SCIENTIFIC REVIEWS AND LECTURES

S.E. Avetisov, S.N. Illarioshkyn, Z.V. Surnina, A.N. Moskalenko, S. Georgiev

POSSIBILITIES OF NEUROIMAGING MARKERS IN THE DIAGNOSIS OF PARKINSON'S DISEASE

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The review summarizes the results of studies on the application of the principle of neuroimaging for the early diagnosis of Parkinson's disease (PD). The term "neuroimaging" combines various methods of directly or indirectly displaying the structure, functions and biochemical characteristics of the components of the nervous system. Indication of specific defects in brain structures has become possible thanks to such methods as positron emission tomography, single photon emission computed tomography, transcranial sonography in B-mode, MRI of the brain in SWI mode, and neuromelanin-sensitive MRI (NM-MRI). The ocular component of neuroimaging in PD may be associated with the study of the structural and functional state of various neuroelements of the eye, in particular, with the assessment of the state of the corneal nerve fibers (CNF). The difficulties of conducting research in this area of neuroimaging may be associated not only with the reliable detection of CNF changes in PD, but also with the assessment of the specificity of these changes, taking into account their potential polyetiology.

Keywords: Parkinson's disease, neuroimaging, corneal nerve fibers.

Parkinson's disease (PD) is a chronic, steadily progressive neurodegenerative disease that occurs predominantly in older people. PD is the second most important and common neurodegenerative disease after Alzheimer's disease. The incidence among the population is on average 1 case per 1000 people, while there is a regular increase in PD cases with age. So, at the age of up to 65 years, the number of cases is 1-2%, while up to 80 years - already 4% of the population, while more than 300 thousand new cases of PD are registered annually [33].

The disease was originally described by James Parkinson in his 1817 Essay on Shaking Palsy, which outlined the main motor signs of the disease [27]. Currently, the diagnosis is based on clinical data, and there is no reliable method for the early detection of PD, except for genetic testing, which is limited to rare cases of monogenic forms of the disease. In the presence of severe clinical symptoms, the diagnosis of PD does not cause difficulties, however, it should be taken into account that a significant motor deficit appears only after the death of more than 50% of neurons in the substantia nigra of the brain [7,16]. In the early stages, the diagnosis causes certain difficulties, even with the correct application of the updated diagnostic criteria .

The clinical picture of PD is represented by the syndrome of parkinsonism, which includes hypokinesia, muscle rigidity, rest tremor, and postural disturbances [29]. Among the various diseases, the clinical picture of which is represented by the syndrome of parkinsonism, the most common, according to the data of pathomorphological and epidemiological studies, is PD [17]. Other diseases with a leading syndrome of parkinsonism include the so-called parkinsonism-plus diseases or atypical parkinsonism: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal degeneration, etc. All of the above diseases are the result of impaired function of the nigrostriatal system and belong to the group of diseases with degenerative forms of parkinsonism. In addition, non-degenerative forms are distinguished, for example, vascular, drug-induced, toxic, psychogenic parkinsonism, etc. The main distinguishing feature of this group of diseases is the preservation of the presynaptic nigrostiatic pathway [31]. The need for a differential diagnosis between non- and degenerative parkinsonism is due to the different course and prognosis of diseases, as well as approaches to therapy.

The etiology and pathogenesis of PD are still poorly understood, and early diagnosis of the disease is very difficult. As a rule, the genesis of the disease is idiopathic, but familial cases are often found in practice. According to a number of studies, the main pathomorphological findings in PD are Lewy bodies containing phosphorylated alpha-synuclein (p-α-syn), as well as the loss of dopaminergic neurons in the substantia nigra (SN), leading to difficulty in voluntary movements [11]. In addition to the central structures, p-α-syn deposits were also found in the peripheral nervous system: skin nerve fibers, laryngeal nerves, submandibular nerves, as well as in the minor salivary glands and ganglia of the digestive system [2,30,13,28]. In the conducted retrospective studies on a sufficient sample of patients (1376 patients with PD), changes in thin non-myelinated peripheral nerve fibers (TnNF) were detected in 53.4% of cases, while in large peripheral nerve fibers (LPNF) - in 16.3% of cases [13] . In addition, in PD, a decrease in the density of small intraepidermal nerve fibers and a deterioration in the innervation of the sweat glands and m. erector pili (hair lifting muscle). Based on the above, it was suggested that there is a single mechanism of changes in the central and peripheral nervous systems in PD, which confirms the presence of p-α-syn in the SN and biopathies of damaged peripheral nerve fibers of the skin. Thus, PD is currently considered to be a multisystem disease of the nervous system [2].

It should be noted that changes in the peripheral nervous system in PD may be a consequence of not only the underlying disease, but also the result of a neurodegenerative process caused by long-term

AVETISOV Sergey Eduardovich – academician of the Russian Academy of Sciences, Professor, Ph.D., Sechenov 1st Moscow Medical University, Eye Diseases Research Institute; https:/orcid.org/0000-0001-7115-4275; **ILLARIOSHKIN Sergey Nikolayevich** – corresponding member, RAS, Ph.D.M., Prof, deputy director of science, chief coordinator of the 5th neurol. department, Federal State Budgetary Institution Neurology Scientific Center, the laboratory of neural cerebral structures; FBHNU NTN, https://orcid.org/0000-0002-2704-6282; **SURNINA Zoya Vasilyevna** – Candidate of Medical Sciences, senior researcher, Eye Diseases Research Institute, https:/orcid1800.00-015692, MEDZOE@yandex.ru; **MOSKALENKO Anna Nikolayevna** – neurologist, postgraduate student of the Eye Diseases Research Institute, https://orcid.org/00-0003-3843-6435; **GEORGIEV Stefan** – PhD student of the Eye Diseases Research Institute, ophthalmologist of the Yakut Republican Ophthalmologic Clinic, Yakutsk, https:/orcid.org/000000000201299X

therapy of the underlying disease with levodopa [20]. In one of the studies, to assess the degree of neurodegeneration of peripheral nerve fibers in PD without sensory impairment, confocal microscopy of material obtained by skin biopsy and stained with specific antibodies was used in 85 patients [21]. Patients were divided into the following groups: 1) receiving levodopa; 2) without levodopa therapy (37 and 48 cases, respectively). It was found that LPNF are damaged to a greater extent during levodopa therapy, and TnNV degeneration occurs to the same extent in both groups. It was also noted that pronounced changes in TnNV are already present in the early stages of the disease in most patients.

So far, reliable biomarkers have not yet been identified to reliably determine the presence of PD at the preclinical stage (i.e., before most of the dopaminergic neurons are lost). The study of the possibilities of early diagnosis and monitoring of the disease is carried out in several directions. One of the promising directions involves the use of the principle of neuroimaging. The term "neuroimaging" combines various methods of directly or indirectly displaying the structure, functions and biochemical characteristics of the components of the nervous system. Preliminary data indicate the promise of modern neuroimaging methods for the development of specific biomarkers for PD and other extrapyramidal diseases . Thus, the indication of specific defects in the brain structures became possible thanks to such methods as positron emission tomography (PET), single photon emission computed tomography (SPECT), transcranial sonography in B-mode (TCS), MR brain studies in SWI mode (magnetic susceptibility-weighted images), neuromelanin-sensitive MRI (NM-MRI), etc. [32].

Taking into account the fact that neurodegeneration of dopaminergic structures plays a key role in the pathogenesis of PD, leading to the development of neurotransmitter imbalance, PET and SPECT scanning, which allow assessing dopamine metabolism and the integrity of post- or presynaptic dopaminergic pathways, have firmly established themselves as effective methods for diagnosing degenerative parkinsonism. . These studies make it possible to visualize functional processes in the brain by detecting a radioactive ligand after it enters the systemic circulation and binds to a molecular target. It should be noted that in the updated criteria for diagnosing PD, among all the proposed neuroimaging markers, only the absence of a dopamine metabolism disorder according to SPECT data is an absolute exclusion criterion for the disease, and myocardial scintigraphy with metaiodobenzylguanidine is a confirming criterion [11,22]. However, despite the undoubted diagnostic advantages of PET and SPECT, these techniques have a number of limitations, in particular, the safety profile associated with contact with radioactive isotopes; high cost of research; the impossibility of unequivocal differentiation of PD from other forms of degenerative parkinsonism.

The TCS technique is based on obtaining a hyperechoic signal from the emergency in PD. The exact mechanism of hyperechoic SN is not entirely clear, it is believed that the hyperechoic signal occurs as a result of accumulation or increased iron content [4]. The results of TCS differ in PD and other forms of both degenerative and non-degenerative parkinsonism, which makes it possible to use the technique for differential diagnosis . TCS also has a number of disadvantages, such as the likelihood of various artifacts and the high dependence of the results obtained on the technical characteristics of the device and the qualifications of the doctor performing the scan. In addition, in some cases, hyperechogenicity of the CS can also occur in a healthy population [6].

MRI in standard modes does not allow to determine pathognomonic changes for PD and is applicable only to exclude other organic pathology that can cause secondary parkinsonism. With the widespread introduction of high-field tomographs into clinical practice, a detailed assessment of the structural characteristics of brain regions, primarily involved in the pathological process in PD, has become possible. Thus, the following potential biomarkers of PD have been proposed: the absence of visualization of nigrosomes and a decrease in the neuromelanin pigment in the SN. The term nigrosome refers to clusters of dopaminergic neurons in the compact part of the SN. When visualizing nigrosomes using a standard protocol that includes the SWI sequence (images weighted by magnetic susceptibility), in PD, a loss of dorsolateral nigral intensity is noted due to the pronounced involvement of nigrosomes in the neurodegenerative pathological process . NM-MRI (MRI with T1-weighted images) is used to visualize neuromelanin in the SN . In patients with PD, there is a decrease in the area and contrast ratio of T1-high-signal pigmentation of the NM in the SN [19].

The above methods have high sensitivity and specificity in the diagnosis of early stages of PD. However, it should be noted that when using MRI markers for the differential assessment of various variants of degenerative parkinsonism, conflicting results were obtained, and therefore the differential diagnostic value of structural MRI requires further study in prospective studies [18].

According to the literature, the ocular manifestations of PD include disturbances in color perception and pupillary reactions, an increase in the latent period during saccadic eye movements, a decrease in the thickness of the retinal nerve fiber layer, the presence of scotomas, as well as a decrease in tear film rupture time and corneal thickness [9,15,20]. Taking into account the fact that the neurodegenerative process in PD affects both the central and peripheral nervous systems, structural changes in the corneal nerve fibers are also considered as another promising biomarker [33]. Thus, the ocular component of neuroimaging in PD can be associated with the study of the structural and functional state of various eye neurons using visual evoked potentials (VEP), oculography to record saccadic eye movements, optical coherence tomography (OCT) of the retina and optic nerve, as well as confocal microscopy of corneal nerve fibers.

At the stage of hemiparkinsonism, an increase in the latency of a positive P100 response was noted, as well as a decrease in the maximum amplitude of late oscillations compared to the “uninvolved” hemisphere; as the disease progressed, the asymmetry of latencies and amplitudes practically disappeared [34]. The N75 and N145 components correlate with the severity of motor manifestations and duration of the disease [34]. Changes in VEP are explained by biochemical and electrophysiological changes in the retina, the neurons of which are rich in dopamine, which is confirmed by electroretinography data. At the same time, in another study of VEP on a reverse checkerboard pattern in patients with PD, no significant amplitude-temporal asymmetry of the components between the more and less affected sides was found during stimulation of the corresponding eye [35]. Also, no correlations were found between these indicators and the clinical manifestations of PD, with the exception of bradykinesia, and when analyzing the results of the study of VEP for a flash of light, there was no dependence of the indicators on the stage of the disease.

Saccadic eye movements are also considered as one of the potential markers reflecting age-related and pathological changes in the central nervous sys-

tem. Saccades are fast, jerky movements of the eyeballs, with the help of which the points of fixation of the gaze change. The presence of saccades is determined by the coordinated work of various parts of the brain, including stem structures, subcortical nuclei, and various parts of the cerebral cortex. In PD, there was an increase in the latent period, reaction time, and the proportion of multisaccades, which are mainly fixed when the gaze is directed towards the limbs with pronounced clinical signs of the disease [3].

Optical coherence tomography of the retina and optic nerve can be used as an additional diagnostic test in PD. Thus, one study revealed thinning of retinal ganglion cells, the inner plexiform and peripapillary layer of nerve fibers in this disease [10]. Another study reported a significant correlation between the presence of progressive supranuclear palsy and the thickness of the retinal nerve fiber layer, but no such changes were found in the control group and the group of patients with PD. The authors suggest using the technique as an additional study for the differential diagnosis of PD and progressive supranuclear palsy, but there is a need for further researches due to the small cohort of patients [25].

Taking into account the above data on the predominant change in thin non-myelinated peripheral nerve fibers and a decrease in the density of small intraepidermal nerve fibers in PD [31,13], it is promising to analyze potential changes in corneal nerve fibers (CNFs). The possibility of intravital visualization of CNF is due to the transparency of the cornea and the parallel location of the nerve plexus in relation to the surface of the cornea. It was noted that the highest concentration of peripheral unmyelinated thin nerve fibers is located in the subbasal corneal nerve plexus. At the same time, the cornea is the most innervated structure of the human body – the density of nociceptors reaches 7000 per square millimeter [12,26].

In a series of previous studies using confocal microscopy of the cornea, age-related features, as well as changes in CNF, were studied both in ocular and systemic diseases [3,5,8,14,23,24,30]. Age-related changes are manifested in a significant decrease in the density of CNF, while there is a sharp decrease in the number of central epithelial nerve terminals, as well as a significant increase in irregularly shaped nerve fibrils located under the basal layer of the cornea.These observations indicate the need for a clear standardization of comparison groups when conducting scientific research on induced by any reason changes in CNF. In the absence of such reasons, the structure of the corneal plexus remains unchanged for at least three years, while the specified time interval is limited to the intervalongoing research [23]. Changes in CNF can occur with ophthalmohypertension, wearing contact lenses, as a result of keratoectatic diseases, after keratorefractive interventions, phaco- and antiglaucoma surgery, and even panretinal laser photocoagulation of the retina [8,14,1]. A number of studies have shown the possibility of using the CNF state as a biomarker of pathological changes in the peripheral nervous system in systemic diseases (diabetes mellitus, Graves' disease) [1,5,24].

In a few studies, the results of which can be regarded as preliminary, the state of thin unmyelinated CNF in PD has been studied. In one of them, based on confocal microscopy using proprietary software, CNF changes were analyzed in 24 patients (48 eyes) with PD (the control group included 26 healthy volunteers) [30]. Simultaneously, a skin biopsy of the dorsal surface of both feet was performed, followed by a histological analysis of the state of the intraepidermal nerve fibers. In PD, there was a simultaneous decrease and increase in the density of CNF in different parts of the cornea, as well as heterogeneous CNF branching in severity, which, according to the authors, reflects the variable ability of CNF to regenerate at different stages of the disease. The degree of degenerative changes in CNF coincided with the data of the functional assessment of the parasympathetic nervous system, however, there was no correlation between the duration of levodopa therapy, the severity of the disease, and changes in the structure of CNF. At the same time, changes in intraepidermal nerve fibers, correlated with both the severity of the disease and the duration of levodopa therapy.

In another preliminary study on a small sample of observations, the state of CNF in PD was assessed using the author's quantitative indicators [3]. A significant decrease in the directivity anisotropy coefficient and an increase in the CNF directivity symmetry coefficient were established. Along with this, CNFs were pronouncedly tortuous, multidirectional, "clearly shaped", and an increased number of branches from the main nerve trunks was observed.

The results of the studies presented in this review indicate the prospects for further study of various methods for the early diagnosis of PD, which are based on the principle of neuroimaging. From the point of view of the supposed simplicity and accessibility, the direction associated with assessing the state of CNF in PD is of particular interest. The difficulties of conducting research in this area of neuroimaging may be associated not only with the reliable detection of CNF changes in PD, but also with the assessment of the specificity of these changes, taking into account their potential polyetiology.

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