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TIME COURSE OF COGNITIVE FUNCTIONING DURING THE FIRST YEAR AFTER ISCHEMIC NON-LACUNAR STROKES IN PATIENTS WITH ATRIAL FIBRILLATION

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Atrial fibrillation is a significant risk factor for the development of post-stroke cognitive impairment. We studied the regularities of the changes in cognition during the first year after ischemic non-lacunar stroke in patients with atrial fibrillation. We recruited patients with persistent (paroxysmal) and permanent forms of atrial fibrillation, and patients with regular sinus rhythm who experienced an ischemic non-lacunar stroke within the last 6 months. Cognitive testing (Mini-Mental State Examination, Montreal Cognitive Assessment, Clock Drawing Test, and Frontal Assessment Battery) was performed after inclusion in the study and then again at 6, 9, and 12 months following the stroke. In the first year after ischemic non-lacunar strokes, people with permanent (paroxysmal) and persistent atrial fibrillation had statistically significant detrimental modifications in global cognition (as evaluated by Mini-Mental State Examination and Montreal Cognitive Assessment) when compared to patients with regular sinus rhythm. In patients with both types of atrial fibrillation, visuospatial and executive functions exhibit worsening during the first year after ischemic non-lacunar strokes (significant decline in the "Visuospatial-executive" domain of Montreal Cognitive Assessment, in clock drawing test, and frontal assessment battery).

Key words: atrial fibrillation, ischemic non-lacunar stroke, global cognition, executive functions, longitudinal study.

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ОСОБЛИВОСТІ ЗМІН КОГНІТИВНИХ ФУНКЦІЙ ПРОТЯГОМ ПЕРШОГО РОКУ ПІСЛЯ ІШЕМІЧНИХ ІНСУЛЬТІВ У ПАЦІЄНТІВ З ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ

Фібриляція передсердь є значущим фактором ризику постінсультних когнітивних порушень. Ми вивчали закономірності змін когнітивних функцій протягом першого року після ішемічного нелакунарного інсульту у пацієнтів з фібриляцією передсердь. Нами були відібрані пацієнти з персистуючою (пароксизмальною) та постійною формами фібриляції передсердь, а також пацієнти з регулярним синусовим ритмом, які перенесли ішемічний нелакунарний інсульт протягом останніх 6 місяців. Когнітивне тестування (коротка шкала оцінки психічного статусу, Монреальська шкала оцінки когнітивних функцій, тест малювання годинника та батарея лобної дисфункції) проводили після включення пацієнта в дослідження, а потім повторно через 6, 9 та 12 місяців після інсульту. Протягом першого року після ішемічного нелакунарного інсульту пацієнти з постійною (пароксизмальною) та персистуючою формою фібриляції передсердь мали статистично значущі негативні зміни в глобальній когнітивній сфері (за короткою шкалою оцінки психічного статусу та Монреальською шкалою оцінки когнітивних функцій), порівняно з пацієнтами з регулярним синусовим ритмом. У пацієнтів з обома типами фібриляції передсердь спостерігається значне погіршення візуально-просторових та виконавчих функцій протягом першого року після ішемічного нелакунарного інсульту (достовірне погіршення в домені «Візуально-просторові та виконавчі функції» Монреальської шкали оцінки когнітивних функцій, в тесті малювання годинника та в батареї лобної дисфункції).

Ключові слова: фібриляція передсердь, ішемічний нелакунарний інсульт, когніція, виконавчі функції, лонгітюдне дослідження.

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Because of the military actions in Ukraine that destroyed healthcare facilities and stopped the providing healthcare, optimizing rehabilitation procedures for a variety of diseases is imperative [6].

As known, cognitive conditions largely determine the patient's professional, social, and everyday capabilities and significantly affects the quality of life. Cognition is a fundamental skill for learning, planning, and executing new and known tasks in the context of stroke recovery and rehabilitation [12]. Cognitive deficits of varying severity and qualitative characteristics are present in over 70 % of stroke survivors, depending on stroke type, definition, and time point of assessment [13].

In recent decades, the cognitive state of post-stroke patients has been considered as a dynamic phenomenon with changeable characteristics, especially within the first year of stroke onset. It has been found that stroke survivors may show no cognitive deficits, may improve or decline, initially decline and then improve (or vice versa), remain stable, or progress to dementia over time [1, 15].

Understanding the underlying mechanisms of post-stroke cognitive impairment is of paramount significance for developing of effective prevention and treatment approaches [5]. In recent decades there is growing recognition that the risk of post-stroke cognitive impairment and temporal trajectory of cognition is determined by an interplay of multiple modifiable and unmodifiable factors [11].

It has long been proven in numerous studies that in general population atrial fibrillation (AF) is a significant and independent risk factor for cognitive impairment. The last decade has also revealed that AF is a significant risk factor for the development of post-stroke cognitive impairment after an acute ischemic event independent of other risk factors for impaired cognition [3, 7]. Until now, the mechanisms mediating the negative impact of AF on cognitive performance in general and after stroke in particular are not fully understood. In accordance with the literature, AF may result in downstream cerebral hypoperfusion, heightened inflammatory responses, silent cerebral ischemia, reduced brain volumes, and cerebral microbleeds, all of which have been implicated in post-stroke cognitive impairment [9].

However, up to now, temporal cognitive changes in AF patients in the post-stroke period have not yet been studied. At the same time, understanding the regularities of the cognitive changes can be useful for predicting the course of cognition in patients with AF.

The purpose of the study was to investigate the regularities of the cognitive changes during the first year after ischemic non-lacunar stroke in patients with atrial fibrillation.

Material and methods. This study was approved by the Ethics Committee of Poltava State Medical University in accordance with the Declaration of Helsinki (protocol No.189/2020). The written informed consent was obtained for all patients before their inclusion in the study.

Criteria for inclusion of patients in the study.

1. Ischemic non-lacunar stroke occurring within the last 6 months.
2. Non-valvular AF verified on the basis of clinical and electrocardiographic data.
3. Age from 18 to 75 years.
4. Written patient consent.

Criteria for exclusion of patients from the study.

1. Documented cognitive impairment in the pre-stroke period.
2. Speech disorders that significantly limit communication with the patient.
3. Impaired writing function, which does not allow for proper completion of the questionnaires.
4. Neurological diseases that can cause cognitive disorders (infectious, degenerative, demyelinating, toxic, tumor, traumatic, etc.)
5. Decompensated somatic pathology.
6. Psychiatric and narcological pathology.
7. Use of psychoactive drugs that affect cognitive functions.

All included patients underwent an assessment of cognitive functions. We used several cognitive scales – Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), and Frontal Assessment Battery (FAB).

We recruited 63 patients with a persistent or paroxysmal form of AF (53 patients within 3 months and 10 patients within 3–6 months after stroke occurrence), 40 patients with a permanent form of AF (32 patients within 3 months and 8 patients within 3–6 months after stroke occurrence). As a control group, there were 41 patients with regular sinus rhythm (RSR) who had experienced an ischemic non-lacunar stroke (38 patients within 3 months and 3 patients within 3–6 months after stroke occurrence).

Cognitive testing was performed after the inclusion of a patient in the study and then again at 6, 9, and 12 months following the stroke (if the patient was included in the study during the first three months following the stroke) or at 9, and 12 months following the stroke (if the patient was included in the study between three and six months following the stroke).

Quantitative values were presented as mean and standard deviation. Qualitative values were presented as numbers (n) and percentages. Quantitative values were compared using the Mann–Whitney test. Qualitative variables were compared using Fisher's exact test. Differences at $p<0.05$ were considered significant.

Results of the study and their discussion. The age of patients with persistent (paroxysmal) AF was 69.2±4.2 years, patients with permanent AF – 69.7±3.1 years, and patients with RSR – 68.2±3.2 years. The persistent (paroxysmal) AF group consisted of 40 (63.5 %) males and 23 (36.5 %) females; the respective rates in the permanent AF group were – 27 (67.5 %) and 13 (32.5 %), in the RSR group – 22 (53.7 %) and 19 (46.3 %).

The cognitive tests in the persistent (paroxysmal) AF group, the permanent AF group, and the RSR group had the following scores at the time of the initial assessment: MMSE – 23.7±3.7, 23.0±3.6 and 24.8±3.0; MoCA – 22.3±3.8, 20.9±3.5 and 25.0±3.4; CDT – 6.9±1.4, 7.1±1.5 and 7.6±1.4; FAB – 12.8±1.7, 13.5±1.8 and 14.6±1.2.

During the follow-up, patients dropped out of the study for various reasons, including death, relocation, transportation issues, and an unwillingness to continue cooperating. In the persistent

(paroxysmal) AF group, 23 patients dropped out of the study (dropout rate 36.5 %). The dropout rate in the persistent AF group was 15 (37.5 %), and in the RSR group – 12 (29.3 %).

For determining the time course of cognitive functioning, we studied the changes of all used scales between two consecutive examinations.

The first step was to compare the rates of certain cognitive outcomes in the patients' groups during each 3-month interval. For this purpose we distinguished the following cognitive outcomes "Cognitive improvement" – an increase in the values of any used scale by 1 point or more in comparison with a previous visit and "Cognitive worsening" – a decrease in the values of any used scale by 1 point or more in comparison with a previous visit.

Table 1

Cognitive outcomes during 3-months intervals after ischemic non-lacunar stroke, n (%)

Test	Post-stroke interval	Cognitive outcome	Patients' group		
			persistent (paroxysmal) AF	permanent AF	RSR
MMSE	3–6 months	improvement	8 (18.2 %) *	5 (19.2 %)	14 (43.8 %)
		worsening	21 (47.7 %) **	13 (50.0 %) **	7 (21.9 %)
	6–9 months	improvement	4 (8.3 %)	2 (6.9 %)	8 (25.8 %)
		worsening	15 (31.3 %)	11 (37.9 %) **	4 (12.9 %)
	9–12 months	improvement	3 (7.5 %)	1 (4.0 %)	5 (17.2 %)
		worsening	16 (40.0 %) **	9 (36.0 %) **	3 (10.3 %)
MoCA	3–6 months	improvement	9 (20.5 %) *	6 (23.1 %) *	17 (53.1 %)
		worsening	27 (61.4 %) **	13 (50.0 %) **	7 (21.9 %)
	6–9 months	improvement	5 (10.4 %) *	2 (6.9 %) *	10 (32.3 %)
		worsening	20 (41.7 %)	15 (51.7 %) **	7 (22.6 %)
	9–12 months	improvement	4 (10.0 %)	3 (12.0 %)	8 (27.6 %)
		worsening	15 (37.5 %) **	12 (48.0 %) **	4 (13.8 %)
CDT	3–6 months	improvement	7 (15.9 %) *	3 (11.5 %) *	7 (15.9 %)
		worsening	25 (56.8 %) **	14 (53.8 %)	9 (28.1 %)
	6–9 months	improvement	4 (8.3 %)	2 (6.9 %)	8 (25.8 %)
		worsening	25 (52.1 %) **	17 (58.6 %) **	8 (25.8 %)
	9–12 months	improvement	3 (7.5 %)	3 (12.0 %)	6 (20.7 %)
		worsening	18 (45.0 %) **	13 (52.0 %) **	5 (17.2 %)
FAB	3–6 months	improvement	6 (13.6 %) *	3 (11.5 %) *	14 (43.8 %)
		worsening	23 (52.3 %) **	12 (46.2 %)	8 (25.0 %)
	6–9 months	improvement	5 (10.4 %)	4 (13.8 %)	9 (29.0 %)
		worsening	27 (56.3 %) **	18 (62.1 %) **	9 (29.0 %)
	9–12 months	improvement	4 (10.0 %)	4 (16.0 %)	6 (20.7 %)
		worsening	17 (42.5 %) **	11 (44.0 %) **	5 (17.2 %)

* a statistically significant difference in the rates of "Cognitive improvement" compared to the RSR group, according to the Fisher exact test. ** a statistically significant difference in the rates of "Cognitive worsening" compared to the RSR group, according to the Fisher exact test.

Regardless of the used cognitive test, the patients with persistent (paroxysmal) AF and the patients with permanent AF have a significantly worse overall structure of cognitive outcomes during the first year after stroke compared to the patients with RSR. Also, regardless of the cognitive test, we observed a similar pattern of cognitive outcomes during the 3-month intervals in both patient groups with AF. During all studied 3-month intervals, in the group with persistent (paroxysmal) AF as well as in the group with permanent AF, there was a significantly higher incidence of "Cognitive worsening" outcome compared to the group of patients with RSR. Moreover, during a 3–6 months interval, both AF groups showed significantly less rare "Cognitive improvement" outcomes than the patients with RSR; also, the same pattern of cognitive outcomes was present during 6–9 months intervals due to the MOCA. Quite interesting is the fact that in the patients with persistent (paroxysmal) AF and the patients with permanent AF in any studied 3-month period, there were no significant differences in the frequency of "Cognitive improvement" and "Cognitive worsening" outcomes, according to each of the used cognitive test.

Additionally, we studied the rates of the same cognitive outcomes (the changes in the values of 1 point or more) in each domain of the MMSE and MOCA during each 3 months interval. There was no significant difference in the rates of "Cognitive improvement" outcome and the rates of "Cognitive worsening" outcome between patients' groups in any of the MMSE domains ("Time orientation", "Spatial orientation", "Registration", "Attention and calculation", "Recall", "Nomination and repetition", "Language") and the MoCA domains ("Naming", "Attention", "Concentration", "Language", "Abstraction", "Delayed recall", "Orientation") during any studied 3-month interval. At the same time, for

the entire observation period, there was a significantly higher ($p<0.05$) incidence of "Cognitive worsening" outcome for the "Visuospatial-executive" MoCA domain in the group with persistent (paroxysmal) AF (18 cases, 35 %) and in the group with permanent AF (10 cases, 40 %) compared to the group of patients with RSR (3 cases, 10 %).

The next step was to study and compare the changes in the absolute values of each used cognitive test during each studied 3-month interval (Table 2).

Table 2

Changes of cognitive tests values during 3-month intervals after ischemic non-lacunar stroke (mean±standard deviation)

Test	Post-stroke interval	Patients' group		
		persistent (paroxysmal) AF	permanent AF	RSR
MMSE	3–6 months	-0.3±0.8 *	-0.3±0.8 *	0.3±0.8
	6–9 months	-0.3±0.7 *	-0.4±0.7 *	0.1±0.7
	9–12 months	-0.4±0.6 *	-0.4±0.6	0.1±0.6
	3–12 months	-0.7±1.5 *	-1.1±1.4 *	0.4±1.4
MoCA	3–6 months	-0.4±0.9 *	-0.3±1.0 *	0.3±1.0
	6–9 months	-0.4±0.8 *	-0.4±0.7 *	0.1±0.9
	9–12 months	-0.3±0.8 *	-0.4±0.7	0.0±0.9
	3–12 months	-1.0±1.9 *	-1.1±1.6 *	0.5±2.0
CDT	3–6 months	-0.4±0.8 *	-0.3±0.8 *	0.2±0.8
	6–9 months	-0.4±0.6 *	-0.6±0.6 *	0.0±0.8
	9–12 months	-0.4±0.6 *	-0.5±0.8 *	0.0±0.7
	3–12 months	-1.4±1.2 *	-1.5±1.3 *	0.0±0.7
FAB	3–6 months	-0.4±0.7 *	-0.4±0.8 *	0.2±1.3
	6–9 months	-0.4±0.8 *	-0.4±1.1	0.1±1.0
	9–12 months	-0.3±0.9	-0.4±0.9	0.1±1.2
	3–12 months	-1.1±1.5 *	-1.3±1.5 *	0.3±1.5

* statistically significant differences ($p<0.05$), according to the Mann-Whitney test, in comparison with the RSR group.

Despite the cognitive tests that were used, during all 3-month intervals, and, as a result, during the entire observation period, we found the same patterns of changes in absolute tests' values. Patients with RSR show positive dynamics of all used cognitive tests' scores throughout the first year after stroke occurrence. On the contrary, in both groups of patients with AF, there is a negative dynamic of all used tests' values throughout the first year after stroke. With rare exceptions (mainly for the FAB scores), the patients with persistent (paroxysmal) AF, as well as the patients with permanent AF, have significantly worse changes in cognitive scores compared to the RSR patients throughout all studied 3-month intervals. Also, in patients with persistent (paroxysmal) AF and patients with permanent AF, there are no significant differences in the changes of each used cognitive test values during any studied 3-month period.

Finally, there is no significant difference in the changes of MMSE and MoCA domain scores between 3 groups of patients during any studied 3-month interval. On the other hand, the changes in the absolute values of the MOCA "Visuospatial-executive" domain between the first and 12-month examinations in the persistent (paroxysmal) AF group and the permanent AF group were significantly worse ($p<0.05$) compared to the RSR group – -0.5±0.8 and -0.4±0.6 versus 0.0±0.6.

Thus, we have identified the peculiarities of cognitive changes in AF patients during the first year after ischemic non-lacunar strokes.

It is known that the temporal evolution of post-stroke cognition could be different, but usually, within the first months after stroke, there is a cognitive improvement [2, 10]. However, we found that due to MMSE and MoCA changes, in patients with AF, regardless of the type of AF, global cognitive function gradually and consistently declines during the first year after stroke. On the contrary, the RSR patients show positive dynamics of the MMSE and MoCA scores during the first post-stroke year, especially during the first half of the year. As a consequence, patients with AF have statistically significant negative changes in global cognition (according to MMSE and MoCA scales) compared with the RSR patients. It is important to emphasize that declines in global cognition after stroke have a lot of consequences, including a significant increase in the risk of mortality, dementia, depression, and accelerated functional decline [8].

According to our data, visuospatial and executive function scores show a substantial decline in the first year following ischemic non-lacunar strokes in both AF patient groups compared to the RSR patients. We found AF is associated with a statistically significant worsening of scores of the "Visuospatial-executive" MoCA domain, scores of CDT (visuospatial and executive functions), and scores of FAB (executive functions). Also, according to cognitive outcomes due to CDT and FAB, AF, regardless of its

type, is associated with a significantly higher incidence of "Cognitive worsening" outcome and a significantly rare incidence of "Cognitive improvement" outcome compared to the group of patients with RSR during the first year after ischemic non-lacunar strokes. According to the literature, patterns of post-stroke cognitive changes could be different for certain cognitive domains [4]. In a recent systematic review and meta-analysis of 14 longitudinal studies of post-stroke cognition, Tang EY et al. revealed no clear trajectory of executive function after stroke [15]. However, in our study, the main pattern of changes in cognitive executive functions in AF patients was declining. As well as worsening of global cognition, executive function impairments in post-stroke patients are also associated with negative consequences, including significant limitations in basic and instrumental activities of daily living [14].

From a clinical perspective, our findings imply that individuals with AF who have experienced an ischemic non-lacunar stroke should be monitored for cognitive functioning for at least one year after the event.

Conclusion

When compared to the RSR patients, individuals with permanent (paroxysmal) and persistent AF experienced statistically significant adverse alterations in global cognition (as measured by MMSE and MoCA) in the first year following ischemic non-lacunar strokes. Visuospatial and executive functions show a substantial decline in the first year following ischemic non-lacunar strokes in patients with permanent (paroxysmal) AF and persistent AF compared to the RSR patients, in the form of a significant decline in the "Visuospatial-executive" MoCA domain, CDT (visuospatial and executive functions), and FAB (executive functions).

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