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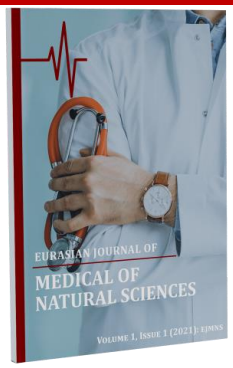

MODERN DIAGNOSTIC APPROACHES TO DETECTING PARKINSON'S DISEASE AT THE INITIAL STAGE OF DEVELOPMENT

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ABSTRACT

To date, the diagnosis of PD is based solely on the clinical picture of the disease. To diagnose PD, the criteria of the British PD Society are used, which include the diagnosis of Parkinsonism syndrome, as well as criteria that exclude and confirm PD. However, their use results in up to 24% of incorrect diagnoses of PD. Therefore, the question arises about the search for additional criteria (biochemical, neuroimaging, neurophysiological, genetic) that can improve the accuracy of diagnosis.

Introduction. Parkinson's disease (PD) is one of the most common neurodegenerative diseases, ranking second after Alzheimer's disease in terms of frequency among age-related neurodegenerations. According to the World Health Organization, there are more than 10 million people with the disease worldwide, with about 1 million new cases diagnosed each year.

The problem of early diagnosis of Parkinson's disease is of particular relevance, since by the time classical motor symptoms appear, more than 60% of the dopaminergic neurons of the substantia nigra have died. This means that the pathological process begins long before the clinical manifestation of the disease, which creates a "therapeutic window" for potential neuroprotective treatment.

Modern research shows that non-motor symptoms such as olfactory disorders, sleep disorders with rapid eye movements, constipation, depression, and anxiety may precede the development of classical motor symptoms by several years or even decades. This opens up new opportunities for the development and implementation of methods for early diagnosis of the disease.

The socio-economic burden of Parkinson's disease is significant: the cost of treating a single patient in developed countries can reach USD 25,000 per year, while the indirect costs associated with disability and the need for outside care significantly exceed the direct medical costs. Early detection of the disease allows not only to improve the prognosis and quality of life of patients, but also to optimize the economic costs of treatment.

In recent years, significant progress has been made in the development of new diagnostic approaches, including biomarkers, neuroimaging techniques, genetic testing, and

digital technologies for assessing motor functions. However, the integration of these methods into clinical practice remains a difficult task requiring standardization and validation of diagnostic protocols.

Of particular importance is the development of an integrated approach to the early diagnosis of Parkinson's disease, combining clinical, instrumental and laboratory research methods. This approach should take into account both the classical motor manifestations of the disease and a wide range of non-motor symptoms, which will increase the sensitivity and specificity of diagnosis in the early stages.

The development of artificial intelligence and machine learning technologies opens up new perspectives in the field of early diagnosis of Parkinson's disease, allowing us to analyze large amounts of data and identify subtle patterns characteristic of the preclinical stage of the disease. This creates prerequisites for the development of personalized diagnostic algorithms and predictive models.

In recent years, due to the increase in the elderly population in developed countries, there has been a steady increase in neurodegenerative diseases, including Parkinson's disease (PD). The prevalence of PD ranges from 100 to 300 people per 100,000 population. In the age group over 65, the prevalence is characterized by higher rates — from 1,280 to 1,500 per 100,000 population.

Despite the sufficient study of the disease, its diagnosis is often delayed. One of the reasons for the late diagnosis is an untimely visit to a doctor. An analysis of the treatment of PD patients in one of the Moscow districts showed that the majority of patients first sought medical help during the period when there were already sufficiently pronounced manifestations of the disease: 67% had stage 2-2.5 of the disease with bilateral symptoms; 5% were at stage 3 and only 28% had stage 1the 1st stage of BP. According to a study conducted in the United States, 25% of patients were not diagnosed with PD within 2 years of the onset of the first symptoms, while 46% of them went to a doctor within 6 months after the development of clinical manifestations. The second most important factor of late diagnosis is the imperfection of diagnostic criteria.

Since PD involves the death of neurons in a certain structure, the substantia nigra, neuroimaging methods are reasonably considered as the only additional methods that can detect the presence of a pathological process characteristic of PD. Such methods include positron emission tomography (PET), single-photon emission computed tomography (SPECT), and proton magnetic resonance spectroscopy ((1H)-MRS).

Using PET with [F]-fluorodopa, presynaptic dopaminergic terminals can be labeled, the number of which is progressively decreasing in PD. PD is characterized by a decrease in the capture of [F]-flurodope by shell neurons on the side opposite to the motor symptoms. Similar changes are noted on the other side, but to a lesser extent, reflecting the asymmetry of the neurodegenerative process. The rate of accumulation of [18F]-fluorodopa in the striatum reflects the process of fluorodopa transport into striatal vesicles and its subsequent decarboxylation. The BP criterion is to reduce the capture of this radioligand by 30% or more. When examining twins, one of whom suffered from PD, a decrease in the capture of labeled fluorodopa in the striatum was found in 44% of clinically healthy monozygotic and 11% of dizygotic twins. Examination of healthy relatives of PD patients in 7 families revealed cases of

asymptomatic disease. The PET prediction index showed the probability of clinical onset of PD in the IV-VII decade of life in 34% of the surveyed. After 1 year, this forecast was confirmed in 36% of cases.

The use of PET allowed us to calculate the rate of loss of dopaminergic neurons per year. According to various authors, this amount ranges from 2 to 9% annually, and, accordingly, the calculated duration of the preclinical stage of PD is 6.0±3.0 years.

It is possible to assess the state of presynaptic structures using other radiopharmacological drugs, for example [C]-dihydrotetrabenazine. This radioligand allows the labeling of vesicular monoamine transporters. A more accessible technique is PET with F—deoxyglucose, but its informative value is low. There was no expected reduction in the local glucose utilization rate in the striatum. In patients in the initial stages of PD, small-focal minor hypometabolism is observed in various structures of the cerebral cortex of a mosaic nature or the absence of pathological changes in metabolism.

Performing SPECT with pathogen-based drugs ([I]-β-CIT, [I]-FP-CIT or [C]-CFT allows you to determine the amount of dopamine transporter in the synoptic cleft. These radioligands bind at the ends of nigrostriatal neurons to the membrane dopamine transporter, which ensures the reuptake of dopamine. BP is characterized by an asymmetric decrease in capture in the shell. Binding to the membrane dopamine transporter is a more sensitive marker of the early period of the disease with a greater decrease in uptake at the onset of the disease compared to dihydrotetrabenazine and fluorodopa. A less pronounced decrease in [F]-fluorodopa uptake in the early period may reflect a compensatory increase in decarboxylase activity. When this compensation becomes insufficient, symptoms appear.

It is possible to assess the state of dopamine receptors by performing PET or SPECT with the dopamine D2 receptor ligand [C]-racloprid. It has been established that in the initial stages of the disease there is an increase in the density of D2 receptors (the density of postsynaptic D1 receptors does not change). It is believed that such shifts reflect compensation mechanisms in conditions of dopamine deficiency. In the later stages, the density of D1 receptors decreases to a greater extent, with the relative preservation of D2 receptors. These changes occur in the striatum contralateral to the side of the symptoms.

The (H)-MRS method allows us to evaluate metabolism in almost any area of the brain. According to I.V. Litvinenko, PD primarily shows a decrease in the level of N-acetylaspartate (NAA) and an increase in the concentration of choline (Cho) in the projection of the compact part of the substantia nigra, which leads to a significant decrease in the NAA/Cho ratio. In patients with early stages of PD (stages I—II on the Hen and Yar scale), these metabolic shifts were the only changes according to the (1H)-MRS data. There were no changes in the projection of the shell and pale ball at the initial stages of BP.

Despite the high informative value of functional neuroimaging methods, unfortunately, they cannot be used in practical medicine due to technologically complex equipment that can only be available to large medical centers. Therefore, all over the world, these studies are used primarily for scientific purposes.

Methods of structural neuroimaging

In this case, we are talking about X-ray computed tomography (CT) and magnetic resonance computed tomography (MRI). It should be recognized that these methods are not

informative enough in terms of confirming the diagnosis of PD, but they may be important for excluding secondary Parkinsonism caused by traumatic brain injuries, tumors, vascular lesions, etc.

The main structural changes in patients with PD are cerebral atrophy in the form of expansion of the cortical sulci and ventricular system of the brain. The severity of atrophy increases in parallel with an increase in the severity and duration of the disease. Thus, in stages I-III of the disease, cerebral atrophy is detected in 23.5%, in stages IV-V — in 100% of cases. The severity of the atrophic process in the akinetic-rigid form of PD is higher than in the tremulous form.

Attempts to use a morphometric assessment of the width of the zone corresponding to the compact part of the substantia nigra as a diagnostic criterion for PD were unsuccessful — there is an "overlap" in this indicator between PD patients and the control group. According to F. Lallement et al., MRI in PD may show a bilateral decrease in signal intensity in the posterior part of the shell. However, this feature is non-specific and can be detected in other neurodegenerative diseases.

Biochemical markers of PD

A decrease in the activity of mitochondrial complex I, which is detected not only in the substantia nigra, but also in platelets and skeletal muscle cells, can act as a biochemical marker. Attempts are being made to determine the level of tyrosine hydroxylase, dopamine, and dopamine receptors in peripheral blood lymphocytes, the number of which may decrease already with the initial manifestations of PD.

In recent years, increased attention has been paid to the mechanisms of oxidative stress in the pathogenesis of PD. As a marker of oxidative stress in peripheral blood, an increase in the activity of the enzyme hydroxyd dismutase in red blood cells, related to natural antioxidants, is detected. According to other studies, the content of 8-hydroxy-2-deoxyguanosine, which is one of the products of oxidative DNA damage, increases in blood serum and urine.

PD shows increased levels of glycine, glutamate, and aspartate in blood plasma, which is explained by excitotoxicity mechanisms involved in the process of neuron degeneration. There was also a decrease in the levels of glutamate (including in the early stages), aspartate, and GABA in the cerebrospinal fluid. PD is characterized by a decrease in isoleucine, alanine, and lysine in the cerebrospinal fluid and a moderate increase in glutamine. In patients with PD, an increase in the concentration of pyruvate in blood plasma is often noted, associated with a change in the activity of pyruvate dehydrogenase. Increased dopamine catabolism is indicated by a significant decrease in the ratio of dopamine/DOPAMINE (3,4-dioxyphenylacetic acid) in urine and a decrease in the excretion of dopamine, 3,4-dioxyphenylalanine (DOPA), norepinephrine, which correlates with the severity of symptoms. Recent experimental studies have confirmed that a decrease in the content of DOPA in urine, especially DOPA, directly correlates with the degree of destruction of dopaminergic neurons in the brain of rats.

Thus, today it is impossible to talk about any specific biochemical marker of the disease. A number of characteristic changes have been identified, specific not only for PD, but also for a number of other diseases. Work in this direction will continue, and perhaps after some time

it will be possible to select markers, the detection of which will allow the patient to be included in the risk group for PD.

Transcranial ultrasound scan of the brain

The use of transcranial sonography (TCS) in PD is based on obtaining a hyperechoic signal from the substantia nigra due to its increased iron content. Hyperechogenicity in the initial stages of PD is detected on the contralateral side of motor disorders in more than 90% of patients. Approximately 40% of first-degree relatives of PD patients show changes in TCS. Hyperechogenicity of substantia nigra can also be detected in 9% of clinically healthy people. Additionally, it should be noted that in healthy individuals with enhanced echogenicity of the substantia nigra, PET showed a significant decrease in the accumulation of [18F]-fluorodopha in the striatum in 60% of cases compared with the control. Despite the limited experience of using TCS in the diagnosis of PD, 8 cases of hyperechogenicity of substantia nigra have already been described in the literature, followed by the manifestation of PD symptoms over several years. The undoubted advantages of the method are low cost, non-invasiveness, short duration of the study, and the possibility of repeated repetition of the study over time. Perhaps, with sufficient experience, this method can be used as a screening examination, but its results need to be confirmed by other methods.

Olfactory research

According to the concept of H. Braak et al., the neurodegenerative process in PD initially captures the olfactory bulb, the anterior olfactory nucleus, and the dorsal nucleus of the vagal nerve (stage I), then it spreads along the brainstem, involving the blue spot, suture nuclei, and areas responsible for REM sleep (stage II), and only then passes on the black substance of the striatum (stage III). Therefore, olfactory dysfunction (hyposmia, anosmia) is one of the first signs of PD. For diagnosis, an assessment of the olfactory threshold, the ability to distinguish and identify odors is carried out. In a case—control study, changes were detected in 68% of patients with early stages of PD, whereas in the control, loss of sense of smell was observed in only 3%. In the examination of 30 people with idiopathic loss of sense of smell using TCS and SPECT, 11 revealed an enhanced echo signal from the substantia nigra, and 5 of these 11 patients showed a decrease in radioligand uptake during SPECT. Olfactory dysfunction is also observed in 10-23% of healthy relatives of PD patients. When monitoring twins, one of whom suffered from PD, cases of Parkinsonism symptoms were described in previously healthy twins who had lower olfactory test scores several years earlier compared to other healthy twins.

Transcranial magnetic stimulation

A number of studies have shown a decrease in the time of central motor behavior (CMP) and an increase in the amplitude of the evoked motor response (IMR). The greater the increase in amplitude, the more pronounced the symptoms of the disease were. The shortening of the CMP was associated with the possible activation of the fastest—conducting motor neurons, and the increase in the amplitude of the CME was associated with increased excitability of cortical and/or spinal motor neurons. These changes are probably based on an imbalance of excitatory and inhibitory influences with a predominance of excitatory choline and glutamatergic systems.

Recording of saccadic eye movements

PD is characterized by a change in the parameters of saccadic eye movements, which is explained by a decrease in the inhibitory connections of the reticular part of the substantia nigra with the upper lumps of the quadriceps against the background of a decrease in dopamine production. Saccades are abrupt, rapid, friendly, fixing eye movements that occur when looking from one stationary object to another. Oculographic examination of patients with the initial stages of PD (stage I—II on the Hen and Yar scale) reveals higher than normal average values of latency periods (the time interval from changing the position of significant visual stimuli to the beginning of the saccade), as well as the time of gaze movement, which is associated with an increase in the proportion of a special group of eye movements — multisaccade, when the eye reaches the target not by one, but by several (two, three or more) consecutive saccades.

Electroencephalography (EEG)

On the EEG in patients with PD, there is a decrease in α-activity and an increase in the power of slow rhythms (θ- and δ-) in both hemispheres. The θ-rhythm has the greatest representation in the spectrum. A slowdown in the electrical activity of the brain is detected already in the early stages of the disease, is more pronounced in the akineticorigid form and increases as PD progresses and the motor defect worsens in patients. The main feature of the α-rhythm in PD is its approximation to the lower limit of the spectrum. A correlation is found between the severity of akinesia and the slowing of the alpha rhythm in the waking state. On the contrary, a number of authors in Parkinsonism pointed to a tendency to desynchronize the background EEG with the appearance of fast rhythms with a frequency of up to 100 in 1 s. In patients with mild and moderate stages of the disease, a decrease in the power of β- and γ-activity was found along with its increase in the θ- and α1-frequency ranges, and in patients with advanced stages of PD, an increase in β—activity was found.

Evoked Potentials (VP)

Examination of patients with visual visual disturbances at the stage of hemiparkinsonism showed a decrease in the maximum amplitude of the late components and an increase in the latency of the early positive component of the P100 response compared with the "intact" hemisphere. The asymmetry of amplitudes and latencies disappeared as the disease progressed. PD increases the latency of not only the P100 component, but also N75 and N145, while its values correlate with the severity of motor manifestations and the duration of the disease. The changes in PV are explained by biochemical and electrophysiological changes in the retina, the neurons of which are rich in dopamine, which is confirmed by the data of electroretinography. At the same time, another study of the STD on a reversible checkerboard pattern in patients with PD, conducted by S. Ozden et al., did not find a significant amplitude-time asymmetry of the components between the more and less affected sides when the corresponding eye was stimulated. There was also no correlation between these indicators and the clinical manifestations of PD, with the exception of bradykinesia. When analyzing the results of the ZVP study for a flash of light, there was no difference in the indicators in patients depending on the stage of the disease.

The study of somatosensory VP (SSVP) in PD reveals a decrease in the amplitudes and an increase in the latencies of individual peaks, in particular, a decrease in the amplitude of peaks P37 and N50 during stimulation of the lower extremities, a decrease in the amplitude of

component N31 and an increase in latency P44, correlating with the age of patients. Changes in CVD indicators at the stage of unilateral clinical manifestations were studied, and a decrease in the N30 peak was noted, while no relationship was found between the amplitude-time characteristics of this component and the side of clinical manifestations.

When studying short-latency stem cells for acoustic stimulation, a significant increase in latency and a decrease in the amplitude parameters of the V component were revealed. However, an increase in the peak latency of components I and V is typical only for PD in combination with dementia, and the group of patients without dementia (i.e., the initial stages of the disease) and the control had no significant differences in this indicator at all. An increase in the latency period of peaks I and III in BP was noted.

When studying cognitive evoked potentials in PD, there is a decrease in the amplitude of the P300 potential in the parietal regions with its maximum values in the frontal leads and an elongation of the latency period. Changes in the P300 potential are characteristic only for patients with dementia, and patients without dementia do not differ in these indicators from the control group. In PD without dementia, there is no interhemispheric asymmetry during nonverbal stimulation, which may indicate a dysfunction of the subdominant hemisphere.

PD is characterized by a decrease in the amplitudes of the main components of olfactory evoked potentials until their disappearance and an increase in peak latencies even in the absence of violations on the main olfactory tests.

Electromyography and electroneuromyography

An electromyographic examination using cutaneous electrodes reveals a number of changes in EMG in patients with PD. In patients with the tremulous form of the disease, salvo activity is recorded with high-voltage fluctuations in the biopotential of muscles at rest, according to the type of volleys with a frequency of 4-8 in 1 s, which reflects the rhythm of tremor. Electromyographic registration of tremor showed that salvo activity is reciprocal, i.e. at the moment of pause in the agonist, there is a salvo discharge in the antagonist. In the akineticorigid form of the disease, the electromyogram is of a stationary type and is formed on the basis of rhythmic asynchronous stationary activity of motor units. With the progression of PD, the tremor amplitude increases, and the frequency of volleys decreases. It is believed that low-frequency tremor has a higher amplitude and a longer duration of the salvo. As muscle tone increases in the later stages of the disease, salvo activity is suppressed.

Changes in EMG can be detected in the subclinical and early stages of PD. They can also be detected in 17.3% of healthy people of middle age and 26.2% of the elderly, which reflects the presence of latent extrapyramidal insufficiency and the weakening of inhibitory suprasegmental effects with age. In healthy relatives of patients with Parkinsonism, in 45% of cases, the presence of salvo activity on EMG is detected. Examination of clinically intact limbs in patients with stage I PD using EMG with spectral analysis revealed changes in 71% of cases in the upper and 58% in the lower extremities. These data are of particular interest as a promising opportunity to use this technique as a tool to facilitate early diagnosis of PD.

The results of the use of stimulation myography — electroneuromyography in patients with PD are contradictory. Some authors have noted a decrease in the amplitude of the M-response to ENMG. According to the results of our research, the early stages of PD are characterized by an increase in the amplitude of the M-response in the muscles of the hands

and feet on the side of the onset of motor disorders, which is confirmed by the results of other studies. In patients with PD, the amplitude of the M-response in the hand muscles is higher than in patients with vascular Parkinsonism. The rate of conduction of an impulse (SPI) along peripheral nerves in patients with PD also undergoes changes: there is a decrease in SPI in PD, probably associated with a weakening of descending supraspinal and intrasegmental tonic impulses and an improvement in the function of α-motor neurons. An increase in CPI in PD is described. According to our data, in patients with the initial stages of PD, peripheral nerve conduction increases along the motor fibers, which is manifested in an increase in CPI and a decrease in M-response latency. The high values of SPI are apparently explained by a decrease in the downward inhibitory effects of the nigrospinal tract on the interneurons of the tonic stretching reflex and an increase in the excitability of spinal motor neurons. To assess the functional state of the motor neuronal apparatus of the spinal cord, monosynaptic testing (H-reflex) is also used, the study of which, as a rule, indicates increased excitability of the spinal α-motor neuronal apparatus. In PD, there is a decrease in the latency period, a decrease in the threshold of evocation, and an increase in the amplitude of the H-response.

Conclusion. The above review shows that to date there is not a single method (with the exception of poorly available PET and SPECT options) that would allow to identify certain signs (criteria) of the disease. Perhaps in the next decade it will be possible to identify a range of additional studies that will have a sufficient level of evidence to recommend them to the list of necessary methods for diagnosing PD. These will probably be several biomarkers that are easily available for analysis. Currently, according to the protocol for the management of patients with PD, approved by the Ministry of Health of the Russian Federation (2005), the list of medical services for PD includes only medical history collection and neurological examination. MRI and CT scans are recommended in the presence of symptoms that are not characteristic of PD, in order to exclude other diseases. The development of biomarkers will significantly increase the accuracy of diagnosis in the early stages of the disease and will make it possible to identify a risk group for this disease when changes are detected in clinically healthy people.

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