%) ($P<0.001$, see Table 1). It is important that in 70 % of dementia cases (86 patients) dementia progressed from amnestic type of MCI (multifunctional amnestic type predominantly) and in 30% of cases (37 patients) — from non-amnestic type of MCI. Within one year 54 patients with non-amnestic profile of MCI (22% of all patients with MCI) and 32 individuals with monofunctional amnestic profile (13%) had a transformation to multifunctional amnestic type of MCI. Therefore, the population with multifunctional amnestic type of MCI didn't significantly decrease in one year period (see Table 2).

Assessment of clinical phenomenology of cognitive impairment by quartile division according to the NLC rate showed the prevalence of patients with dementia in the 4th quartile — 86.7% of the total number within the quartile ($P_{IV–I}<0.001$, $P_{IV–II}<0.001$, $P_{IV–III}<0.001$) and in the 3rd quartile — 35.2% ($P_{III–I}<0.001$, $P_{III–II}<0.001$); in the 1st quartile 10.8% of patients had dementia, and only 5.6% ($P_{I–II}=0.089$) — in the 2nd quartile. In the 4th and 3rd quartiles percentage of patients with mixed dementia was 74.7% ($P_{IV–I}<0.001$, $P_{IV–II}<0.001$, $P_{IV–III}<0.001$), and 20.0% ($P_{III–I}=0.030$, $P_{III–II}<0.001$) of the total number within the corresponding quartile in contrast to 8.1% and 2.8% in the 1st and 2nd quartiles respectively ($P_{I–II}=0.107$, see Table 2).

Table 5. *The quartile distribution of cognitive impairments according to the severity of the process after ten-year follow-up, n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
MCI	12 (42,9)	29 (52,8)	2 (20,0)	0 (0)	43 (44,8)
Demetia	16 (57,1)	27 (48,2)	8 (80,0)	2 (100)	53 (55,2)
Total	28 (100)	56 (100)	10 (100)	2 (100)	96 (100)

Table 6. *Distribution of patients into quartiles based on NCL rate according to cognitive impairment type after ten-year follow-up, n (%)*

MCI	NLC				Total
	quartile I	quartile II	quartile III	quartile IV	
Monofunctional:					
non-amnestic type	2 (7,1)	3 (5,4)	0 (0)	0 (0)	5 (5,2)
amnestic type	1 (3,6)	0 (0)	0 (0)	0 (0)	1 (1,0)
Multifunctional:					
non-amnestic type	6 (21,4)	13 (23,2)	0 (0)	0 (0)	19 (19,8)
amnestic type	3 (10,7)	13 (23,2)	2 (20,0)	0 (0)	18 (18,8)
Dementia:					
disregulatory dementia	5 (17,9)	14 (25,0)	1 (10,0)	0 (0)	20 (20,8)
mixed dementia	11 (39,3)	13 (23,2)	7 (70,0)	2 (100)	33 (34,4)
Total	28 (100)	56 (100)	10 (100)	2 (100)	96 (100)

After five years of follow-up 262 patients were left in the study (110 participants discontinued participation in the study for various reasons). The total number of patients with dementia had increased by that time up to 63.5% (see Table 3). Differentiation of dementia types on the basis of clinical phenomenology still revealed the prevalence of mixed dementia over disregulatory type (51.5% and 11.8% respectively of all participants $P<0.001$). Distribution of patients into quartiles showed an association of severe cognitive impairment with a high range of speed of passive transmembrane ion transport. The overall number of patients with dementia (excluding neuropsychological profile) was 100% in the 4th quartile ($P_{IV–I}=0.002$, $P_{IV–II}<0.001$, $P_{IV–III}=0.200$) and 91.8% in the 3rd quartile ($P_{III–I}<0.001$, $P_{III–II}<0.001$). The number of patients with dementia in the 2nd quartile was 37.5% and in the 1st — 62.1% ($P_{I–II}=0.002$, see Table 3). Analysis of clinical types of dementia showed that mixed dementia was significantly more common in the 4th and 3rd quartiles compared with the 1st and 2nd ones: 100% in the 4th quartile ($P_{IV–I}<0.001$, $P_{IV–II}<0.001$, $P_{IV–III}=0.111$) and 87.7% in the 3rd, in contrast to 47% in the 1st quartile, and 20.2% in the 2nd quartile ($P_{I–II}<0.001$, see Table 4).

After ten years of follow-up no significant difference among the groups of patients was found because of a small number of participants in some groups (276 patients discontinued participation in the study for various reasons). Nevertheless, according to the obtained data the previous trend had continued, and the total number of patients with dementia prevailed in the 4th and 3rd quartiles — 100% ($P_{IV–I}=0.182$, $P_{IV–II}=0.156$ $P_{IV–III}=0.504$) and 80% ($P_{III–I}=0.206$, $P_{III–II}=0.068$) of the total number within the quartile respectively, in contrast to 57.1% and 48.2% in the 1st and 2nd quartiles ($P_{I–II}=0.444$, see Table 5). As the previous studies showed, the proportion of mixed dementia prevailed in the 4th and 3rd quartiles — 100% ($P_{IV–I}=0.105$, $P_{IV–II}=0.018$, $P_{IV–III}=0.392$) and 70% ($P_{III–I}=0.104$, $P_{III–II}=0.004$) respectively, compared with the 1st and 2nd quartiles — 39.3% and 23.2% ($P_{I–II}=0.127$) respectively (see Table 6).

Discussion. The study showed heterogeneity and variability of clinical phenomenology of MCI over time. Multifunctional amnestic MCI is considered to be the most unfavorable type in regard to progression of dementia (10—15% during one year) [18, 19]. However, MCI doesn't always progress to dementia. Over the last years considerable attention has been paid to critical biomarkers which can predict the risk of cognitive decline in healthy elderly people and provide early diagnosis. The most promising of them are considered to be determination of β-amyloid and Tau-protein levels in the brain and CSF, activity of various metabolites, in particular glucose, in different regions of the brain, localization and severity of brain atrophy on MRI scans and genotyping. Nevertheless, functional importance of these biomarkers is relative. For instance, β-amyloid deposition in the brain tissue was revealed in elderly patients who did not show cognitive function impairment according to prospective observation [20, 21]. The role of β-amyloid in differential diagnosis is also limited because it is frequently revealed in patients with other forms of neurodegenerative diseases, for instance dementia with Lewy bodies. [21,22]. Revealing of impaired Tau-protein metabolism is the most diagnostically valuable approach as it mostly correlates with alterations in various cognitive spheres [21,22]. The study of genetic polymorphisms of sporadic forms of Alzheimer disease (accounting for 95% of all cases) associated with cognitive impairment progress showed that identification of separate disease-related genes is sometimes not sufficient. Only polygene risk assessment of combined effects of several previously determined genetic variants based on the race is informative [23—25]. As the investigation of biomarkers is economically and methodological-

ly expensive, it is applied only in research projects, even in the countries with high income level.

It is well known that vascular factor contributes to neurodegenerative process. However, abnormal signals related to cerebrovascular dysfunction are frequently incidental findings on MRI scans of healthy elderly people. A recent study showed that severity of vascular impairment of a particular brain region has a stronger effect on cognitive function than overall vascular impairment [26]. Adequate prediction of cognitive decline in patients with CVD apparently can be based on comprehensive study of variety of risk factors including multiple pathogenic pathway of VCI. All the above mentioned motivates the search for new predictors of clinical progression of VCI which can improve diagnostics and treatment effectiveness and will be available in routine clinical practice. In our research clinical phenomenology of VCI in patients with different rates of passive transmembrane ion transport has been studied.

The results of longitudinal study of cognitive function in elderly patients with CVD showed an association of different clinical types of VCI and tempo of transformation of MCI into dementia with genetically determined membrane characteristics identified by the study of NLC rate in erythrocytes. Potentially "pernicious" multifunctional amnestic type of MCI significantly prevailed in patients with a high rate of passive transmembrane ion transport in initially comparable groups of patients with amnestic and non-amnestic types of MCI (see Table 1). In further observation mixed dementia prevailed in patients who progressed to severe cognitive impairment including executive function impairment and profound impairment of operational components with primary deficit of memory, which presumably indicates progression of neurodegeneration. In patients with a high rate of passive transmembrane ion transport assigned to the 4th and 3th quartile percentage of dementia after one year follow-up was significantly higher compared to patients with low and moderate NLC rates (see Table 2).

Five- and ten-year follow-up of the patients confirmed the previous trends (see Tables 3—6). All the above stated represents a high rate of passive transmembrane ion transport as the most disruptive characteristic associated with a high percentage of MCI transformation into dementia with predominance of clinical variants typical of neurodegeneration. The most favorable clinical course of MCI was observed in patients with moderate passive transmembrane ion transport rates assigned to the 2nd quartile on the basis of NLC study, which corresponds to the previous evidence [10—12]. Based on the obtained data, we can assume that high rates of passive transmembrane ion transport affected by CVD contribute to the alteration in Na^+/K^+-ATPase regulation resulting in clinical manifestations of neurodegenerative process in aged patients.

To sum up, passive transmembrane ion transport can be one of the factors that allow to predict MCI course and, consequently, choose a therapy.

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