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A Modern View to Optimize the Diagnosis of the Course of Parkinson's Disease

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ABSTRACT

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 PD shows that the study of the prodromic markers and the criteria of 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 of the Black Substance.

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

INTRODUCTION

Currently, due to an increase in life expectancy in developed countries and an 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 predominant damage 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 people over 65 years of age [2].

The incidence is 100–250 cases per 100,000 population [3]; in European countries, the number of patients with PD 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 of 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, in the structure of parkinsonian syndromes, it is customary to distinguish:

- 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 find themselves bedridden or wheelchair-bound. PD occurs almost everywhere; about 5 million people worldwide suffer from PD [4].

In addition to motor symptoms, patients with PD have a number of non-motor manifestations (impaired sense of smell, changes in visuospatial coordination, mo-

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tor disorders in the rapid eye movement sleep phase, gastrointestinal motility disorders, mild and 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, the 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 level of dopamine 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 stage of the disease, ideally at its preclinical stage [5].

Primary parkinsonism includes Parkinson's disease (PD), the second most common neurodegenerative disease and a significant medical and socioeconomic problem, as well as juvenile parkinsonism.

RESULTS & DISCUSSIONS

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 pronounced variability in the phenotypic manifestations of the disease with the same genotype has been shown, even among relatives in the same family [4].

Studies of the last decade have proven that some of the non-motor symptoms (hyposmia, orthostatic hypotension, constipation, behaviour disorder in the REM phase of sleep, depression, etc.) precede the manifestation of motor manifestations of the disease by 5-20 years [3].

Some early symptoms of PD also include mild cognitive impairment, which, according to our data, is observed in 30% of patients with newly diagnosed PD. The presence of premotor and prodromal phases of the disease is confirmed by pathomorphological and neuroimaging data. researchers [6].

The morphological basis of non-motor disorders of PD in the premotor phase of the disease is explained by the modern concept H. Braak et al [4].

The pathobiochemical cascade of PD is based on a violation of the conformation of the protein alpha-synuclein, which is normally present only in presynaptic cells. terminals of the brain. In PD, this protein accumu-

lates and forms thread-like structures with a diameter of 20-40 nm inside neurons, which represents the first stage of the formation of specific intracellular inclusions - Lewy bodies [4].

Based on the immunohistochemical detection of alpha-synuclein and Lewy bodies in autopsy samples from an extensive brain bank. Braak put forward a 6-stage theory of the development of the pathological neurodegenerative process in PD [4].

According to the author, at stage 1, damage occurs to 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 [4].

According to the currently developed H. Braak's double-whammy hypothesis suggests that the trigger that triggers a cascade of neurodegenerative changes in the brain is a slow virus that enters the nervous system through the nasal and intestinal mucosa. At stage II, the process spreads to the nuclei of the medulla oblongata and the pons, including the raphe nucleus, the locus coeruleus, and the reticular formation. Stage III is characterized by damage to the midbrain, including the substantia nigra, amygdala, and basal forebrain. Stage IV involves the temporal mesocortex and hippocampus. In the final (V and VI) stages, Lewy bodies appear in the cerebral cortex, first in the associative zones of the prefrontal, temporal and parietal cortices, 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 dysfunction of mainly non-dopaminergic systems: noradrenergic, serotonergic, cholinergic, etc. [4,8].

The rate of neurodegeneration in the early stages is not known, but by the time motor symptoms manifest (stage II-IV according to H. Braak), the number of dead nigrostriatal neurons decreases dramatically and reaches 60 % of the initial level, while the number of striatal dopamine is reduced by 80% [4]. Attempts at neuroprotection in the later stages of PD may not be successful, which is why the ability to detect the disease at 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 neuroimaging methods, only ultrasound examination is transcranial sonography accessible and generally accepted in the diagnosis of parkinsonism [5,7].

Modern neuroscience research 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 premotor phase of PD [6, 8].

For diagnosis, the olfactory threshold, and the ability to distinguish and identify odours are assessed using 16 special pencils with different odours. In 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 in only 3% of subjects [8].

Olfactory dysfunction was detected in 10-23% of healthy relatives of patients with PD [6].

The odour identification test is especially specific. At the same time, in other neurodegenerative diseases, vascular parkinsonism and «parkinsonism-plus» syndromes, the olfactory function is not impaired. The phenomenon of hyperechogenicity of the substantia nigra detected in PD, associated with excessive iron deposition, 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, need to be clarified. Markers of PD 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 colliculus by the reticular part of the substantia nigra is disrupted, and the cortical influences on the oculomotor system of the brainstem, mediated by the basal ganglia, also change [7].

Objective assessments of colour perception, retinal thickness, and oculomotor parameters are also promising [5].

Almost all PD biomarkers are being considered for their use in diagnosing the early and premotor stages of the disease. The risk of developing PD is considered to increase within 4 years after the diagnosis of hyposmia; as the period increases 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 motor manifestations that underlie the diagnosis.

Meanwhile, as the results of experimental studies show, any potential neuroprotective interventions for this disease are most effective at the earliest 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, multiple system atrophy, progressive supranuclear palsy, etc. That is why the search for biomarkers is currently considered extremely relevant to neurodegenerative process in PD - biochemical, neurophysiological, neuroimaging, etc. [3, 8].

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 possibility of implementing neuroprotective strategies and preventive therapy in patients with PD. In 2015, the International Movement Disorder Society first proposed criteria for diagnosing prodromal PD for use in 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 drinking coffee (reduces the risk of the disease), the presence of a family history of the disease, carriage of mutations and hyperechogenicity of the substantia nigra, and prodromal markers include hyposmia, behavioural disturbances in the phase rapid eye movement sleep, 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 in samples of the general population (they require a large number of subjects and a long observation period), and in «enriched» samples consisting of individuals with an already identified risk factor/prodromal marker of the disease [5].

Of dissomnia disorders found in PD, behavioural disorders in the REM phase of sleep (Rapid eye movement, syn. - REM sleep phase, REM phase - rapid eye movement sleep). They are characterized by the absence of normal muscle atonia in the REM phase of sleep with motor restlessness, sometimes significantly pronounced, falling, and screaming, in accordance with the content of the night dream. Polysomnographic studies reveal behavioural disturbances in the REM sleep phase in 1/3 of patients with PD, another 1/3 have an asymptomatic loss of muscle atonia in this sleep phase. Behavioural disturbances in

the REM sleep phase are also very common in multiple system atrophy and dementia with Lewy bodies [4].

Several prospective studies have shown that the risk of developing the neurodegenerative disease in individuals with REM sleep behaviour disorder ranges from 19 to 38% at 5 years of follow-up and from 40 to 65% after 10 years. Almost half of them develop PD, 50-60% develop dementia (mainly dementia with Lewy bodies). Thus, the high risk of developing the disease and the long latency period make behavioural disturbances in the REM sleep phase an ideal marker for predicting PD. The only limitation is that diagnosis requires polysomnography, a time-consuming and expensive procedure. A questionnaire has been developed to detect behavioural disorders in the REM phase of sleep with a sensitivity of 96% and a sensitivity of 92%. It should be noted that patients with behavioural disorders in the REM phase of sleep exhibit varying degrees of cognitive impairment. Convincing markers of PD risk 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 can be present up to 20 years before the development of motor disorders in PD, but their frequency increases significantly during the 3-6 years before the diagnosis of PD. Patients with depression have a risk of developing PD 2.24-3.22 times higher than in the control group without depressive disorders. Deterioration of colour vision and impairment of saccadic eye movements can be considered as additional markers for diagnosing early manifestations of PD.

Subtle motor disorders play a certain role, but the predictive value of this factor is low since subtle motor disorders are found in 40% of older people. In addition, these disorders are a marker of stage 4 according to Beilai, and accordingly, 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 make it possible 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 substantia nigra. Early diagnosis of PD is difficult due to the similarity of clinical manifestations in the early stages with essential tremor, multiple system atrophy, progressive supranuclear palsy, etc.

CONCLUSIONS

That is why, at present, the creation and improvement of diagnostic algorithms for PD (as well as other neurodegenerative diseases) at the prodromal stage is considered extremely relevant; today it is recognized as one of the most pressing challenges facing neurology. From our point of view, it is important for practising physicians to understand that PD begins not with the known clinical symptoms of damage to the substantia nigra, but with non-motor manifestations of the disease. Their detection will allow us to correctly determine the treatment strategy and thereby improve the quality of life of patients with PD.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open the publication.

Availability of data and material – Available.

Competing interests – No.

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PARKINSON KASALLIGI TASHXISINI OPTIMAL QARASHLAR

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Toshkent tibbiyot akademiyasi

ABSTRAKT

Parkinsonizm 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, nevrodegenerativ 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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АБСТРАКТ

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.