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METHODS OF DIAGNOSIS EARLY STAGE OF PARKINSON'S DISEASE

Kasimov A.A.
Mamurova M.M.
Zaripov S. Sh.
Mamatov J.X.
Department of Neurological Diseases
Samarkand State Medical University

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Abstract:

In recent years, due to the increasing elderly population in developed countries, there has been a steady increase in neurodegenerative diseases, which include Parkinson's disease (PD). The prevalence of PD ranges from 100 to 300 people per 100,000 population. In the age group older than 65 years, the prevalence is higher, ranging from 1,280 to 1,500 per 100,000 population

Keywords: Parkinson's disease, early stages, diagnosis, biomarkers

INTRODUCTION. Although the disease is well understood, it is often diagnosed late. One of the reasons for late diagnosis is untimely treatment. The analysis of BP treatment demand in one district of Moscow showed that most patients first applied for medical care when the manifestations of the disease were quite significant: 67% of them had stage 2-2.5 with bilateral symptoms; 5% - were in the 3rd stage, and only 28% had stage 1 PD. In a study in the United States, 25% of patients were not diagnosed with PD within 2 years of the onset of symptoms, and 46% of these patients consulted a physician within 6 months of onset. The second most important factor for inadequate diagnosis is inadequate diagnostic criteria.

Currently, the diagnosis of PD is based solely on the clinical presentation of the disease. The British PD Society criteria are used to make the diagnosis of PD, which include the diagnosis of parkinsonian syndrome, as well as criteria that exclude and confirm PD. However, the use of these criteria results in up to 24% of misdiagnoses of PD. This raises the question of finding additional criteria (biochemical, neuroimaging, neurophysiological, and genetic) that can improve diagnostic accuracy.

Functional neuroimaging techniques

Since in PD we are talking about the death of neurons in a certain structure - substantia nigra, then neuroimaging methods are reasonably considered as the only additional methods that can in vivo to identify the presence of a pathological process characteristic of PD. These include positron emission tomography (PET), single-photon emission computed tomography (SPECT), and proton magnetic resonance spectroscopy ((H)-MRS).

PET with [F]-fluorodopa can label presynaptic dopaminergic terminals, which are progressively reduced in PD. PD is characterized by a decrease in [F]-fluorodopa uptake by shell neurons on the side opposite to the motor symptoms. Similar changes are observed on the other side, but to a lesser extent, reflecting the asymmetry of the neurodegenerative process. The [F]-fluorodopa accumulation rate in the striatum reflects the process of fluorodopa transport into striatal vesicles and its subsequent decarboxylation. The criterion for PD is a 30% or more decrease in the uptake of this radioligand. In a study of twins, one of whom had PD, decreased uptake 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 asymptomatic cases. The prognostic PET index showed the probability of clinical debut PD in the fourth to seventh decade of life in 34% of those examined. Already after 1 year, this prognosis was confirmed in 36% of cases.

The use of PET has made it possible to calculate the rate of loss of dopaminergic neurons per year. This number, according to different authors, ranges from 2 to 9% annually, and the correspondingly calculated duration of the preclinical stage of PD is 6.0±3.0 years.

Presynaptic structures can be assessed using other radio pharmacological agents such as [C]-dihydrotetrabenazine. This radioligand allows the tagging of vesicular monoamine. A more readily available technique is PET with F18-deoxyglucose, but its informative value is low. The expected reduction in the local rate of glucose utilization in the striatum has not been demonstrated. Patients in the initial stages of PD show small focal non-significant hypometabolism in various cortical structures of a mosaic nature or no pathological metabolic changes .

Dopamine receptor status can be assessed by performing PET or SPECT with the dopamine D2-

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receptor ligand [C]- raclopride. It has been shown 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). Such shifts are thought to reflect compensation mechanisms in a dopamine-deficient environment. In the later stages, the density of D1 receptors decreases to a greater extent, while the D2 receptors remain largely intact. These changes occur in the striatum contralateral to the symptomatic side.

The (H)-MRS method makes it possible to assess metabolism in almost any area of the brain. According to I.V. Litvinenko, in PD, first of all, a decrease in N-acetyl aspartate (NAA) level and increase in choline (Cho) concentration are revealed in the projection of the compact part of the substantia nigra, which leads to a significant decrease in the NAA/Cho ratio. These metabolic shifts were the only changes in patients with early stages of PD (stage I- II according to Chen and Yar scale) according to (H)-MRS data. There were no changes in the shell and pale balloon projection in the initial stages of PD.

Despite the high information content of the method's functional neuroimaging, they, unfortunately, cannot be used in practical medicine due to technologically sophisticated equipment[1], which may be available only to large medical centers. Therefore, these studies are used worldwide mainly for scientific purposes.

Structural neuroimaging techniques

In this case, we are talking about X-ray computed tomography (CT) and magnetic resonance computed tomography (MRT). The diagnosis of PD can be confirmed by a cranio-cerebral imaging (MRT) scan. It should be acknowledged that these methods are of little value in confirming the diagnosis of PD, but may be important in excluding secondary Parkinsonism caused by craniocerebral trauma, tumor masses, juvenile lesions, etc.

The main structural changes in PD patients are cerebral atrophy in the form of enlargement of the cortical sulcus and ventricular system of the brain. The severity of the atrophy increases with the severity and duration of the disease. Cerebral atrophy is present in 23.5% of cases in stages I-III, and in 100% of cases in stages IV-V. The severity of the atrophic process is greater in akinetic and rigid PD than in shivering PD .

Attempts to use morphometric assessment of the width of the zone corresponding to the compact part of the substantia nigra as a diagnostic criterion for PD have failed - there is an overlap between PD patients and controls. According to F.Lallement et al., MRT in PD can show a bilateral decrease in signal intensity in the posterior part of the shell. However, this sign is nonspecific and can be seen in other neurodegenerative diseases.

Biochemical markers of PD

A decreased activity of mitochondrial complex I, which is detected not only in substantia nigra but also in platelets and skeletal muscle cells, can be a biochemical marker. Attempts have been made to determine the levels of tyrosine hydroxylase, dopamine, and dopamine receptors in peripheral blood lymphocytes, which can be reduced in 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, increased activity of the enzyme superoxide dismutase in erythrocytes related to natural antioxidants has been detected. According to other studies, the content of 8-hydroxy-2- deoxyguanosine, a product of oxidative DNA damage, is increased in serum and urine .

In PD, increased plasma levels of glycine, glutamate, and aspartate have been shown, which is explained by the mechanisms of excitotoxicity involved in the process of neuronal degranulation. Decreased levels of glutamate (including at early stages), aspartate, and GABA in CSF have also been detected. PD is characterized by decreased cerebrospinal fluid levels of isoleucine, alanine, lysine, and a moderate increase in glutamine. An increase in plasma pyruvate concentration associated with altered pyruvate dehydrogenase activity is often seen in PD patients. About amplification dopamine catabolism indicates a significant decrease in the ratio of dopamine / DOFUA (3,4-dihydroxyphenylacetic acid) in the urine and a decrease in excretion dopamine, 3,4-dioxyphenylalanine (DOPA), norepinephrine, which correlates with the severity of symptoms. Recent experimental studies have confirmed that a decrease in urinary DOPA, especially DOFUA, directly correlates with the degree of dopaminergic neuronal damage in the rat brain.

Thus, no specific biochemical marker of the disease can be identified at present. A number of characteristic changes specific not only to PD but also to a number of other diseases have been identified. We will continue to work on this, and it may be possible in time to select markers whose detection would allow a patient to be included in the PD risk group.

Transcranial ultrasound scan of the brain

Transcranial sonography (TSC) in PD is based on a hyperechogenic signal from the substantia nigra due to its increased iron content. Hyper echogenicity in the initial stages of PD is detected on the side contralateral

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to the motor impairment in over 90% of patients. Approximately 40% of first-degree relatives of patients with PD show changes in TCS. Hyper echogenicity of the substantia nigra can also be detected in 9% of clinically healthy individuals. In addition, a significant reduction in [F]-fluor deficiency accumulation in the striatum was found in healthy subjects with enhanced substantia nigra echogenicity in PET in 60% of cases compared to controls. Despite the limited experience in the use of TCS in PD diagnosis, 8 cases of substantia nigra hyper echogenicity with subsequent manifestation of PD symptoms within a few years have already been described in the literature. The undoubted advantages of the method are its low cost, noninvasiveness, short study time, and the possibility of multiple repetitions of the study in dynamics. It is possible that this method can be used as a screening test if sufficient experience has been gained, but the results need to be confirmed by other techniques.

Investigating olfaction

According to Braak et al., the neurodegenerative process in PD initially involves the olfactory bulb, the anterior olfactory nucleus, and the dorsal nucleus of the vagus nerve (stage I), then it spreads through the brain stem involving the bluetongue, suture nuclei, and areas responsible for REM sleep (stage II), and only then proceeds to the substantia nigra of the striatum (stage III) [49]. Therefore, olfactory dysfunction (hyposmia, anosmia) is one of the first signs of PD. Olfactory threshold, the ability to distinguish and identify odors, is assessed for diagnosis. A "case-control" study found changes in 68% of patients with initial stages of PD, whereas only 3% of controls had olfactory loss. In the examination of 30 people with idiopathic olfactory loss with TCS and SPECT, an enhanced echo signal from the substantia nigra was detected in 11, and 5 of these 11 patients showed decreased radioligand capture on SPECT. Olfactory dysfunction is also observed in 10–23% of healthy relatives of patients with PD [98]. In the follow-up of twins, one of whom had PD, there have also been cases of previously healthy twins developing parkinsonian symptoms, with a few years before that twin having poorer olfactory test scores than other healthy twins.

Transcranial magnetic stimulation

A number of studies, have shown a decrease in central motor behavior time (CMT) and an increase in the amplitude of the evoked motor response (AMR). The increase in amplitude was greater the more severe the symptoms of the disease. The shortening of the VSMR was associated with the possible activation of the fastest conducting motoneurons, while the incipient amplitude of the MMR was associated with increased excitability of cortical and/or spinal motoneurons. These changes are probably based on an imbalance of excitatory and inhibitory influences with the predominance of excitatory choline and glutamatergic systems.

Recording saccadic eye movements

PD is characterized by changes in the parameters of saccadic eye movements, which is explained by a decrease in the reticular part of the substantia nigra with the superior tubercle of the quadriplegia in the background of a decline in dopamine production. Saccades are sudden, rapid, concomitant fixation eye movements that occur when gaze is shifted from one stationary object to another. Oculographic examination of patients with initial stages of PD (stage I-II according to the Chen and Yar scale) reveals longer than normal mean values of latent periods (the time interval between changing the position of the significant visual stimuli and the onset of saccades), as well as the time of gaze movement, which is associated with an increase in the proportion of a special group of eye movements: multiaccess, when the eye reaches the target by several (two, three, or more) sequential saccades.

Electroencephalography (EEG)

EEG in PD patients shows decreased α-activity and increased power of slow rhythms (θ- and δ-) in both hemispheres. The θ-rhythm has the highest representation in the spectrum. The slowing of electrical activity of the brain is evident in the early stages of the disease, is more pronounced in the akinetic and rigid form, and increases with PD progression and aggravation of motor deficits in patients. The main feature of the α-rhythm in PD is its approach to the lower end of the spectrum.There is a correlation between the severity of akinesia and a slowing of the α-rhythm in the waking state. In contrast, some authors, in parkinsonism have shown a tendency to desynchronize the background EEG with fast rhythms up to 100 per 1 s. A decrease in β- and γ-activity power along with an increase in θ- and α_1 -bands was found in patients with mild and advanced stages of PD, while an increase in β-activity was found in patients with advanced stages of PD.

Evoked potentials (EP)

Examination of patients using visual EPs (VEPs) in the stage of hemi parkinsonism showed a decrease in the maximum amplitude of late components and an increase in the latency of the early positive component of the P100 response compared to the "intact" hemisphere. The asymmetry of amplitudes and latencies disappeared with disease progression. Not

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only P100 component, but also N75 and N145 latency increased in PD, and its values correlate with the severity of motor manifestations and the duration of the disease. Changes in VEP are explained by biochemical and electrophysiological changes in the retina, whose neurons are rich in dopamine, as evidenced by electroretinography data. At the same time, another study of VEP for reversible checkerboard pattern in PD patients by S. Ozden et al., found no significant amplitude-temporal asymmetry of the components between the more and less affected sides during stimulation of the corresponding eye. There was also no correlation between these indices and clinical manifestations of PD except for bradykinesia. When analyzing the results of VEP to flash light, there was no difference between the patients depending on the stage of the disease.

Studies of somatosensory EP (SSEP) in PD show decreased amplitudes and increased latencies of some peaks, in particular, decreased amplitude of the peaks P37 and N50 when stimulating the lower limbs, decreased amplitude of the component N31 and increased latency P44, which correlate with the age of patients. Changes in SSEP parameters at the stage of unilateral clinical manifestations were studied; a decrease in the N30 peak was observed, while no relationship between the amplitude-time characteristics of this component and the side of clinical manifestations was found .

A significant increase in the latency and decrease in the amplitude parameters of the V component was found in the study of short-latency EPs to acoustic stimulation. However, an increase in the interpeak latency of components I and V is characteristic only for PD in combination with dementia, while the group of patients without dementia (i.e., the initial stages of the disease) and controls had no significant differences in this parameter at all. An increase in the latent period of peaks I and III was observed in PD.

In studies of cognitive evoked potentials in PD, there is a decrease in the amplitude of the P300 potential in the parietal regions, with maximum values in the frontal leads , and a prolongation of the latent period. Changes in P300 potential are characteristic only for patients with dementia, while patients without dementia do not differ from the control group in these indicators. In PD without dementia, there is a lack of interhemispheric asymmetry during nonverbal stimulation, which may indicate subdominant hemisphere dysfunction.

PD is characterized by a decrease in the amplitudes of the main components of olfactory evoked potentials until they disappear and an increase in the latency of the peaks even when the main olfactory tests are not impaired.

Electromyography and electroneuromyography

Electromyographic examination with cutaneous electrodes reveals a number of changes in EMG in patients with PD. In patients with the tremor form of the disease, hall activity is recorded with high-voltage fluctuations of the muscle bio-potential at rest in the type of volleys with a frequency of 4-8 per 1 s, which reflects the tremor rhythm. Electromyographic recording of the tremor showed that the volley activity is reciprocal, i.e., the moment of a pause in the agonist is followed by a volley discharge in the antagonist. In the kinetic and rigid form of the disease, the electromyogram is of the stationary type and is formed on the basis of rhythmic asynchronous stationary activity of motor units. As PD progresses, the amplitude of the tremor increases and the volley frequency decreases. Low- frequency tremor is considered to have a higher amplitude and longer volley duration. As muscle tone increases in the later stages of the disease, the volley activity is suppressed.

EMG changes can be detected in the subclinical and early stages of PD. They can also be detected in 17.3% of healthy middle-aged and 26.2% of elderly people, reflecting the presence of latent extrapyramidal insufficiency and weakening of the inhibitory suprasegmental effects with age . In healthy relatives of patients with parkinsonism, salvo activity on EMG is detected in 45% of cases. 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 extremities and 58% in the lower extremities. These data are of some interest as a promising possibility of using this technique as an instrument to facilitate the early diagnosis of PD.

The results of stimulation myography - electroneuromyography in PD patients are contradictory. Some authors noted a decrease in the amplitude of the M response on ENMG . According to the results of our studies, the early stages of PD are characterized by increased amplitude of M-response in the hand and foot muscles on the side of the motor disorder onset, which is confirmed by the results of other studies. Patients with PD have a higher amplitude of M-response in the hand muscles than in patients with vascular parkinsonism. Impulse conduction velocity (ICV) along the peripheral nerves in PD patients also undergoes changes: there is a decrease in ICV in PD, probably related to the weakening of descending supraspinal and intersegmental tonic impulses and facilitation of α-motoneuron function. An increase in SPI in PD has

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been described. According to our data, patients with the initial stages of PD have increased conduction along the motor fibers of peripheral nerves, which is manifested by an increase in SPI and a decrease in M-response latency values. The high values of SPI are apparently explained by a decrease in the downward inhibitory effects of the nigrospinal tract on interneurons of the stretch reflex and increased excitability of spinal motoneurons. For rate functional state of the motor neuron apparatus of the spinal cord, monosynaptic testing (H-reflex) is also used, the study of which, as a rule, indicates an increased excitability of the spinal α-motor neuronal apparatus. In PD, there is a decrease in the latency period, a decrease in the evocation threshold, and an increase in the amplitude of the H-response.

CONCLUSION: This review shows that, to date, there is no single method (except for low-availability PET and SPECT variants) that can detect certain signs (criteria) of the disease. It is possible that 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 are likely to be several bio-markers readily available for analysis. At the moment, according to the protocol for the management of patients with PD approved by the Ministry of Health of the Russian Federation, only history taking and neurological examination are included in the list of medical services in PD. MRI and CT scanning are recommended in the presence of symptoms not characteristic of PD to exclude other diseases. The development of biomarkers will significantly improve diagnostic accuracy in the early stages of the disease and allow the identification of a risk group for this disease when changes are detected in clinically healthy individuals.

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