Current Understanding of Parkinson's Disease

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ABSTRACT

Patients with Parkinson's disease (PD) usually suffer from a wide range of non-motor manifestations of the disease, such as cognitive and affective disorders, fatigue, pain and various autonomic disorders, among which upper and lower gastrointestinal (GI) dysfunction plays a major role. These symptoms impair patients' ability to carry out daily activities and independence from others, and certainly have a negative impact on their quality of life.

Keywords: Parkinson's disease, sleep disorders, neurology

Introduction. Parkinson's disease is a brain disorder that impairs motor activity and causes mental impairment, sleep disorders, pain and other health problems. Symptoms of the disease tend to worsen over time.

Refers to degenerative diseases of the extrapyramidal motor system. It is caused by progressive destruction and death of neurons that produce the neurotransmitter dopamine[4] - primarily in the substantia nigra, but also in other parts of the central nervous system. Insufficient dopamine production leads to an inhibitory[5] influence of the basal ganglia on the cerebral cortex. The leading (core, or cardinal) symptoms are:

Muscle rigidity;
hypokinesia;
tremor;
postural instability.

Modern medicine cannot yet cure this disease, but the existing methods of conservative and surgical treatment can significantly improve the quality of life of patients and slow the progression of the disease[6].

The term "parkinsonism" is a general term for a number of diseases and conditions with the above-mentioned leading symptoms. However,

the most significant of the forms of parkinsonism is Parkinson's disease, an idiopathic disease (meaning the disease is independent, not caused by genetic disorders or other diseases).

Parkinson's disease owes its name to the French neurologist Jean Charcot. He suggested that it be named in honour of James Parkinson, a British physician and author of "An Essay on Shaking Palsy", whose work was not properly appreciated during his lifetime.

In Parkinson's disease, the structures of the extrapyramidal system - basal nuclei and substantia nigra, locus coeruleus, and others[3,10] - are affected. The most pronounced changes are noted in the anterior parts of the substantia nigra. Symptoms characteristic of Parkinson's disease occur when 60-80% of neurons in this anatomical entity die. Macroscopic changes are characterised by depigmentation of melanin-containing areas of the substantia nigra and the locus coeruleus. Microscopic examination of the affected areas reveals a decrease in the number of nerve cells. The presence of Lewy bodies is detected in them. There is also death of astrocytes (a type of glial cells) and activation of microglia. Lewy bodies are formed due to the accumulation of α-synuclein protein in the cytoplasm [2]. The presence of Lewy bodies is one of the hallmarks of Parkinson's disease[12]. Lewy bodies are also found in other neurodegenerative diseases. Therefore, they are not considered a specific marker of Parkinson's disease. In addition, "pale corpuscles", intracellular granular inclusions that replace decaying melanin, have been found in the substantia nigra and locus coeruleus [9].

According to the classification proposed by Braak et al, in the asymptomatic stage of Parkinson's disease, Levi's corpuscles appear in nerve cells of the olfactory bulb, medulla oblongata, and varicella. As the disease progresses, the presence of these pathological cells is noted in neurons of the substantia nigra, midbrain, basal ganglia and, at the final stages, in cells of the cerebral cortex.

Pathological physiology.

The close relationship between the extrapyramidal system components, the pallidum and striatum, is provided by numerous bundles of nerve fibres. Thanks to the connections between the thalamus and the striopallidar system, reflex arcs are formed that ensure the performance of numerous stereotyped and automated movements (e.g. walking, running, swimming, cycling, etc.). The close connection of the striopallidar system with the hypothalamic nuclei determines its role in the mechanisms of emotional reactions[4].

In norm, the extrapyramidal system sends impulses to peripheral motor neurons. These signals play an important role in providing myostatics by making muscles ready for voluntary movements. From the activity of this department of the central nervous system depends on the ability of a person to take the optimal posture for the intended action, the necessary ratio of tone of agonist and antagonist muscles is achieved, as well as smoothness and proportionality of voluntary movements in time and space[14].

The character of clinical manifestations of the disease depends on which part of the striopallidar system is affected - striatum or pallidum. If the inhibitory influence of the striatum is excessive, hypokinesia - poverty of movements, amimia - occurs. Hypofunction of striatum leads to excessive involuntary movements - hyperkinesis[8]. Pallidum has an inhibitory effect on striatum structures. Parkinson's disease is characterised by a decrease in the inhibitory effect of the pallidum on the striatum. Damage to the pallidum results in "inhibition of inhibition of inhibition" of peripheral motor neurons[3, 5].

The discovery of the role of neurotransmitters has helped to explain the functions of the extrapyramidal system as well as the causes of the clinical manifestations of Parkinson's disease and parkinsonism. There are several dopaminergic systems in the brain. One of them starts in the neurons of the substantia nigra, the axons of which reach the corpus striatum through the cerebral peduncle, internal capsule, and pale globe. The terminal parts of these axons contain large amounts of dopamine and its derivatives. Degeneration of this nigrostriatal dopaminergic pathway is a major

causative factor in the development of Parkinson's disease. The second ascending dopaminergic system is the mesolimbic pathway. It starts from cells in the interpeduncular nucleus of the midbrain and ends in the hypothalamus and frontal lobes of the brain. This pathway is involved in the control of mood, behaviour and controls the initiation of motor act and affective response movements (movements that accompany emotions)[7].

The basis of all forms of parkinsonism is a dramatic decrease in the amount of dopamine in the substantia nigra and corpus striatum[4] and a corresponding impairment in the functioning of the dopaminergic conductive pathways of the brain.

Characteristic symptoms of GI dysfunction in parkinson's disease include salivary and swallowing disorders, gastroparesis resulting in dyspeptic phenomena such as appetite disturbances, nausea and bacterial overgrowth syndrome in the small intestine (signs of upper GI dysfunction), and constipation and defecatory dysfunction (signs of lower GI dysfunction) [1]. Weight change is another characteristic of parkinson's disease: as the disease progresses, some patients gain weight, but most patients lose weight [2]. The role of GI dysfunction in this process needs to be clarified [3-5]. Most gastrointestinal dysfunctions are most pronounced in the advanced stages of parkinson's disease, but they may occur in the initial stages and even precede the appearance of motor disorders, so they require attention from the very beginning of the disease. Dysphagia is the most significant symptom of upper GI dysfunction in Parkinson's disease. All phases of swallowing are impaired: oral, pharyngeal, oesophageal, and swallowing efficiency gradually decreases. Oropharyngeal dysfunction includes inadequate chewing, poor bolus formation, difficulty in initiating swallowing and gagging as a sign of aspiration, it is considered as a motor symptom and often improves at the beginning of treatment [6]. In advanced stages of parkinson's disease, dysphagia leads to malnutrition and weight loss, dehydration, difficulty taking medications, aspiration and increases the risk of pneumonia [7]. Swallowing disorders in these patients significantly reduce the quality of life according to the QoL questionnaire [8], cause fear of aspiration and choking, the need to change eating habits and dependence on other compensatory techniques for eating, and affect social and psychological well-being [9]. In clinical practice, dysphagia in parkinson's disease is underestimated [10], and aspiration pneumonia is one of the leading causes of death in these patients [11, 12]. Oropharyngeal and oesophageal motility disorders are thought to be present in 60-80% of patients with parkinson's disease, but are often asymptomatic and difficult to diagnose. In a significant proportion of patients, objective dysphagia is not subjectively perceived. According to a recently published meta-analysis, the prevalence of oropharyngeal dysphagia in parkinson's disease is as high as 82% , but only 20-40% of patients are aware of swallowing impairment, and less than 10% report their complaints without prompting (barium swallowing studies and video fluoroscopy) [14, 15]. This is presumably due to early hypersensitivity of the pharynx A number of studies have shown that dysphagia is not only a symptom of the late stage of parkinson's disease, but can occur at any time, including the preclinical stage [13]. In a study by C. Pflug et al. [1, 9] aspiration was found in 20% of patients with disease duration of less than 2 years, 12% of patients with stage II parkinson's disease according to Hen and Yahr suffered from severe aspiration. Therefore, swallowing function should be investigated early in the disease when its clinical predictors can be identified. Risk factors for dysphagia in parkinson's disease in several studies have been found to include a Hoehn and Yahr stage above III, weight loss, a body mass index (BMI) below 20 kg/m2 , sialorrhoea and dementia as well as male gender, age and duration of disease [2, 3]. Therefore, current recommendations are to screen for dysphagia during the onset phase for all patients with parkinson's disease from Hen and Yahr stage III, as well as for signs of dementia, dysphagia (coughing while eating or drinking, difficulty swallowing), sialorrhoea, weight loss and low BMI, even if the disease

stage is less than Hen and Yahr stage III [2,10]. Dysphagia may also occur in patients with earlier stages of parkinson's disease, but it is not clear whether it is clinically relevant in terms of risk of aspiration and malnutrition, and to what extent it affects quality of life in this cohort of patients.

Salivation (sialorrhoea) is an often underestimated but important symptom of parkinson's disease, with a prevalence ranging from 10 to 84% [2, 4]. The wide range is likely due to the lack of a standard definition, diagnostic criteria and differences in the parkinson's disease populations studied. Salivation in parkinson's disease is not due to hypersecretion of saliva; on the contrary, secretion is often even reduced - patients with parkinson's disease secrete less saliva per day than healthy individuals (approximately 750 ml/day, with a normal range of 1000- 1500 ml). It is believed that the cause of saliva accumulation in the mouth and its leakage is primarily swallowing disorders, hypomimia, sensory and postural disorders, cognitive decline , and the side effects of some medications, especially neuroleptics, are also possible. Traditionally, salivation has been associated with age, duration and severity of parkinson's disease, as well as with reduced quality of life [2, 8], which, however, is disputed in a number of studies and needs to be clarified. Patients with Parkinson's disease and daily salivation are characterised by asymptomatic aspiration and penetration of saliva into the larynx, presumably caused by laryngeal hypoesthesia and lack of protective reflexes [3,10]. B. Rodrigues et al. examined 28 patients with parkinson's disease and 18 controls using fibre-optic swallowing assessment: asymptomatic aspiration of saliva was found in 10.7% of patients and asymptomatic penetration of saliva into the larynx near the vocal folds in 28.6% of patients with parkinson's disease and none of the controls. Thus, sialorrhoea is not a benign symptom and requires attention and therapy. The pathogenesis of swallowing and salivation disorders in parkinson's disease is complex and incompletely understood, and is based on impairment of both dopaminergic and underdopaminergic pathways (which reduces the potential for dopaminergic therapy). In addition, aging is also associated with multifactorial changes in swallowing physiology (presbyphagia). Further research is needed to better understand the mechanisms of upper GI dysfunction in parkinson's disease, to establish markers for its early detection and progression, and to develop treatment options. Correction of salivary and swallowing disorders in parkinson's disease, as a rule, causes difficulties for medical practitioners, since no generally accepted standards have been developed yet, and the pathogenesis of these phenomena is not fully understood. The effects of dopaminergic drugs and levodopa on swallowing function and their role in the treatment of dysphagia are controversial. No randomised controlled trials have been conducted to investigate this issue, and there is only one meta-analysis that found that levodopa administration is not associated with significant improvement in swallowing function in Parkinson's disease. Some papers suggest positive effects of dopaminergic agonists (ADRs), apomorphine and transdermal rotigotine which may be more effective than levodopa [3,5]. Further studies are needed to determine the efficacy of different treatments for dysphagia in Parkinson's disease.

Symptoms of upper GI dysfunction in the form of salivation and/or swallowing disorders of mild to moderate severity were observed in 51.2% of patients, which indicates a fairly early involvement of these parts in the pathological process, since the patients were at stages I-III of the disease. Swallowing disorders in the form of choking were found in 26.7% of patients, which generally corresponds to the results of earlier studies indicating that 20-40% of patients are aware of swallowing disorders [13]. The obtained results support the opinion about early involvement of swallowing function in the pathological process [19] - we found swallowing impairment in 22.2% of patients in stage I of parkinson's disease and in 24.3% in stage II. The severity of dysphagia in the observed cohort of patients depended on the duration of parkinson's disease, which is consistent with the data of E. Cereda et al. [3], and on the daily doses of levodopa preparations. The latter,

apparently, reflects the relationship with the severity of the neurodegenerative process even more accurately than the stage of the disease, since the Hen and Yahr scale takes into account only motor manifestations of the disease, assessed against the background of dopaminergic therapy. Disease stage ≥III on the Hen and Yahr scale is considered a predictor of dysphagia [10], but we did not find a direct correlation between swallowing disorders and the stage of parkinson's disease on this scale. This is partly due to the specificity of the sample - the study included patients up to and including stage III, all of whom reported mild to moderate impairment without severe dysphagia. Another predictor or consequence of dysphagia is considered to be decreased body weight (BMI≤20 kg/m2) [42]. In the patients observed, there was an association between BMI and dysphagia, BMI ≤20 was found in 9.6% of patients. In contrast, overweight or grade I-II obesity was noted in 62.5% of patients. In the advanced stages of parkinson's disease, it has been suggested that malnutrition and dysphagia, as well as increased energy expenditure due to the occurrence and/or worsening of dyskinesia and rigidity, contribute to weight loss [4,13]. In the initial stages (as in the cohort we observed), body weight may increase, probably due to dopaminergic treatment, which eliminates motor symptoms and may modulate eating behaviour [15]. Based on these findings, in patients with parkinson's disease in stages i-iii, dysphagia appeared to be associated with a long history of parkinson's disease, low BMI, high doses of levodopa, and low scores on the Schwab and Inghland Daily Activity Scale. Severe salivation in parkinson's disease is also associated with dysphagia, as it is not considered to be the result of increased salivation, but primarily an impairment of saliva swallowing [4]. At the same time, it has been reported that salivation is present in 86% of patients with parkinson's disease with dysphagia and 44% without dysphagia [2, 9], thus swallowing disorders appear to contribute to salivation but are not the sole cause. In the study, mild to moderate sialorrhoea was detected in 44.5% of patients from the total group, and no severe salivation was observed. It is noteworthy that impaired salivation was present in 38.9% of patients with stage I parkinson's disease and in 42.9% with stage II, indicating the possibility of an early debut of this symptom, as in the case of dysphagia. We found no correlation between salivation and the severity of dysphagia; on the other hand, we found an inverse relationship with lower BMI, which is considered an indirect sign of dysphagia. BMI was found to be associated with both indicators studied, dysphagia and sialorrhoea. The amount of saliva secreted was positively correlated with the severity of salivation and anorexia according to the UPDRS scale. Several authors have found a correlation between the severity of salivation and age, duration and severity of parkinson's disease [2]. In our cohort of patients, an association was found only with older patient age and low BMI. Swallowing disorders and hypersalivation are thought to reduce the quality of life of patients in the advanced stages of the disease [8], but their impact in the early stages of parkinson's disease is not so obvious. Thus, G. Arboleda-Montealegre et al. [9] examined 62 patients at stages I-IV of parkinson's disease and found salivation in 32 of them; when comparing them with patients without salivation, no difference was found in PDQ-39 scores both in total score and in individual items, and no differences were found depending on the stage, duration of the disease, sex and age of patients. On the other hand, J. Leibner et al. [5] showed that only 18.8% of patients with parkinson's DISEASE with salivation in socially significant situations were not bothered by saliva accumulation, 18.8% stated that they coped with the situation although they knew that strangers could notice the saliva, and 3.1% stopped visiting public places altogether, whereas patients without salivation had none of the above problems.

Patients with salivation showed worse results on the PDQ-39 item "Activities of daily living", in addition, they found it more difficult to talk, eat and interact socially. In our cohort of patients with stages I-III, no association of dysphagia and sialorrhoea with the overall PDQ-39 quality of life score was found. There was a correlation between the severity of dysphagia and the activities section of the PDQ-39

questionnaire and the Schwab and Ingland scales. Hypersalivation was also found to be correlated with the Communication item of the PDQ-39 questionnaire.

Conclusions: Thus, based on the data obtained, we can speak about a reduced quality of life in patients in the early stages of parkinson's disease associated with impaired salivation and swallowing, which manifests itself in difficulty in daily activities and difficulties in communication. Usually, patients in stages I-III of parkinson's disease have compensated pathology, so salivary and swallowing problems are quite variable and clinical assessments are often normal. It is believed that dysphagia can be reduced when dopaminergic therapy is optimised by improving the motor component, especially in the early stages of the disease, saliva accumulation in the mouth and salivation associated with swallowing disorders should decrease accordingly. In a study of 53 patients with parkinson's disease, 53 patients were treated with ADR therapy with piribedil at a dose of 150-250 mg for 6 months. A significant reduction in salivation and dysphagia severity according to UPDRS after 1.5 and 6 months of therapy was shown, as well as an increase in daily activity of daily living according to the Schwab and England scale already after 1.5 months of therapy, which was maintained after 6 months. The severity of salivary and swallowing disorders after 6 months of therapy with piribedil in patients who received and did not receive basic levodopa therapy did not differ, and the difference in the change in scores was not significant, indicating the same positive effect of piribedil both in monotherapy and when added to levodopa. At the beginning of piribedil therapy, 37% of patients experienced mild to moderate GI side effects in the form of nausea or discomfort in the epigastrium, which were transient and did not interfere with patient compliance. In general, the obtained data indicate the possibility of ADRs, in particular piribedil, to significantly improve the state of salivation and swallowing in patients in stages I-III of parkinson's disease.

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