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ETIOLOGICAL AND PATHOGENETIC FACTORS IN THE DEVELOPMENT OF COGNITIVE DISORDERS IN PARKINSON'S DISEASE

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Abstract: Parkinson's disease (PD) is rightly recognized as one of the most common age-related diseases of the brain. Despite the well-known definition of PD as a movement disorder, a large amount of information has recently accumulated with the recognition of this disease as a heterogeneous multisystem disorder in which neurotransmitter systems (serotonergic, noradrenergic and cholinergic) play an important role. These neurotransmitters determine the severity of the non-motor signs of PD. The development of dementia in PD generates a heavy burden not only of an economic but also of a social nature. In this regard, over the past 30 years, scientists in this field of medicine have been conducting more and more research to identify the role and place of biomarkers in predicting the development of dementia in PD, which will also allow the development of preventive methods of correction at the early stages of cognitive impairment. This review article summarised the primary modern information regarding the aetiology and pathogenesis of cognitive disorders in PD.

Key words: Parkinson's disease, cognitive disorders, dementia.

INTRODUCTION

The modern understanding of the pathogenesis of the development of Parkinson's disease (PD) is based on the study of multisystem disorders, which include a wide range of both motor and non-motor manifestations of the symptoms of the disease. At the same time, among the non-motor manifestations of the disease, it is necessary to consider a decrease in cognitive abilities, which, along with dementia, should be considered the leading cause of the growth of disability, and according to the statistics of G. Levy et al. [1] also mortality among patients with PD. In addition to the above, Y. Winter et al. [2] proved that patients with cognitive impairments increase the financial and economic burden on the medical and social spheres.

Back in 2004, based on the results of their research, A.E. Lang and J.A. Obeso [3] concluded that there is a direct relationship between the chronology of the development of PD and the damage to various neural networks in the pathogenesis of cognitive impairment, which indicates the presence of a complex nature of the mechanisms of the formation of this complication of the disease. It has been proven that the temporal variation in cognitive decline in people with Parkinson's disease is extensive, which creates significant difficulties in understanding its entire pathogenesis. Therefore, the study of pathogenetic factors in developing cognitive disorders in PD is of the most significant importance.

METHODS

In order to solve the problem of identifying the features of etiological and pathogenetic factors in the development of cognitive disorders in PD, we analyzed the literature

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sources from the PubMed and CrossRef catalogues. The keywords "Parkinson's disease", "cognitive disorders", "aetiology of cognitive disorders", and "pathogenetic factors of cognitive disorders" were included. In total, information was obtained from 1458 scientific sources, of which 144 were of a review nature. Clinical examples were not considered.

RESULTS AND DISCUSSION

Among the currently known factors for the development of cognitive disorders, clinicians distinguish the sex of the patient; the presence of comorbidities, in particular, Alzheimer's disease (AD); sleep disorders, frequent mood swings; and the presence of chronic stress; chronic diseases of the cardiovascular system; diabetes mellitus.

The first assumption about the importance of gender in the development of cognitive disorders in PD was made by a group of scientists from the Oxford Parkinson's Center based on the results of studies conducted by K. Szewczyk-Krolikowski et al. [4]. It has been proven that the male sex is more susceptible to the development of cognitive impairment in PD. The selected separate mono-gender cohorts of patients had a history of at least 3 years after diagnosis of PD. Montreal Cognitive Scale (MoCA) studies and other verbal fluency tests (both semantic and phonemic) were conducted, the results showed that male patients had significantly worse verbal fluency than female patients. At the same time, the clinicians did not find much difference in the assessment of mini-mental examination (MMSE) scores in gender cohorts. Similarly, behavioural disorders in the REM sleep phase and hypotension of an orthostatic nature were also identified in male patients.

A group of scientists from the National Parkinson's Institute (USA) led by E.F. Augustine [5] conducted a large-scale, randomized, multicenter, double-masked, placebo-controlled study to study differences in the clinical manifestations of PD separately in men and women. Based on the study results, scientists concluded that, in general, both in men and women, there are no significant differences in clinical and motor signs in the early stages of PD. However, there was a precise gender gradation for non-motor cognitive symptoms. In women, the results of the SCOPA-COG and Symbol Digit Modality measurements were significantly better than in male patients.

At the same time, scientists from the Southern Medical University of Guangzhou (China) believe that cognitive impairment is more common and severe in women with PD—a group of Chinese scientists led by L. Gao et al. [6] examined 311 patients with PD comprehensively. Of these, 172 were male patients, and 139 were female patients. The data obtained showed that the values of the MMSE of patients did not have a significant difference between gender cohorts. However, the MoCA scores were significantly higher in male and female patients. Overall, a cohort of male patients performed relatively better regarding visuospatial function, naming, and abstraction. Female patients had lower scores on information, vocabulary, picture completion, block design, and picture placement. However, as the authors point out, in contrast to the male cohort of patients, the level of education among the female cohort was much lower, which, can serve as an explanation for such results of the studies.

Divergent opinions regarding gender significance in the development of cognitive disorders indicate the need for more in-depth research in this direction. In any case, the findings showed that changes were seen among patients with early-stage PD. The

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question of preserving gender differences in the late stages of PD also remains unanswered.

Investigating the significance of assessing changes in the level of α-synuclein in the cerebrospinal fluid in predicting the course of motor and cognitive disorders in PD, T. Stewart et al. [7] concluded that α-synuclein studies may predict cognitive decline and future long-term studies should include this outcome for further validation. The studies' data indicated that limbic and cortical Lewy pathology correlated with dementia in PD.

The article by D.G. Coughlin et al. [8] provides information on the relationship between the results of a clinical study of biomarkers and autopsy of Lewy body disorders. The authors hypothesized that Alzheimer's disease pathology is one of several likely pathological factors influencing the clinical heterogeneity of Lewy body disorders.

Lewy bodies are commonly found in Alzheimer's disease, and at the same time, Alzheimer's disease is found in Lewy body disease. However, it is increasingly recognized that Lewy pathology is not the only factor that determines cortical dysfunction and cognitive decline in PD. The role and place of comorbidities in neurodegenerative diseases remains unknown. In order to find an answer to this problem, J.L. Robinson and colleagues [9] conducted a study to assess proteinopathy by the level of changes in tau-, amyloid-β, α-synuclein, and TDP-43 in 766 autopsy individuals representing a wide range of clinical neurodegenerative diseases. They found strong evidence that amyloid and tau protein abnormalities also contribute to cognitive changes.

High oligomeric values and low levels of total α-synuclein in cerebrospinal fluid have been identified in PD. However, the interpretation of these data is often contradictory. In order to find an answer to the level of significance of these proteins, Y. Compta et al. [10] studied the content of oligomeric and total α-synuclein in the cerebrospinal fluid in separate groups of patients with PD (depending on the presence or absence of cognitive impairment). As a control, the same data were examined in healthy people. Low levels of total α-synuclein in the cerebrospinal fluid are associated with phonetic fluency dysfunction in PD. At the same time, the associations of high total α-synuclein of the cerebrospinal fluid with neuropsychological deficit of the posterior cortex of the brain in Parkinson's disease and with thinning of the posterior cortex of the brain in PD in dementia were due to the high content of cerebrospinal fluid of oligomeric proteins. These data suggest that the oligomeric and total α-synuclein of the cerebrospinal fluid have different clinical and neuropsychological correlates in the proposed variant of the course of PD with premotor dementia. The revealed correlations of total α-synuclein in cerebrospinal fluid support the hypothesis of an interaction between these proteins in PD.

Along with Alzheimer's disease, the presence of cerebral amyloid angiopathy can also contribute to the development of cognitive disorders in PD. This assumption was made with a high incidence of this pathology in PD with dementia [11].

Lewy body dementia and Parkinson's dementia, known as Lewy body dementia, have overlapping clinical and neuropathological signs. In clinical practice, both cases include a combination of Lewy body pathology and AD. Cerebral amyloid angiopathy (cerebral amyloid angiopathy), often seen in AD, is increasingly recognized due to its association with dementia. Based on this theory, D. Hansen et al. [12] set out

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to study the clinical and neurological differences between Lewy body dementia and dementia in PD. The study included 52 cases of dementia in Parkinson's disease and 16 cases of dementia with Lewy bodies from the Queen Square Brain Bank (QSBB) for neurological disorders. Comprehensive clinical data on motor and cognitive traits were obtained from medical records. The neuropathological evaluation included examination of cerebral amyloid angiopathy, Lewy body pathology, and AD. The severity of cerebral amyloid angiopathy was shown to be greater in Lewy body dementia than in PD dementia, with significantly higher cerebral amyloid angiopathy scores in the parietal lobe and occipital lobe and Lewy body dementia than in PD dementia. Survival analysis showed a worse prognosis for Lewy body dementia, as Lewy body dementia reached each clinical stage earlier than Parkinson's dementia. The absence of dyskinesia in Lewy body dementia is associated with a significantly lower cumulative lifetime dose of levodopa compared to dementia in PD. All of this confirms that more severe cerebral amyloid angiopathy and rapid disease progression, as measured by clinical milestones, distinguish Lewy body dementia from PD dementia.

The development of cognitive changes in Parkinson's disease can also occur in chronic sleep disorders [13]. Cognitive decline is a common phenomenon in PD, and identifying patients at the highest risk of developing it is important not only clinically but also fundamentally [14]. A group of scientists from the University of Pennsylvania School of Medicine (USA), led by L.M. Chahine [15], studied the effect of a possible behaviour disorder during REM sleep on the rate of cognitive decline in the early stages of PD. The results confirmed the earlier assumption about the decline in cognitive functions in PD, particularly in the field of attention and memorization of information by patients.

A more extensive study on this problem was conducted in 2020 by scientists at the Philadelphia PD Research Center (USA) under the leadership of E. Forbes [16]. They proved that REM sleep disorders lead to a faster progression of cognitive impairment in Parkinson's disease. A more extended study period, which included more than 8 years of follow-up, found a significant link between cognitive decline and excessive daytime sleepiness.

In investigating rapid outward eye movement disorder to determine the risk of dementia in PD, some researchers conducted a prospective study. Studies have shown that sleep behaviour disorders lead to the development of hallucinations and cognitive fluctuations in PD, which may be a harbinger of the risk of dementia in this pathology. This indicates that sleep behaviour disorder may be a marker of a relatively diffuse, complex subtype of PD.

The rapid progression of cognitive impairment in the early stages of PD may also be associated with mood disorders. More illustrative results on this problem were obtained in the study of a cohort of PD patients who were followed for up to 8 years. Over time, in patients with depression and anxiety, clinicians noted a decrease in MoCA scores.

In 2019, Chinese scientists at Qingdao University (Qingdao, China) systematically analysed the scientific literature on the risk factors and pathogenesis of the development of cognitive disorders in Parkinson's disease [17]. They concluded that effective interventions in the treatment of PD symptoms, comorbidities, and lifestyle may be promising for reducing the risk of developing this disease with cognitive impairment, which further confirms the assumption about the

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important role of reducing the level of quality and lifestyle of patients.

Pathology of the cardiovascular system is also one of the leading factors in the development of cognitive disorders. M. Kivipelto et al. [18] conducted studies to develop affordable methods for predicting the risk of dementia in the elderly and senile age. For this purpose, studies were started in the middle age of patients and continued for the next 20 years. 1409 people took part in the study. The ultimate goal of the study was to identify the risk of dementia in the presence of pathologies of the cardiovascular system in middle age. It was concluded that metabolic syndrome with such pathological components as arterial hypertension, diabetes mellitus, obesity, and dyslipidemia are directly related to the development of cognitive impairment and dementia.

Along with this, other results were obtained in the studies of L.M. Chahine et al. [19], which proved that in PD, pathologies of the cardiovascular system (arterial hypertension, obesity, dyslipidemia, type 2 diabetes mellitus) accelerate the process of development of cognitive impairment. Also, among patients in the studied cohort, the risk of developing cognitive disorders in PD accelerates exponentially with the progression of cardiovascular pathology. Researchers attribute this phenomenon to white matter hyperintensity in the common frontal and temporal regions of the brain, which is known to reflect the ischemic process in the brain. From this, we can assume that radiological detection of hyperintensity of the white matter of the brain can directly serve as a prognostic criterion for impaired cognitive functions, including in PD.

A review of the literature showed that the same results of the relationship with the development of cognitive disorders in PD with pathologies of metabolic syndrome only confirm the above assumptions. These factors include an increase in fasting glucose levels (insulin resistance), high levels of glycated hemoglobin, elevated serum levels of C-reactive protein, and high body mass index.

Thus, recent studies have shown that in the presence of patients in the early stages of Parkinson's disease, an increase in body mass index revealed a direct relationship with the tendency to develop cognitive disorders. However, in the case of weight loss with a decrease in patients' body mass index, scientists have also identified regression in cognitive abilities during PD.

In general, the identified pattern between the intensity of weight gain or loss and the development of cognitive disorders in PD is obvious. However, the pathogenetic mechanisms of these transformations have yet to be explored in prospective studies.

Unstable blood pressure levels can also be a factor in the development of cognitive impairment. Thus, it was proved that the instability of diastolic blood pressure, the violation of which determines the development of orthostatic hypotension, was associated with the development of cognitive disorders up to dementia in PD. At the same time, the increase in the incidence (chronic) of a decrease in cerebral perfusion in a horizontal position of the patient on his back can be considered one of the leading pathogenetic mechanisms for developing cognitive disorders in PD.

It has also been suggested that orthoptic hypotension plays a role in the development of cognitive disorders in PD. Drug therapy aimed at treating arterial hypotension as a result of autonomic disorders with the progression of the underlying pathology also has the property of developing cognitive disorders. In general, the risk of developing ischemic brain injury may also

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be increased in the setting of chronic hypertension, and accordingly, cognitive abilities in PD may be reduced.

The pathogenetic mechanisms of the development of cognitive disorders in PD in the presence of metabolic syndrome are closely related to the primary disease - type 2 diabetes mellitus. In this regard, the literature provides various information regarding the intensity of the influence of type 2 diabetes mellitus on the degree of development of cognitive disorders in PD.

The studied data characterize the relationship between the pathogenesis of type 2 diabetes mellitus and cognitive disorders in PD as diseases with identical molecular pathways. Such conclusions were reached after painstaking genetic and epidemiological studies.

A close relationship has been proven between the incidence of dementia in PD and the intensity of insulin resistance compared to those of patients without cognitive impairment.

In the studies of G. Pagano et al. [20], it was proved that type 2 diabetes mellitus is highly likely to predict cognitive disorders in PD, having a close pathogenetic relationship with development. However, as the authors point out, this relationship's exact mechanisms are still unknown.

Excluding this theory, in studies conducted by a group of Korean scientists led by S.J. Chung [21] using the MMSE rating scale, it was proved that there is no relationship between cognitive disorders in PD and the history of various types of diabetes. Meanwhile, as the authors themselves point out, during a detailed neuropsychological study, patients with type 2 diabetes mellitus were found to have worse indicators of attention, working memory and the presence of frontal executive dysfunction.

CONCLUSION

The above information also confirms that until now, neurologists do not know the exact mechanisms of the development of cognitive disorders in PD in the presence of diabetes mellitus. The search for solutions to this problem has yet to be achieved.

The literature also traces the results of studies aimed at studying the mechanisms of pathogenetic pathways of the development of cognitive disorders in PD in the presence of hyperuricemia, inflammation and oxidative stress, the consequences of traumatic brain injury, environmental disorders and toxic effects on the body of various pesticides, tobacco abuse, genetic disorders, as well as several other factors. All this indicates the presence of a multifactorial etiological mechanism for the development of cognitive disorders in PD, on the one hand, and the lack of consensus on its pathogenesis at the present stage of the development of medical science, which determines the relevance of research in this direction.

Conflict of interest – none

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