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NEUROTROPHIC FACTORS: PATHOGENETIC ROLE AND DIAGNOSTIC VALUE IN THE DEVELOPMENT OF PARKINSON'S DISEASE

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Abstract: This review article presents the results of recent studies on the characterization of neurotrophic factors and their involvement in brain neurodegeneration, as well as the processes of differentiation and growth of nerve tissues. Data on pathogenesis and diagnostic markers of cognitive impairments in patients with Parkinson's disease are presented.
Keywords : Parkinson's disease, dementia, neurotrophic factors.

Parkinson's disease is one of the most common neurodegenerative diseases of the nervous system, and this disease is one of the urgent problems not only in Uzbekistan but also in all countries of the world. The frequency of this pathological condition varies from 100 to 250 cases per 100,000 population.

One of the issues of society in the health care system remains diseases that affect the quality of life of patients. Diseases such as Parkinsonism, Huntington's disease, and Alzheimer's disease have long been the basis of fundamental science and in many countries of the world require large financial and resource costs for research[1,3].

Parkinson's disease is one of the foremost neurodegenerative diseases of the nervous system, this disease is one of the urgent problems not only in Uzbekistan but also in all countries of the world [14].

Back in 2017, the World Health Organization concluded that Parkinsonism is widespread. "The frequency of this pathological condition varies from 100 to 250 cases per 100,000 population. At the same time, the increase in the life expectancy of the population leads to an increase in the incidence of Parkinsonism. There's proof that the recurrence can reach 1700 cases per 100,000 populace".

"Published in 2019, The Working Group on Parkinson's Disease provides data on 8.5 million people with Parkinson's disease. At the same time, according to the same data, every patient out of 10 was younger than 50 years. Parkinson's disease accounts for about 80% of cases of Parkinsonism, which, in combination with other syndromes, can occur in several other diseases". Historically, it so happened that even 100 years ago, it was believed that Parkinson's disease is a pathology exclusively of the motor sphere [2,25].

The main manifestations of the disease are slowness of movement, tremors, and postural instability. The severity of these disorders largely determines the severity of the patient's condition [21].

In recent years, more and more work has been devoted to the study of cognitive impairment in Parkinson's disease. For example, studies provide information on the prevalence of dementia, which can reach up to 80% of cases. The proportion of the general population aged 60 years and over with dementia at any point in time is estimated to be between 5% and 8%. [16].

"Dementia, as a severe form of cognitive impairment, according to the World Health Organization (WHO), is one of the most "expensive" diseases for society, along with oncological and cardiological diseases". Most often, cerebrovascular disorders are detected in the elderly, but in recent years there has been a trend toward an increase in the prevalence of this pathology in young and middle-aged people [4,11]. This determines

the priority of early diagnosis of initial and moderate cognitive impairment since it is at this stage that therapeutic intervention is most effective.

The role of other factors is discussed, among which are the duration of the disease, the forms of the disease, the presence of affective and psychotic disorders, the level of education, and gender [5,17,24].

Clinical practice shows that the hippocampus is aparticularly vulnerable areaof the brain to diseases associated with obesity, diabetes, hypertension, ischemic disorders, brain injury, and depressive and bipolar disorders. Patients with these diseases often have apronounced decrease in cognitive functions that are combined with hippocampal atrophy. Volume reduction hippocampus, detected by magnetic resonance imaging, is a recognized indicator of the transition from the normal aging process to moderate cognitive disorders and dementia. On the other hand, the hippocampus is akey areaof neurogenesis: cause-induced atrophy of the hippocampus is associated with leveling neurogenesis. Thus, in a healthy, age-related, and "sick" brain, out to be a structural-functional triad: hippocampus - neurogenesis - cognitive function [6,7,15].

It is important to note that neurotrophic factors play an important role in both the development and maintenance of the central nervous system and the peripheral nervous system. They take part in the regulation of growth, development, differentiation, and survival of cell populations, the processes of their adaptation to external influences [27].

In addition, it is important to note that neurotrophins have functional diversity due to the interaction of a small number of polypeptides with the receptor apparatus of neurons, not due to a large set of factors. This allows nerve tissue to retain its plasticity and forms mechanisms for restoring neurological function has been damaged. Neuronal degeneration is prevented by these proteins [8]. They also stimulate the survival of different types of nerve cells, which is a prerequisite for considering them as possible drugs for the treatment of neurodegenerative diseases.[19,26]. The family of neurotrophins includes nerve growth factor (NGF), neurotrophic brain factor (BDNF), NT3, and NT4/5 neurotrophins. They support different populations of neurons to individual cells, signals for survival, differentiation, or act to prevent initiation of apoptosis in a neuron. They also induce the differentiation of progenitor cells and the formation of neurons. Neurotrophic factors play an important role in the functioning of the nervous system, and the regeneration of damaged neuronal structures.[17,20].

Neurogenesis - the process of creating new neurons from neuronal stem cells - is partially retained in the adult mammalian brain, despite the vast majority of neurons being formed during embryonic development. Neurotrophic factors control and stimulate this process. Neurotrophic factors are known to possess both trophic (ensuring survival) and tropic (directing axonal growth) properties. These properties may help them be used to treat neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, as well as peripheral neuropathies. NT3 is agrowth factor with mm.13.6 kDa. NT3 plays a role in the development of the sympathetic nervous system. In mice elevated levels of NT3 were found in sympathetic ganglia and organs during hyperinnervation and spontaneous hypertension. [13].

Brain-derived neurotrophic factor (BDNF), which acts through LNGFR and TrkB receptors, is one of the factors that can control the metabolism of brain cells in oxygen deficiency [4,10]. The binding of BDNF to Trk-B leads to an increase in trophic influence, which is associated with the main effects of this neurotrophin.

The influence mediated through p75 NTR receptors is more complex and ambiguous. Thus, these receptors are capable of both potentiating and inhibiting the neurotrophic action of Trk-B receptors or independently of them, triggering the apoptotic signaling cascade [23]. Normally, in most areas of the adult brain, mediated through p75 NTR

receptors, activity is inhibited due to their downregulation. However, in pathological conditions, for example, with brain damage,p75 NTR receptor activity is rapidly expressed, which can cause neuronal death [29]. Trk-B receptors consist of extra- and intracellular domains.

The extracellular domain is represented by five subunits of which the first and the third are cysteine-rich fragments, the second is leucine-rich, and the last two, the fourth and fifth immunoglobulin-like fragments stimulate the Trk-B receptor by the BDNF molecule triggers three cascades reactions mediated by the activation of an intracellular domain connected to the extracellular part of the receptor. BDNF is involved in the differentiation of neurons, their functional maturation, and also in synaptogenesis. In an adult organism, its neuroprotective function increases for brain neurons during ischemic attacks, as well as for motor neurons during axotomy [10].

Parkinson's disease is caused by the degeneration of dopaminergic neurons in the substantia nigra of the brain. At the same time, a pronounced decrease in the content of BDNF was noted in the pars compacta of this structure. Considering that it is in this part of the black matter that the most dramatic loss occurs in neurons, it can be assumed that this factor explains the decrease in the content of BDNF.[12]. However, analysis of surviving substantia nigra neurons showed that the content of BDNF in them was also reduced [8]. Howells et al. found that 65% of melanin-containing neurons in controls produced BDNF, while in controls BP BDNF was found only in 9.6% of pigment-containing neurons.

Moreover, a protein immunoreactive to BDNF was found in Lewy bodies. This indicates that, despite the presence of BDNF in the cell, pathological changes typical of PD may develop [21]

The glial neurotrophic factor (GDNF), which was initially discovered in glioma cell cultures, turns out to be mostly present in astrocytes, which are the cells that create most of these cells. The pathology of astrocytes has recently received significant attention in the occurrence of degenerative processes in the human central nervous system [6, 18]. This is important to emphasize. The trophic effect of GDNF on dopaminergic neuron culture was immediately demonstrated [7]. GDNF is now acknowledged as a factor essential for the development, maintenance, and protection of nigrostriatal dopaminergic neurons, including as a potential factor preserving and restoring dopaminergic neurons affected by Parkinson's disease [9,12]. GDNF constitutes a family of structurally similar proteins with neuroturin, artemin, and which assist the migration, differentiation, proliferation, and survival of the neuronal population.

Extracellular receptors (GFR 1-4), each of which is specific for the associated family member, are used by members of GDNF families to signal. The strongest affinity for GFR 1 is shown by GDNF. The extracellular domain of the receptor tyrosine kinase is where the GDNF-GFR-1 receptor complex attaches, influencing a number of intracellular signaling cascades [22]. In addition, Src-like kinases and MAP kinases can be activated by GDNF's direct binding to neuronal cell adhesion molecules (NCAM).

The proform of GDNF, known as proGDNF, is physiologically active and is expressed in the majority of brain regions as well as in astrocytes and and dopaminergic neurons [13].

In addition to GDNF, proGDNF is broken down to yield biologically active peptides called DNSP 11 in humans and BEP in rats. In the hippocampus, BEP increases synaptic excitation in pyramidal neurons [14], while DNSP 11 protects dopaminergic neurons just as well as the mature version of GDNF [15]. The dopaminergic area of midbrain neurons is not the only location where GDNF and its receptors are found. Numerous different brain areas include GDNF receptors, as well as their transcripts

and proteins, demonstrating the versatility of GDNF [16]. Participation in synaptogenesis in the hippocampus is one of them.Ectopic presynaptic sites are induced by GDNF and GFR1, which play an instructive role in synapse development [17]. Interestingly, in ASC mice prone to depressive behavior, GDNF enhances spatial learning. [18].

This was discovered two weeks after a single GDNF injection into the brain's lateral ventricle and could be linked to GDNF-controlled synapse remodeling. According to several studies, GDNF/GFR 1 signaling may be crucial for the growth and operation of different types of GABAergic neurons in the human brain [20]. The blood-brain barrier's cellular components are maintained by GDNF [7,8]. When there is inflammation, astrocytes and microglial cells produce more GDNF, which suggests that GDNF is an activator of microglia and an inhibitor of neural inflammation [24]. GDNF expression also increases following the introduction of bacterial lipopolysaccharide [3] and during inflammation.

Ciliary neurotrophic factor is a distinct neurotrophic factor that is involved in glial cell development and promotes the process of apoptosis due to its high concentration. Molecular weight is 22.7 kDa, and it has 220 amino acid residues. It was first identified as a trophic factor in parasympathetic neurons of an 8-day-old chicken embryo by R. Adler and colleagues in 1979.produced in the central and peripheral nervous systems by glial cells. The amount of the destruction of nerve tissue is determined by the marker ciliary neurotrophic factor. This substance also has the ability to harm spinal nodes, hippocampus, and retinal neurons.

Nerve growth factor (NGF) was the firrst to be discovered by Levi-Montalchini [18] NGF was the ancestor of a special and most specific in its biological activity of group of factors called the neurotrophin family. It is common for neurotrophins to form homodimers due to their highly homologous amino acid sequences. Dimerization is an indispensable condition for the implementation of the biological functions of neurotrophins [2,28]. These data suggest that monitoring such NGF during PD may provide a means to predict early disturbances in the dopaminergic system. Such information could enhance therapies as well as assist in improving means to protect surviving neurons [30].

Thus, measuring NGF serum levels in PD patients at different stages of the disorder as well as in experimental models provides a means to further establish relationships between NGF and the degree of dopaminergic degeneration. The mechanisms which govern modifcations in NGF in systems undergoing dopaminergic degeneration need to be further cerebrospinal fluid, such as emotional stress are accompanied by increases in accompanied by decreasein neurotrophicic factor [3].

Metalloproteinases are a family of zinc-dependent endopeptidases, counting framework metalloproteinases (MMPs), and protein peptidases included within the debasement of extracellular framework (ECM) proteins. Metalloproteinases perform numerous capacities: they control the movement of other proteinases, development variables, chemokines, and cell receptors, and can moreover influence forms such as movement, separation, expansion, and survival of cells [26] Later proof recommends that brain aggravation may impact nearby aggravation in brain illnesses coming about within the enactment of a few incendiaries go-betweens such as network metalloproteinases (MMPs), which in turn may influence capacities, counting movement, or apoptosis.

In addition, raised levels of many pro-inflammatory components, counting cytokines, peptides, and pathogenic structures, within the central apprehensive framework have been found in patients with brain maladies such as Advertisement or PD [29].

Within the course of the conducted test thinks about, it was proved that the adjustment within the framework of trophic and development variables guarantees the conservation of brain tissue amid basic periods. This secures the brain tissue from the harming

eff` 1ects of damaging operators. These think about was based on the objective of presenting the components of neurotrophic components into the brain parenchyma [30]. Lattice metalloproteinases (MMPs) are proteases that redesign the extracellular network. Lattice metalloproteinase-9 (MMP-9), a major component of the storm cellar film, may contribute to the pathogenesis of neurodegenerative maladies such as Alzheimer's illness, and PD by actuating neuronal passing [22]. Levels of tissue inhibitors of MMPs counting MMP-9 are hoisted within the cerebrospinal liquid of people with PD and the skin, and serum. [3,9].

Based on the results of the conducted tests, it has been demonstrated that the adjustment to trophic and developmental variables ensures the preservation of brain tissue during basic periods. This secures the brain tissue from the harming effects of damaging operators. These think about was based on the objective of presenting the components of neurotrophic components into the brain parenchyma [30]. Lattice metalloproteinases (MMPs) are proteases that redesign the extracellular network. The lattice metalloproteinase-9 (MMP-9) in the storm cellar film may contribute to the pathogenesis of neurodegenerative diseases like Alzheimer's illness and Parkinson's disease [19]. "Levels of tissue inhibitors of MMPs checking MMP-9 are lifted inside the cerebrospinal fluid of individuals with PD and inside the skin, serum. [3,9]. Essential refined mesencephalic neurons from MMP-3 KO appeared higher [5] dopaminergic take-up capability compared to that of a wild sort. The number of tyrosine hydroxylase -immunopositive neurons and the length of the normal dendritic department was too more noteworthy. This showed up to be particular for the dopaminergic framework, since [11] On the other hand, no contrasts were famous within the levels of the striatal dopaminergic and tyrosine hydroxylase protein between the KO and wild sort. Interests, tyrosine hydroxylase immunogenicity per cell was lower within the dopaminergic neurons of MMP-3 KO both in essential culture and in vivo, proposing the nearness of a compensatory component. These results encourage showing a part of MMP-3 within the end of dopaminergic neurons and propose MMP-3 as a candidate cellular target for neuroprotective treatment" [22]

In postmortem brain tissue from Parkinson's disease patients and age-matched control cases, Stefan Lorenzl and David S Albers examined matrix metalloproteinase 2 and matrix metalloproteinase localization. Using zymography, we found reduced MMP-2 levels in PD cases in the substantia nigra as compared to controls; levels of MMP-2 were not significantly changed in the cortex and the hippocampus. MMP-9 levels were unchanged in the investigated brain regions. Immunohistochemically,

They found that MMP-2 was predominantly found in astrocytes and microglia, while MMP-9 was overwhelmingly found in neurons. Levels of TIMP-1, an endogenous tissue inhibitor of MMPs, were altogether lifted within the substantia nigra, but not within the cortex and hippocampus. TIMP-2 levels were unaltered in PD. The MMP-1 levels in the substantia nigra were measured using Western blots to determine whether TIMP-1 levels are increased because MMP-1 expression is increased. Comparing PD cases to controls, MMP-1 levels were unaltered. Based on these findings, it appears that MMP-2 and TIMP-1 levels may be altered within the substantia nigra of patients with PD, suggesting that MMPs and TIMPs may contribute to the pathogenesis of the illness. [28]

Conclusion. In Parkinson's disease, neurotrophic factors play a significant role. It will be possible to determine the degree of cognitive impairment and the progress of Parkinson's disease by determining the level of neurotrophic factors in the blood of Parkinson's patients at different stages of the disease.

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