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MODERN VIEW TO OPTIMIZATION OF THE DIAGNOSIS OF THE COURSE OF PARKINSON'S DISEASE

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✓ ***Resume***

Parkinsonism is one of the most significant problems in clinical neurology, both due to its high prevalence in the world's populations and due to the significant disability of patients. The paper analyzes the diagnosis of Parkinson's disease (as well as other neurodegenerative diseases) at the prodromal stage. An overview of the methods of preclinical and early clinical diagnosis of BP shows that the study of the prmodromic markers and the criteria of the Premotor Phase Phase of the BP will allow in the future to significantly change the course of the disease using neuroprotective therapy at the stage preceding the death of a significant number of dopaminergic neurons of the Black Substance.

Key words: Parkinson's disease, patient disability, neuroprotective therapy, long-term markers, black substance.

PARKINSON KASALLIGI TASHXISINI OPTIMAL QARASHLAR

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Parkinsinizm klinik nevrologiyaning muhim muammolari soniga, dunyoning aholisining yuqori darajada tarqalishi va bemorlarning ahamiyatsiz nogironligi tufayli. Qog'oz, Parkinson kasalligi (shuningdek, nevrodegensterativ kasalliklar) ishlab chiqarish bosqichida (shuningdek, nevrodegenergerativ kasalliklar) tahlil qiladi. BPning prinik va erta klinik diagnostikasi usullarini ko'rib chiqish shundaki, shuni ko'rsatadiki prodromik markerlari va premotor fazali fazasi mezonlarini o'rganish kelajakda qora moddaning dopaminergik neyronlarining sonini vafotidan tashqari, kasallik yo'nalishini sezilarli darajada o'zgartirishga imkon beradi.

Kalit so'zlar: Parkinson kasalligi, bemor nogironligi, nevropotektiv terapiya, uzoq muddatli markerlar, qora modda.

СОВРЕМЕННЫЙ ВЗГЛЯД К ОПТИМИЗАЦИИ ДИАГНОСТИКИ ТЕЧЕНИЯ БОЛЕЗНИ ПАРКИНСОНА

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✓ ***Резюме***

Паркинсонизм относится к числу наиболее значимых проблем клинической неврологии – как в силу высокой распространенности в популяциях мира, так и вследствие значительной инвалидизации пациентов. В работе проведен анализ диагностики болезни Паркинсона (как и других нейродегенеративных заболеваний) на продромальной стадии. Обзор методов доклинической и ранней клинической диагностики БП показывает, что, изучение продромальных маркеров и критерии премоторной фазы БП позволит в будущем существенно изменить ход заболевания, используя нейропротективную терапию на этапе, предшествующем гибели значительного числа дофаминергических нейронов чёрной субстанции.

Ключевые слова: болезнь Паркинсона, инвалидизация пациентов, нейропротективная терапия, продромальные маркеры, чёрная субстанция.

Relevance

Currently, due to the increase in life expectancy in developed countries and the increase in the proportion of elderly people in the population, the prevalence of so-called age-related diseases, primarily of a neurodegenerative nature, is noticeably increasing [1,4]. Among them is Parkinson's disease (PD), which ranks second after Alzheimer's disease, a chronic human neurodegenerative disease associated with the primary lesion and death of nigrostriatal neurons and dysfunction of the basal ganglia and is observed with a total frequency of 100–200 cases per 100,000, in including in 2–4% of persons over 65 years of age [2]. The incidence is 100–250 cases per 100,000 population [3]; in European countries, the number of PD patients averages 1.8% in the population of people over 65 years of age and steadily increases with age [4].

Parkinsonism is one of the most significant problems in clinical neurology, both due to its high prevalence in the world's populations and due to the significant disability of patients. In accordance with the existing classification, it is customary to distinguish in the structure of parkinsonian syndromes: 1) primary parkinsonism; 2) atypical parkinsonism; 3) secondary parkinsonism; 4) parkinsonism in hereditary diseases of the central nervous system [2]. On average, 14 years after the onset of motor manifestations of the disease, patients are bedridden or wheelchair-bound. PD occurs almost everywhere, with about 5 million people suffering from PD in the world [4]. In addition to motor symptoms, patients with PD have a range of non-motor manifestations (impaired sense of smell, changes in visuo-spatial coordination, movement disorders during sleep with rapid eye movements, gastrointestinal motility disorders, mild to moderate cognitive impairment, depression, panic attacks etc.) [5].

Purpose of the study. Analysis of the diagnosis of Parkinson's disease (as well as other neurodegenerative diseases) at the prodromal stage.

Materials and methods

Features of the course of the neurodegenerative process in PD, rapid loss of dopamine-producing neurons of the substantia nigra in the prodromal period lead to the fact that the first clinical manifestations appear with the death of more than 70–80% of nigrostriatal neurons and a significant decrease in the dopamine level in the striatum [3]. Meanwhile, as the results of experimental studies show, any potential neuroprotective interventions for this disease are most effective at the earliest possible stage of the disease, ideally at its preclinical stage [5]. Primary parkinsonism includes Parkinson's disease (PD), the second most common neurodegenerative disease that represents a significant medical and socioeconomic problem, as well as juvenile parkinsonism.

Results and its discussion

In recent years, the list of genes associated with the development of primary parkinsonism has expanded significantly. Today, 22 loci and 17 causal genes are already known, and a pronounced variability in the phenotypic manifestations of the disease with the same genotype, even among relatives in the same family, has been shown [4]. Studies of the last decade have shown that some of the non-motor symptoms (hyposmia, orthostatic hypotension, constipation, behavioral disturbances in the REM sleep phase, depression, etc.) precede the manifestation of the motor manifestations of the disease for 5–20 years [3]. Some early symptoms of PD also include mild cognitive impairment, which, according to our data, occurs in 30% of patients with newly diagnosed PD. The presence of the premotor and prodromal phases of the disease is confirmed by the data of pathomorphological and neuroimaging studies [6]. The morphological basis of non-motor disorders of PD in the premotor phase of the disease is explained by the modern concept of H. Braak et al. [4]. The basis of the pathobiochemical cascade of PD is a violation of the conformation of the alpha-synuclein protein, which is normally present only in the presynaptic terminals of the brain. In PD, this protein accumulates and forms filamentous structures 20–40 nm in diameter inside neurons, which is the first stage in the formation of specific intracellular inclusions, Lewy bodies [4].

On the basis of immunohistochemical detection in autopsy samples of an extensive brain bank of alpha-synuclein and Lewy bodies, H. Braak put forward a 6-stage theory of the development of a pathological neurodegenerative process in PD [4]. According to the author, at stage 1, the olfactory bulb, anterior olfactory nucleus and dorsal motor nucleus of the vagus nerve, peripheral ganglia of the autonomic nervous system, pre- and postganglionic sympathetic and parasympathetic structures of the intestinal, cardiac and pelvic plexuses are affected [4]. According to the double-hit hypothesis currently being developed by H.Braak, the provoking factor that triggers the cascade of neurodegenerative changes in the brain is a slow virus that enters the nervous system through the nasal mucosa and intestinal mucosa. At stage II, the process extends to the nuclei of the medulla oblongata and the bridge, including the suture nucleus, the bluish spot, and the reticular formation. Stage III is characterized by damage to the midbrain, including the substantia nigra, amygdala, and basal forebrain. In stage IV, the temporal mesocortex and hippocampus are involved. In the final (V and VI) stages, Lewy bodies appear in the cerebral cortex, first in the association areas of the prefrontal, temporal and parietal cortex, then in the motor and sensory areas of the cortex [4,5].

It has been established that some manifestations are mostly relatively pharmacoresistant to levodopa drugs, since their development is based on the dysfunction of mainly non-dopaminergic systems: noradrenergic, serotonergic, cholinergic, etc. [4,8]. The sequence of occurrence of clinical manifestations of PD in accordance with the staging of the pathological process according to H.Braak is presented in Table 2. The rate of neurodegeneration in the early stages is not known, but by the time of manifestation of motor symptoms (stages II-IV according to H.Braak), the number of dead nigrostriatal neurons dramatically decreases and reaches 60% of the initial level, while the amount of striatal dopamine decreases by 80% [4] . Attempts at neuroprotection in the late stages of PD may not be successful, which is why the ability to detect the disease at the premotor and prodromal stages is so important.

A very urgent task is the identification of markers of the pathological process in PD, the nature of its course and prognosis, as well as the risk of developing the disease. Of all the neuroimaging methods, only ultrasound - transcranial sonography - is available and generally recognized in the diagnosis of parkinsonism [5,7]. Research in modern neurology is aimed at searching for potential markers of the premotor phase of the disease. Since olfactory dysfunction (hyposmia, anosmia) is one of the first clinical manifestations of PD, it can be used (in combination with other methods) as a biomarker of the premotor phase of PD [6,8]. For diagnostics, the olfactory threshold, the ability to distinguish and identify odors are assessed using 16 special pencils with different odors. In the studies carried out by J. Henderson et al. In studies, hyposmia was detected in 68% of patients with the initial stages of PD; in the control group, it was observed only in 3% of the subjects [8]. Olfactory dysfunction has been identified in 10-23% of healthy relatives of patients with PD [6]. The odor identification test is especially specific. At the same time, in other neurodegenerative diseases, vascular parkinsonism and "parkinsonism-plus" syndromes, the olfactory function is not disturbed. The phenomenon of substantia nigra hyperechogenicity detected in PD associated with excessive deposition of iron is of great practical importance and, according to some data, can serve as a marker of the disease even before the development of clinical symptoms [4,8]. At the same time, the dynamics of this indicator over the years, as the neurodegenerative process progresses, needs to be clarified. PD markers also include hyposmia, determined by special quantitative methods. In recent years, there has been renewed interest in the analysis of oculomotor disorders in PD, and various parameters are being studied. Reflex and voluntary saccades, smooth tracking eye movements. It is believed that in PD, the tonic inhibition of the superior colliculi of the quadrigemina by the reticular part of the substantia nigra is impaired, and the cortical influences on the oculomotor system of the trunk, mediated by the basal ganglia, also change [7]. Objective assessments of color perception, retinal thickness, and oculomotor parameters are also promising [5]. Almost all biomarkers of PD are considered for their use in the diagnosis of early and premotor stages of diseases. The risk of developing PD is considered to be increased within 4 years after the detection of hyposmia; with an increase in the period from 4 to 8 years, this factor loses its predictive value (037). There are studies that also prove the role of hyposmia as an important preclinical marker of dementia [3]. It is believed that the neurodegenerative process in PD begins several years and even decades before the onset of the motor manifestations underlying the diagnosis. Meanwhile, as the results of experimental studies show, any potential neuroprotective interventions for this disease are most effective at the earliest possible stage of the disease, ideally at its preclinical stage [1,2]. Early diagnosis of PD is difficult due to the similarity of clinical manifestations in the early stages with essential tremor, multisystem atrophy, progressive supranuclear palsy, etc. That is why the search for biomarkers of the neurodegenerative process in PD is currently recognized as extremely relevant - biochemical, neurophysiological, neuroimaging, etc. [3 ,eight]. In this regard, in recent years there has been considerable interest in the development of approaches to the early diagnosis of the “latent” (prodromal) phase of the disease, which is the most promising in terms of the possibilities of implementing neuroprotective strategies and preventive therapy in patients with PD. In 2015, the International Movement Disorders Society for the first time proposed criteria for diagnosing PD in the prodromal stage for their use for research purposes [2,4]. The diagnosis of the prodromal stage of PD is based on the presence/absence of risk factors and prodromal markers of the disease. Known risk factors include, for example, gender (the risk of PD is higher in men), smoking and coffee consumption (reduce the risk of the disease), the presence of a aggravated family disease, the carriage of mutations and hyperechogenicity of the substantia nigra, and prodromal markers - hyposmia, impaired behavior in the phase sleep with rapid eye movements, depression and a number of autonomic disorders [2,4]. Several studies have been initiated around the world to find the optimal combination of biomarkers of the prodromal stage, both on samples of the general population (they require a large number of subjects and a long observation period), and on “enriched” samples consisting of individuals with an already identified risk factor / prodromal marker of the disease [5].

Of the wide range of dissomnic disorders that occur in PD, behavioral disorders in the REM phase of sleep (from the English. Rapid eye movement, syn. - REM phase, sleep with rapid eye movements) have the greatest predictive value. They are characterized by the absence of normal muscle atony in the REM sleep phase with motor restlessness, sometimes significantly pronounced, falling, cries, according to the

content of the night dream. Polysomnographic studies reveal behavioral disturbances in REM sleep in 1/3 of patients with PD, another 1/3 have asymptomatic loss of muscle atony in this sleep phase. Behavioral disturbances in REM sleep are also very common in multiple system atrophy and dementia with Lewy bodies [4]. Several prospective studies have shown that the risk of developing a neurodegenerative disease in individuals with REM sleep behavior disorders ranges from 19 to 38% within 5 years of follow-up and from 40 to 65% after 10 years of follow-up. Almost half of them develop PD, 50-60% develop dementia (predominantly Lewy body dementia). Thus, the high risk of developing the disease and the long latency period make REM behavioral disturbances an ideal marker for predicting PD. The only limitation is that the diagnosis requires polysomnography, a time-consuming and expensive procedure. A questionnaire was developed to detect REM behavioral disorders with a sensitivity of 96% and a sensitivity of 92%. It should be noted that in patients with behavioral disorders in the REM phase of sleep, cognitive impairments of varying degrees are detected. Convincing markers of the risk of PD also include depressive disorders. Depression is detected in 27.6% of patients with early stages of PD (36). Depression precedes the manifestation of motor disorders in 20% of cases. Depressive disorders may be present for up to 20 years before the development of movement disorders in PD, but their frequency increases significantly during 3-6 years before the diagnosis of PD is made. Patients with depression have a risk of developing PD 2.24-3.22 times higher than in the control group without depressive disorders. As additional markers for diagnosing early manifestations of PD, deterioration in color vision and impaired saccadic eye movements can be considered.

Fine motor disorders play a certain role, but the predictive value of this factor is low, since fine motor disorders are found in 40% of the elderly. In addition, these disorders are a marker of stage 4 according to Balai, so the period for neuroprotective measures is limited.

Thus, a review of methods for preclinical and early clinical diagnosis of PD shows that the study of prodromal markers and criteria for the premotor phase of PD will allow in the future to significantly change the course of the disease using neuroprotective therapy at the stage preceding the death of a significant number of dopaminergic neurons in the substantia nigra. Early diagnosis of PD is difficult due to the similarity of clinical manifestations in the early stages with essential tremor, multisystem atrophy, progressive supranuclear palsy, etc.

Conclusions

That is why the creation and improvement of algorithms for diagnosing PD (as well as other neurodegenerative diseases) at the prodromal stage is currently recognized as one of the most urgent challenges facing neurology. For practicing physicians, it is important, from our point of view, to understand that PD does not begin with known clinical symptoms of substantia nigra, but with non-motor manifestations of the disease. Their detection will make it possible to correctly determine the treatment strategy and thereby improve the quality of life of patients with PD.

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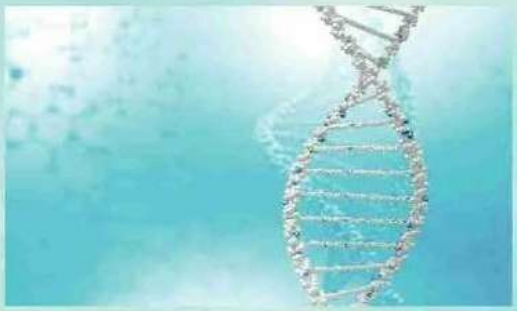

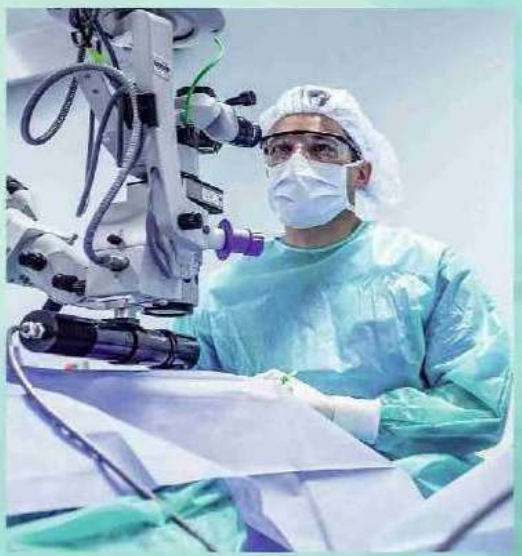

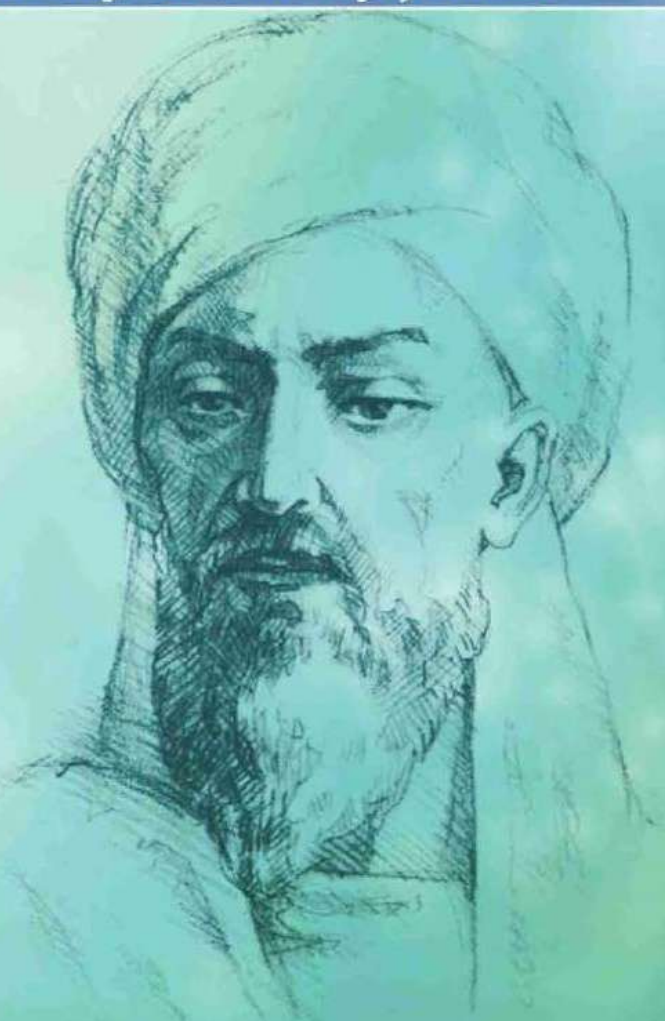

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