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PECULIARITIES OF COGNITIVE DISFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE (LITERATURE REVIEW)

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ABSTRACT

The review article deals with the clinical features of neurological disorders in patients with chronic kidney disease. It is emphasized that at the initial stages the changes in the central nervous system are manifested by the disturbances of attention, memory, and psycho-motor functions. However, as the underlying disease progresses, the frontal defect becomes clinically more pronounced. There is a significant prevalence of polyneuropathic disorders in this category of patients. Polyneuropathy in chronic kidney disease is similar in its manifestations to other mixed sensorimotor axonal polyneuropathies of toxic-metabolic genesis and is characterized by imperceptible onset and slow progression. Recommendations for the examination and management of patients are given.

Introduction. In practice it is often met the diseases which are primary not connected with the nervous system affection, however appearing by neurological disturbances. In the considerable percent of cases at this pathology it is possible to reach essential improvement in the condition of patients at once-in-time diagnostics and adequate therapy of the basic disease. It should be emphasized, however, that presence of potentially curable somatic disease underlying neurological disorders does not mean reversibility of the existing disorders by itself - this reversibility depends largely on timely and correct diagnostics of the underlying disease. Nervous system damage in kidney disease has been known since the time of Hippocrates, although the most active study of this problem began at the beginning of the last century, which was associated with the introduction of haemodialysis into clinical practice. The causes of renal failure are diverse and include glomerulonephritis, pyelonephritis, interstitial nephropathies and arterial disease. In renal failure, many organs and

systems are affected (bone system, cardiovascular system, etc), as well as the central and peripheral nervous system. The neurological abnormalities associated with chronic kidney disease (CKD) are similar to those seen in other dysmetabolic disorders. As in other patients with somatically related cerebral disorders, neurological disorders in this category of patients, in addition to impaired consciousness at a marked stage of renal failure, consist in the appearance of various kinds of neurological disorders, especially in the cognitive sphere (thinking, memory, speech, psychomotor functions, etc.). A specific feature of renal failure is a relatively slow increase in clinical neurological disorders - despite quite significant changes in laboratory parameters. Thus, it turns out that the occurrence of neurological disorders is largely determined not by the degree of impairment of biochemical indicators reflecting renal function, but by the rate of increase of these biochemical disorders. In the initial stages of CKD-induced encephalopathy, patients may show increased fatigue, slowness of mental processes, daytime sleepiness and disturbances of night sleep, as well as other very non-specific signs (in particular, tremor), in some cases accompanied by nausea and vomiting. The condition is characterized by a fluctuating course, with patients changing not only over days but even hours . In the early stages, patients show general weakness, attention deficit, apathy and decreased libido. As CKD progresses, behavioural disorders become more pronounced, mnemonic disturbances increase, and sleep inverses. Cerebral symptoms are more severe and develop quite rapidly in patients with acute renal failure. This is supported by experimental data. In CKD, neurological abnormalities may be compensated for long periods (months or even years) without any clinical manifestation. At the same time, even with rapidly increasing renal failure, neurological deficits may regress quite rapidly after the underlying disease has subsided, in particular after haemodialysis or successful renal transplantation. However, as the underlying pathological process progresses, patients may show marked frontal symptoms in the form of abstract thinking, paratognathia and axial reflexes. It should be emphasized that central neurological symptoms are not specific to primary renal disease and appear clinically rather uniform. Further progression of CKD can be accompanied by the onset of seizures (often generalized clonic-tonic), multifocal myoclonias, asterixis, meningism (about one third of cases), agitation, hallucinations (usually visual), delirium, which lead to coma and death. About half of patients with meningeal syndrome show pleocytosis in the cerebrospinal fluid (CSF), with 60% showing protein elevation. Myoclonia in uremia is similar to postanoxic myoclonia. Respiratory disturbances are not uncommon. A rare complication is the development of so-called posterior reversible leukoencephalopathy, when pathological changes mainly affect the white matter of the occipital and parietal regions of the large cerebral hemispheres. Uraemic coma is characterised by increased muscle tone, hyperreflexia, clonus and positive pathological pyramidal reflexes. Pyramidal symptoms may be asymmetrical, with nearly 20-45% of patients developing hemiparesis. Interestingly, the progression of the disease can be accompanied by a change in

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the severity of the pyramidal deficits. and pyramidal symptoms often regress after successful haemodialysis. Peripheral nerve damage in kidney disease was first described in the mid-19th century, but interest in polyneuropathy in CKD (so-called "uremic polyneuropathy" - a term not entirely accurate, but historically established) emerged from the early 1960s, when distal sensorimotor disorders began to be seen not as manifestations of congenital pathology or dialysis-related disorders, but as secondary, renal disease-related disorders. Signs of peripheral nerve damage, both clinically evident and subclinical, detectable only by electrophysiological or microscopic examination, are seen in almost 70% of patients with CKD, and, surprisingly, less frequently in children, although not all authors support the latter view. However, depending on the criteria and diagnostic methods used in any given study, the incidence ranges from 10 to 83%, and even up to 100%. In any case, in end-stage CKD, peripheral nerve damage, either clinically evident or detectable by electrophysiological examination, is found in 50% of patients . Uremic polyneuropathy is more common in men . At the same time, most neurologists report that they rarely encounter this pathology in their practice . There is no association between the severity of polyneuropathy - and age, ethnicity or the nature of kidney disease. Polyneuropathy in CKD is similar in presentation to other mixed sensorimotor axonal polyneuropathies of toxic-metabolic origin and is characterized by an undetectable onset and slow progression. The sensory (primarily) and motor impairments are symmetrical and initially occur in the distal parts of the lower limbs, followed by their proximal spread. Both sensory and motor fibres are affected. Polyneuropathic disorders are not characteristic of acute renal failure. In the initial stages, myelinated thick sensory fibres are damaged, resulting in unpleasant numbness and tingling sensations in the distal parts of the legs. Burning sensations in the feet may occur in some patients, indicating damage to fine sensory fibres, but this is the exception rather than the rule. The occurrence of these sensations is not related to CKD but to vitamin B deficiency during dialysis. About 2/3 of patients with CKD have painful muscle information (crumpets) and restless leg syndrome, but the genesis of these disorders - whether they are a manifestation of polyneuropathy or reflect non-specific tissue changes due to CKD - is still unclear. In either case, these sensations are extremely uncomfortable for patients and can sometimes occur not only in the legs but also in the hands. Anxious patients with low haemoglobin and high serum phosphate levels are most susceptible to the occurrence of restless legs syndrome . An increase in the severity of sensory disturbances is usually noted during the night hours. The progression of peripheral neurological deficits usually occurs over several months, although more unfavourable variants of the disease are also possible, leading to disability relatively quickly . Sensory deficits can be followed by motor deficits in the form of muscle weakness and muscle atrophy (weak dorsiflexion is common at the onset). Subsequently, the upper extremities are also involved. Most patients have subclinical polyneuropathy, with clinical manifestations appearing as CKD progresses - when creatinine clearance

falls below 5-12 ml/min or glomerular filtration drops below 20 ml/min. However, different figures have been reported in the literature - peripheral nerve pathology, detectable by electrophysiological examination, is seen when glomerular filtration falls below 12 ml/min, and clinical signs of polyneuropathy are seen at 6 ml/min or below. Serum creatinine levels exceed 5-6 mg/dl in this group of patients. Some patients have mild sensory disturbances in the feet, while others have marked sensory disturbances, muscle weakness, and loss of reflexes in both the upper and lower extremities. It should be noted that in end-stage CKD, most patients also have diabetes mellitus, so that the pathogenesis of polyneuropathy in these cases may be concomitant. This category of patients is characterized by a predominance of marked motor disturbances that occur over a period of weeks or months. Isolated polyneuropathy ("purely sensory" or "purely motor" polyneuropathy) is extremely rare. Autonomic symptoms such as sweating disorders, postural hypotension (resulting in dizziness and falls), impotence and gastrointestinal disturbances are also rare. In most (but not all) cases, dysautonomia correlates with the presence and severity of uremic polyneuropathy, but not all authors support this view. Thus, some publications emphasize that autonomic disorders are present in a large proportion of patients, but are subclinical. The course of polyneuropathic disorders is in most cases stable, with no progression of symptoms over months - despite increasing CVD - although in isolated cases there may be a rapid progression of acute or sub-acute increases in movement and respiratory disorders, reminiscent of Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy. Protein levels in the cerebrospinal fluid may be elevated. The occurrence of such cases may be associated with the onset of intensive haemodialysis . Another manifestation of peripheral nervous system damage in CKD is tunneling mononeuropathy (most commonly carpal tunnel syndrome). On examination, amyloid deposition in the surrounding connective tissue and tendons is found in these cases. In addition, the existence of subclinical peripheral nerve damage associated with CKD predisposes to the occurrence of tunneling neuropathies. The symptomatology of tunneling neuropathies may increase after haemodialysis. On neurological examination, the vast majority of patients (over 90%) with CKD polyneuropathy show decreased deep sensitivity in the distal parts of the lower limbs and a lack of deep reflexes (often Achilles and knee). Approximately 40% of patients present with impaired temperature sensitivity in the legs (mainly due to a decreased threshold for sensing elevated temperature). Muscle weakness and weight loss are found in about 15% of cases. In tunnel neuropathies, a positive Tinel's symptom is detected at the site of compression, and in autonomic neuropathy, orthostatic hypotension is more common. Cranial nerves are very rarely involved, the most common being the vestibulocochlear nerve. Hearing loss and intermittent nystagmus may thus be detected in some patients, and in some cases mild miosis, oculomotor disturbances and facial asymmetry may be present. Optic neuropathy may also occur. The differential diagnosis of uremic

polyneuropathy is made with a variety of systemic diseases accompanied by the development of distal symmetrical sensorimotor polyneuropathy. Particular attention should be given to diseases that may lead to both CKD and polyneuropathy - diabetes mellitus, myeloma disease, primary amyloidosis and vasculitis (in nodular periarthritis and systemic lupus erythematosus). Polyneuropathies in these conditions are still more characterised by an acute onset with asymmetric symptoms and severe pain. Among the paraclinical features that may suggest vasculitis are inflammatory changes in the blood. Blood abnormalities alone do not aid in the nosological diagnosis of vasculitis, but their absence renders the diagnosis less likely. Patients, particularly those with systemic disease, often show elevated sedimentation and positive C-reactive protein. It is important to note that in patients with CKD polyneuropathy may be caused by iatrogenic factors such as colchicine, which should also be considered when making a differential diagnosis. In addition, alcohol abuse may be a cause of CKD combined with polyneuropathy. Paraclinical diagnosis There is little correlation between the level of azotemia and the severity of neurological deficits in CKD. Therefore, laboratory findings are important for the diagnosis of renal failure, but do not rule out other causes of neurological deficits. Creatinine levels are also assessed in plasma, which are elevated in end-stage CKD. Low levels of calcium, high levels of phosphate and potassium, decreased haemoglobin and metabolic acidosis may be noted. Renal size can be assessed by ultrasound or CT/MRI; its reduction (usually less than 8 cm) confirms the underlying diagnosis. The CSF of patients with uremia and meningeal syndrome may show signs of aseptic meningitis (up to 250 lymphocytes or polymorphonuclear leukocytes in 1 mm3 , protein elevation up to 1 g/l). In CKD, neuroimaging of the brain (CT or MRI) is of little diagnostic value, but can exclude other pathology (subdural haematoma, hydrocephalus). However, there is a description in the literature of cranial artery calcification, including a.ophtalmica, in a 54-year-old patient with diabetes mellitus and chronic kidney disease, which was visualised by brain CT scan . CKD can present with diffuse cerebral atrophy as well as areas of increased signal intensity in T2-mode and decreased signal intensity in T1-mode MRI in the basal ganglia, periventricular white matter, and inner capsule, and in severe cases, infarcts, often hemorrhagic. These changes are inconstant and may regress after haemodialysis. As noted above, they are of little diagnostic value, and the pathogenetic significance of such changes needs to be investigated. EEG changes in this category of patients consist of an increase in slow-wave activity. When the peripheral nervous system is affected, the diagnosis is to establish polyneuropathy and its association with CKD. The presence of polyneuropathy correlates poorly with serum creatinine and urea levels. The diagnosis of polyneuropathy itself is based on the assessment of the patient's complaints, medical history and clinical neurological examination. Peripheral nerve damage is confirmed by electromyography (EMG), especially of the proximal peripheral nerves. EMG changes reflect the loss of sensory and motor axons. The earliest manifestations are lengthening of H and F wave latencies and decreased action

potential. Even in the absence of subjective and objective neurological symptoms, EMG may reveal delayed spread of excitation in the distal and proximal parts of the peripheral nerves as well as a slight increase in distal latency. In addition, signs of a denervation process are often detected. There is no strict correlation between the severity of clinical abnormalities and EMG findings. Fibrillation or positive sharp waves are not detected in needle EMG. Difficulties in interpreting EMG data arise when CKD is combined with diabetes mellitus. Muscle biopsies show signs of deinnervation and reinnervation. A lumbar puncture reveals a small increase in protein levels in about half of the patients with peripheral nervous system involvement. In the case of atypical manifestations of uremic polyneuropathy (acute onset, asymmetry of clinical manifestations, dominance of pronounced pain in the clinical picture) biopsy of n.suralis and muscle tissue may be necessary to exclude vasculitis or amyloid polyneuropathy. Patients with uremic polyneuropathy may also show signs of autonomic insufficiency, particularly prolongation of the R-R interval. Therapeutic options Hemodialysis or donor kidney transplantation are used to treat patients with CKD who have severe neurological deficits. In addition to haemodialysis, erythropoietin is used to treat cognitive impairment in renal encephalopathy. Correction of vascular risk factors is also necessary. In uremic polyneuropathy, dialysis or renal transplantation may stabilise the process or even slowly reduce the severity of the clinical impairment - despite the persisting changes seen in EMG. Tricyclic antidepressants or anticonvulsants (carbamazepine, clonazepam) are used to control pain in these patients. In mild polyneuropathy, recovery may be complete, but in severe polyneuropathic disorders the symptoms may not diminish and may even increase despite dialysis. In these cases, changing the dialysis regimen (frequency of treatment, etc.) can sometimes help. In severe cases, the recovery process can take years, despite the treatment being given. Residual symptoms usually persist. The literature emphasises that the individual prognosis in this category of patients is extremely difficult. Clonazepam, dopamine agonists, levodopa or codeine are used to treat restless legs syndrome, in addition to the correction of anaemia and hyperphosphatemia, and are administered before bedtime. Haemodialysis can be complicated by episodes of arterial hypotension - irrespective of the presence or absence of dysautonomia - which requires appropriate correction (midodrine is most commonly used in these cases).

Conclusions: CKD thus often leads to neurological abnormalities, both central and peripheral. Neurological disorders, which are non-specific in nature, may be noted in the early stages of the disease. Knowledge of peculiarities of their occurrence helps in timely diagnostics of the underlying disease, allows to carry out in time an adequate therapy.

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