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PATHOGENETIC ASPECTS OF RESTLESS FEET SYNDROME

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Abstract The effect of vitamin D on dopamine metabolism is one of the most studied neurosteroidal effects of vitamin D. These effects are associated with the effect of the active form of the vitamin, calcitriol, on the expression of the gene of the main enzyme of dopamine biosynthesis, tyrosine hydroxylase.

Keywords: vitamin D, nerve growth factor, dopaminergic dysfunction, neurotransmitter, neurotrophins**.**

Introduction. Restless legs syndrome (RLS) is one of the most common neurological diseases affecting up to 10% of the adult population in industrialized countries [4, 5, 7]. Clinically significant RLS, according to various sources, occurs in 2-3% of the adult population [7, 8]. RLS is a multifaceted neuropsychological disorder that includes sensory disturbances, increased resting motor activity, insomnia, and psychoemotional disturbances. In particular, RLS consists of an unavoidable urge to move, often accompanied by sensory discomfort. Other criteria needed to diagnose RLS include worsening symptoms at night with inactivity and relief from movement. As a result of these symptoms, sleep is markedly disturbed, and as a result, depression is a frequent occurrence [4,5]. Other confirmatory psychological symptoms of RLS include impulsivity and decision problems.

Although the pathophysiology of RLS is not fully understood, genetic factors, iron deficiency, and dopaminergic disorders have been suggested as possible mechanisms. Most of the evidence to date suggests that dopaminergic brain dysfunction plays a key role in the development of RLS. Dopamine, a neurotransmitter involved in sensory and motor control as well as behavioral responses, is required for smooth and targeted muscle activity. Dysfunction of the

dopaminergic pathway often leads to involuntary movements, which may explain the mechanism responsible for the development of RLS [6, 8].

Current information on the pathogenesis of restless legs syndrome imply a violation of dopaminergic neurotransmission [6], but the contribution of disorders of vitamin D metabolism in the development of this disease cannot be ruled out. It is believed that 1,25-dihydroxyvitamin D, when acting on dopaminergic neurons, increases the expression of N-cadherin, which is involved in the neurogenesis of dopaminergic neurons and in turn regulates the expression of tyrosine hydroxylase, an enzyme that limits the rate of dopamine synthesis [6,15, 16]. T. Çakır et al. found that in patients with vitamin D deficiency, restless legs syndrome, according to the diagnostic criteria of the International Group for the Study of Restless Legs Syndrome, is more common than in patients with normal vitamin D levels [12]. According to the results of S. Wali et al. In a pilot clinical trial, vitamin D supplementation in patients with restless legs syndrome for three to eight weeks significantly improved symptoms according to the Restless Legs Syndrome Severity Scale [13].

The effect of vitamin D on dopamine metabolism is one of the most studied neurosteroidal effects of vitamin D. These effects are associated with the effect of the active form of the vitamin, calcitriol, on the expression of the gene of the main enzyme of dopamine biosynthesis, tyrosine hydroxylase (TG gene). The maximum increase in the expression of the TG gene (by 2–3 times) was observed at a concentration of 1.25 (OH) 2D of about 10–8 M. The combined effect of 1.25 (OH) 2D3 and 20 μM nicotine had no additive effect on the expression of the TG gene. which indicates the relationship of the mechanism of activation of the expression of this gene with nicotinic acetylcholine receptors [3, 9]. Pretreatment of neurons in culture with 1,25 (OH) 2D3 dose-dependently protects dopaminergic neurons from the neurotoxic effects of glutamate and other dopaminergic toxins (in particular, by reducing oxidative stress) [13,15].

In addition, vitamin D is required to protect dopaminergic neurons from toxins and increases the level of dopamine or its metabolites in the nigrostriatal

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dopaminergic pathway. However, the role of vitamin D in the pathogenesis of RLS is poorly understood. Few studies have examined the relationship between vitamin D and RLS, and those that mainly consist of crossover studies or case series involving relatively small samples [11,14]. Therefore, larger and more representative studies are needed to investigate the relationship between the severity of RLS and vitamin D. sleepiness [10,12]

Considering the pathophysiology of RLS, it is also necessary to review the biological systems that may be involved in the pathogenesis of RLS. These systems exist at the level of ligands and elements, including the dopaminergic and endocrine systems; at the level of systems, including the peripheral arterial and nervous systems; and at the molecular and genetic level, including oxygen determination and genetic pathways.

Neurotrophins are proteins that play an important role in the functioning of the nervous system, regulate cell proliferation, differentiation, the processes of survival and death of neurons, and are involved in the mechanisms of neuronal plasticity. [one]. As a result of a targeted search for neurotrophic factors, the first representative of this class of protein molecules, the nerve growth factor (NGF), was isolated and purified to a homogeneous state [2]. This discovery, subsequently awarded the Nobel Prize, led to the rapid development of this direction and the discovery of other neurotrophic factors. All of them play an important role in the development and functioning of the nervous system, and also, which is especially important for practical medicine, in the regeneration of damaged neuronal structures [Lindsay ea 1996, Lindsay ea 1996, Luer ea 1996, Verge ea 1996, Van ea 1996, Zochodne ea 1996, Grothe ea 1996, Isackson ea 1995, Lapchak ea 1996, Cuello ea 1997, Ebadi ea 1997], [Levi ea 1987] ..

Nerve growth factor (NGF) was originally thought to enhance the growth and maintenance of many neurons derived from the neural crest, including the small cells of the spinal ganglia and postganglionic autonomic neurons. However, it is now known that some neurons of the central nervous system are also sensitive to it.

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NGF is secreted by target cells and binds to specific receptors on neurons that form synapses on these cells. NGF bound to the receptor is captured by neurons (i.e., undergoes endocytosis) and is retrogradely transported into the soma. There, NGF can act directly on the nucleus, altering the formation of enzymes responsible for the synthesis of neurotransmitters and the growth of axons.

Therefore, in addition to the functional activity of nerve cells, it is important to assess the trophic support of their vital activity, which is realized through neurotrophins (NF).

Nerve growth factor is of greatest interest among neurotrophins and as a marker for assessing neurological deficits. It is widely expressed in various tissues, can have a neurotrophic effect on damaged neurons, and promote neurogenesis. In addition, it is very important that glial cells stimulate neurotrophin receptors and a certain level of NGF in the blood is an indicator of normal glial function [1]

FRU is indispensable for the survival and development of sympathetic and sensory neurons. Without it, these neurons are susceptible to apoptosis. Nerve growth factor causes axonal growth: studies have shown that it promotes branching and slight lengthening. NGF binds to at least two classes of receptors: LNGFR and TrkA. Both are associated with neurodegenerative pathologies.

NGF prevents or reduces neuronal degeneration in animals with neurodegenerative diseases. These encouraging results in animals have led to a number of clinical trials in humans. NGF expression is increased in inflammatory diseases in which it suppresses inflammation. In addition, NGF appears during the myelin repair process.

A decrease in the level of NGF is expected in patients with schizophrenia; however, the data are contradictory and complicated by the action of medications. In order to resolve this contradiction in 2009, the first study of psychiatric patients who had not yet received antipsychotic therapy was conducted, in which it was shown that the level of NGF in the cerebrospinal fluid and blood plasma of patients was lowered compared to the norm

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Thus, the analysis of modern data on the study of the pathogenetic aspects of RLS showed that the study of NGF and vitamin D levels in the pathogenesis of RLS and its manifestations as a diagnostic marker in assessing the degree of neurological failure is an urgent problem of modern neurology and requires further deeper study of this nosology.

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