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# FEATURES OF COGNITIVE IMPAIRMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT PREDIALYSIS STAGES

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Article history:		Abstract:
Received: Accepted: Published:	March 10 <sup>st</sup> 2023 April 10 <sup>th</sup> 2023 May 20 <sup>th</sup> 2023	The purpose of the study. To study the features of cognitive impairment (CN) in patients with chronic kidney disease (CKD) at the predialysis stages. Materials and methods. 51 patients with CKD aged 52±10 years were examined, including 20 with stage I—II CKD (glomerular filtration rate — GFR ≥60 ml/min/1.73 m², signs of kidney damage), 20 with stage III CKD (GFR 60-30 ml/min/1.73 m²), 11 with IV CKD stages (GFR 30-15 ml/min/1.73 m²). GFR was calculated using the formula MDRD. A questionnaire was conducted to identify the limitations of daily activity, depression, and neuropsychological testing using a short mental status assessment scale (MMSE), a battery of tests for frontal lobe dysfunction (FAB), a test for short-term and delayed memory (test "10 words" by the method of A.R. Luria), a test for assessing regulatory functions. Magnetic resonance imaging (MRI) was performed to clarify the etiology of CN. Results. In patients with chronic renal insufficiency — CRF (stage III—IV CKD), CN was detected more often than in patients without CRF (stage I—II CKD) — 90.3 and 35%, respectively (p<0.001). Their KN was detected statistically significantly more often on the MMSE scale (p<0.001), FAB (p=0.001) and the test for regulatory functions (p<0.001). There was a statistically significant increase in the severity of CN with an increase in the stage of CKD according to the MMSE, FAB scale, the test for regulatory functions, but not according to the test for short-term and delayed memory. According to the results of MRI of the brain among patients with CN, focal changes were detected in 9 (30%), leukoareosis — in 7 (23.3%), dilation of the lateral ventricles — in 15 (50%), pronounced expansion of the hemispheric furrows — in 3 (10%). Conclusion. An increase in the stage of CKD is associated with an increase in the frequency and severity of CN on the MMSE scale, as well as with a violation of the functions of the anterior parts of the brain. As evidenced by the results of comparisons of clinical and According to MRI data

CKD is based on cerebrovascular disorders.

**Keywords:** chronic kidney disease, cognitive function, moderate cognitive impairment, neuroimaging.

#### **INTRODUCTION**

Chronic kidney disease (CKD) is a global problem whose contribution to the structure of general morbidity and mortality of the population is steadily increasing. This is primarily due to the increase in the prevalence of risk factors in the population for the development of cardiovascular diseases (CVD), which equally determine the progression of CKD. Thus, the medical and socio-economic significance of CKD is defined as its progressive course with the development of

end-stage chronic renal failure (CRF), requiring the use of expensive therapies that replace kidney function, and a high risk of cardiovascular complications and death from them in the working-age population. At the heart of the damage to the cardiovascular system in CKD is the remodeling of the vascular wall, which occurs under the influence of the development of CVD, both traditional and caused by renal insufficiency (anemia, violation of phosphorus-calcium metabolism, hyperhomocysteinemia, uremic toxins, oxidative stress). Remodeling of cerebral vessels in CKD leads to the development of cerebrovascular insufficiency (CVN) and the emergence of cognitive impairment (CN), reaching the degree of dementia in the late stages.

Cerebrovascular complications largely determine the fate of patients with CKD, being the cause of persistent disability and death. In kidney diseases, CN does not only lead to disability of patients, to reduce



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the quality of life of patients and their relatives, but also make it difficult, in particular, to obtain informed consent of the patient if hemodialysis or kidney transplantation is necessary.

In addition, unlike the early stages of CN, the possibilities of therapy for severe CN (dementia) are limited and obviously do not allow achieving sufficient social rehabilitation of patients [8]. In this regard, the detection of cognitive dysfunction (CD) in the early stages is of particular importance: it is known that approximately 50% of patients with chronic CVN and mild or moderate CN (UKN) dementia develops during the first 5 years.

The study of cognitive functions is carried out using a number of neuropsychological tests that allow not only to assess the severity of changes, but also to identify disorders in certain areas of higher brain functions. However, the nature of CN in patients with CKD needs further study, since the currently available data are scattered and extremely contradictory. To determine the severity of CD, it is necessary to study the functional status of the patient using a questionnaire assessing the impact of cognitive a defect in daily activities. Due to the violation of the performance of complex cognitive operations, professional competence of a patient with OCD may be limited, but at the same time, unlike dementia, the performance of a complex of everyday actions that determine the possibility of the patient's independent existence does not suffer.

To clarify the etiology of CN, as well as to assess the risk of their progression to the degree of dementia, the use of neuroimaging examination methods, such as computed tomography, is also considered indicated (CT) and magnetic resonance imaging (MRI) of the brain. Signs of CVN are at least one lacunar infarction or leukoareosis exceeding the age norm in severity. At the same time, cerebral infarcts that manifest themselves in the form of cysts of different diameters ("completed infarcts") or focal changes in white and gray matter without cyst formation ("incomplete infarcts") are considered as the most reliable diagnostic sign. In addition, in favor of chronic CVN, visualized by MRI, there are signs of atrophic changes in the form of expansion of cortical furrows and ventricles of the brain. A number of studies have shown a statistically significant relationship between a decrease in glomerular filtration rate (GFR) in patients with CKD with the volume of white matter lesion, the number of lacunar cerebral infarcts, including "dumb" ones, and the severity of brain atrophy, regardless of the traditional FR of CVD development. At the same time, the presence of "mute" heart attacks served as a prognostic sign of the progression of CKD.

The purpose of this study was to evaluate the frequency, the severity and nature of CN in patients

with CKD at the predialysis stages, as well as the study of clinical and neuroimaging relationships in patients with CKD with CN.

#### **MATERIALS AND METHODS**

The study included 51 patients with CKD (21 men and 30 women) aged 30 to 74 years, average age  $52 \pm 10$  years. CKD was defined as kidney damage of any etiology, accompanied by a violation of their structure and/or function for 3 months or more. The stages of CKD were determined in accordance with the classification of the US National Kidney Foundation (NKFK/DOQI, 2002). The GFR was calculated using the abbreviated formula MDRD (Modification of Diet in Renal Disease Study). All patients they were divided into 2 groups: group 1 - 20 patients without CRF with CKD stages I—II (GFR  $\geq$ 60 ml/min/1.73 m², signs of kidney damage); group 2 — 31 patients with CRF with CKD stages III and IV

(GFR 60-15 ml/min/1.73 m<sup>2</sup>). To assess the severity of CN depending on the stage of CKD, the patients were divided into 3 groups: the 1st consisted of 20 patients with CKD stages I and II, the 2nd - 20patients with CKD stage III (GFR 60-30 ml/min / 1.73 m<sup>2</sup>), the 3rd 11 patients with stage IV CKD (GFR 30-15 ml/min/1.73 m<sup>2</sup>). The study did not include patients with stage V CKD (GFR <15 ml/min/1.73 m<sup>2</sup>), with systemic vasculitis, antiphospholipid syndrome, systemic lupus erythematosus, hepatic insufficiency, hypothyroidism or thyrotoxicosis, HIV infection, alcohol abusers and patients with previously diagnosed neurodegenerative diseases. ΑII patients were surveyed to identify the limitations of daily activity (the scale of basic and instrumental activity in everyday life, ADL and IADL), as well as to assess emotional status (the Beck depression scale). Neuropsychological testing was performed to identify and assess the severity of CN using the following tests: 1) a short scale of assessment of mental status (Mini-mental state examination — MMSE), including the study of the function of gnosis, praxis, speech, auditory-speech memory, attention, counting, visual-spatial functions; 2) batteries of tests for dysfunction of the frontal lobes of the brain (Frontal assessment battery — FAB), with which they study thinking, speech, dynamic praxis, semantic memory, regulatory functions; 3) a test for memorizing 10 words according to the method A.R. Luria for short-term memory (direct reproduction of 10 words, immediately after their presentation); 4) delayed memory (reproduction of words 30 minutes after their presentation); 5) a test to evaluate regulatory functions (sequential connection of letters and numbers, Trail-making test B) reflecting the processes of planning, goal formation, step-by-step implementation of actions, the ability to switch and control the achievement of the planned result. The



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UCN syndrome was established in accordance with the modified criteria of R. Petersen and J. Touchon (2005). To clarify the etiology of KN and The relationship of CD with specific structural changes of the brain was assessed by MRI.

Statistical analysis of the data was carried out using the statistical program SPSS Statistics (IBM Corp.), version 21.0. The normality of the distribution was tested using the Shapiro-Wilk criterion. significance of differences in groups for variables with an interval type of scale was assessed using the Student's t-test (in the absence of significant deviations from the normal distribution) or using the nonparametric Mann-Whitney test (in the case of significant deviations from the normal distribution). The significance of differences in groups for variables with a nominal scale type was assessed using the Fisher exact criterion. For comparison of 3 groups, one-dimensional analysis of variance was used (1-way ANOVA), for a posteriori comparisons, the Tukey criterion was used (in the absence of significant deviations from the normal distribution) or the Kruskal—Wallis criterion (in the case of significant deviations from the normal distribution). The differences were considered statistically significant at p < 0.05.

#### **RESULTS**

Among all examined patients with CKD, 35 (68.6%) were found to have CKD. All patients with CN complained mainly of difficulties remembering new information, forgetfulness of names, names of objects, inability to keep in mind a plan of action, remember where they put this or that object, difficulty concentrating, choosing words when talking, sleep disorders. At the same time, none of the patients had significant restrictions on daily activity based on the results of filling out a questionnaire for assessing social, instrumental activity by them and their relatives,

self-service abilities. In the group of patients without CRF (n=20), CN was observed in 7 (35%), in the group with CRF (n=31) — in 28 (90.3%). The frequency of CN detection in patients with CRF was statistically significantly higher than in the group without CRF (p<0.001). Statistically significant was an increase in the frequency of development of CN according to the results of the MMSE test (p<0.001), tests for the function of the frontal lobes of the brain (p=0.001) and regulatory functions (p<0.001). Violations of short-term and delayed memory were noted in patients of both groups, while the frequency of these violations in investigated the difference in the groups was not statistically significant. When comparing the severity of CN in 3 groups of patients with different stages of CKD, there was a deterioration in the results of the MMSE test, tests for the function of the frontal lobes of the brain and regulatory functions as the stage of CKD increased.

Depression was detected in 26 (51%) patients, of which 21 (41.2%) had mild and 5 (9.8%) have pronounced. Among patients with depression, CN was observed in 18 (69.2%), of which 15 (83.3%) had mild depression, 3 (16.7%) — pronounced. Among 25 (49%) patients without depression, CN was detected in 17 (68%). The incidence of CN in patients with depression practically did not differ from that in patients without depression. We also found no statistically significant differences in the severity of CN in the group of patients with and without depression. Brain MRI was performed on 38 patients (8 with CKD I—II, 30 with CKD III—IV), among them KN were noted in 30. Focal brain changes were detected in 11 (28.9%) patients, of which 10 (26.3%) with localization in the carotid basin, in 1 (2.6%) in the vertebral-basilar; diffuse changes in white matter (leukoareosis) were noted in 9 (23.7%) patients; in 17 (44.7%), lateral ventricular expansion was detected and in 3 (7.9%) — pronounced expansion of the cerebral hemispheric furrows. Among patients with CN, focal changes were noted in 9 (30%), leukoareosis in 7 (23.3%), dilation of the lateral ventricles — in 15 (50%), pronounced expansion of the furrows of the cerebral hemispheres — in 3 (10%). In patients with various structural changes of the brain, the frequency of detection of CN (according to the total assessment of all tests) did not differ statistically significantly from that in patients without changes on MRI. When analyzing the differences in individual cognitive tests, the frequency and severity of CN according to the results of the frontal lobe dysfunction test were greater in leukoarrhoea (p=0.016 and p=0.013, respectively) and dilation of the lateral ventricles of the brain (p=0.046 and p=0.024, respectively). With the expansion of the lateral ventricles, the frequency and severity of CN also increased according to the results of the test for regulatory functions (p=0.025 and p=0.008, respectively).

When comparing the frequency of detection of structural changes in the brain in groups of patients with and without CRF, no statistically significant differences were obtained. A similar pattern was observed when comparing groups of patients with different stages of CKD.

#### RESEARCH RESULTS AND THEIR DISCUSSION

Results of the study of frequency and severity CN in CKD are generally consistent with the results of previously performed studies. Thus, it was found that in patients with CRF (GFR <60 ml/min /1.73 m $^2$ ), a decrease in GFR for every 10 ml/min/1.73 m $^2$ . It is associated with an increase in the risk of developing



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CN by 11-27%. In the study of S. Seliger et al. demonstrated an increase in the risk of developing dementia in elderly patients with mild and moderate CRF by 37% compared with those without CRF. In patients with hyperfiltration also increases the risk of CD development. It has been shown that the frequency and severity of CD increase with the progression of CKD, regardless of demographic indicators and concomitant diseases, including depression; at the same time, CD is detected already at the initial stages of CKD. In our study, in patients with CKD of the initial stages, CN was observed in 35% of cases.

Our study shows a statistically significant increase in frequency and severity CN in the progression of CKD according to the results of a brief mental status assessment scales, studies of frontal lobe function and regulatory functions, but not short-term and delayed memory. These data are consistent with the results of a number of large studies in which, with an increase in the stage of CKD, an increase in the frequency and severity of cognitive impairment was revealed on a short scale of assessment of mental status, attention, regulatory functions, gnosis, but not semantic, shortterm or delayed memory, intelligence. At the same time, a number of other studies have shown a deterioration in the performance of tests for semantic and auditory-speech memory in the absence of differences in the short scale of assessment of mental status and the results of the study of visual-spatial functions. Despite the inconsistency of the data obtained, a common disorder associated with CKD and confirmed by all studies is a defect in regulatory functions. That is why the regulatory function test can be proposed as the most reliable method of early diagnosis of CN in patients with CKD. In our study, patients with CKD the higher stage was demonstrated statistically significantly lower scores in neuropsychological testing, reflects which the deterioration of cognitive functions. However, the indicators of cognitive defect in none of the patients reached the degree of dementia. It should be borne in mind that the selection of patients for the study was carried out in a therapeutic hospital, where patients with dementia are rarely admitted. These data, along with the absence of restrictions on daily activity in the examined patients with CN, allow us to state the development of UCN. Such violations they are detected already in the early stages of CKD and steadily progress with a possible outcome to dementia in the later stages of the disease. Diagnosis of CN in patients CKD in the early stages of kidney damage makes it possible to start adequate therapy in time, aimed, in particular, at improving blood circulation in the brain and eliminating the effects of vascular diseases. This makes it possible to prevent or slow down the

development of dementia and acute vascular complications, maintain a satisfactory quality of life, improve the prognosis and survival of these patients. CN is often combined with emotional and behavioral disorders or is secondary to emotional disorders. The presence of severe depression suggests the secondary nature of CN. In cerebrovascular diseases, depression and CN are a single clinical symptom complex, while depression and cognitive defect reinforce each other. In our study, there were no statistically significant differences between the frequency and severity of CN in patients with and without depression. This may be due to the predominance of mild depression in the majority of patients with UKN (in 83.3% of patients with depression), which worsens cognitive function to a lesser extent than moderate or severe depression. Of the 3 patients we examined with severe depression and UC, 2 showed signs of CVN according to the results of MRI. In the third patient, without changes on MRI, it is impossible to exclude the secondary genesis of UCN, which can be confirmed by positive dynamics in the cognitive sphere against the background of effective antidepressant therapy. The main objective of the brain MRI in the study was to confirm the vascular genesis of UCD in patients with CKD. According to several studies, leukoarrhoea is the most common neuroimaging finding in patients with end-stage CRF who are on dialysis and have CN and is closely related to the severity of kidney damage. In patients with CKD at the predialysis stages, there is practically no data on the relationship of brain changes with the nature and severity of CN. It has been proved that, along with CKD, the number of lacunar cerebral infarcts is independent of FR dysfunction of the frontal lobes of the brain. As shown by the conducted a study based on the development of CN in patients with CKD there are vascular changes in the brain, visualized by MRI. It is important to keep in mind that mixed vascular-degenerative character cannot be excluded in patients with CKD with mnestic-type UCN KN, contributing to the faster development of dementia.

## **CONCLUSION**

In patients with CRF, a statistically significant increase in the frequency of CN development was revealed according to the results of a short scale assessment of mental status, a study of regulatory functions and frontal cortex function compared with patients with kidney damage without CRF. Progression of CKD is associated with an increase in severity Books on the same cognitive spheres. The main substrate of CD in CKD is chronic CVN, which is confirmed by the results of MRI of the brain.

#### **LITERATURE**



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