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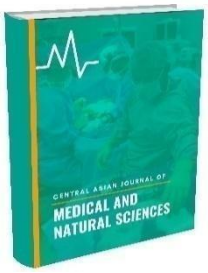

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Clinical-Neurological Features And Assessment Of Cognitive Functions In Patients With Myasthenia Gravis And Optimization Of Treatment

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Annotation: Myasthenia gravis is a severe neuromuscular disease with a progressive course, the main clinical manifestation of which is pathological muscle fatigue, leading to paresis and paralysis. In the genesis of this disease, autoimmune disorders are of great importance - the formation of autoantibodies to nicotinic cholinergic receptors of the end plates of muscle fibers, as a result of which neurotransmission is disturbed at the level of the neuromuscular synapse.

Key words: Myasthenia gravis, autoantibodies, neuromuscular synapse, therapy, autoimmune neuromuscular diseases.

Myasthenia gravis is a common, understudied, difficult to diagnose and severe disease. Difficulties in recognizing myasthenia occur mainly in the initial stages of the development of the disease, when there are single symptoms of the disease or an atypical course [10–15].

Myasthenia gravis is one of the most common and clinically well-studied autoimmune neuromuscular diseases, in the pathogenesis of which the state of the thymus plays a role [1]. Myasthenia gravis can affect people of different sex and age, the peak incidence occurs at the age of 20-40 years, women get sick more often. The progressive nature of the disease, difficulties in diagnosis at the initial stages of the disease, the development of severe movement disorders and life-threatening breathing and swallowing disorders, as well as resistance to immunosuppressive therapy that occurs in some patients, determine the great medical significance of the problem.

Taking into account the incidence and prevalence of myasthenia gravis is also important for economic reasons, since long-term treatment, periodic hospitalizations, decreased performance, and disability of patients are undoubtedly a significant cost item for the healthcare budget. The data published to date clearly illustrate that myasthenia gravis is a high-cost nosology. Thus, the average annual cost for the treatment of patients with myasthenia gravis in the United States in the period from 2008 to 2010 was $24,988 per patient. The total annual cost of drug therapy for myasthenia gravis was $9.4 million, of which 85% was for intravenous immunoglobulins [2]. Thus, epidemiological studies that have already been completed or will be carried out in the future are useful not only for science, but also for organizing medical care for such patients. The studies differed in the way they collected information about patients diagnosed with myasthenia gravis. Archival data of neurological departments, data from registers of myasthenic centers, national electronic registers, and databases on the prescription of pyridostigmine were used. All studies examined such epidemiological indicators as prevalence and incidence, some authors also paid attention to gender analysis (age of onset, incidence in men and women). Such a wide range of incidence rates, apparently, is associated with the methods of selection of patients. Modern

studies conducted in recent decades have used more complete case identification methods than studies from the 1940s to 1990s. The creation of registries of patients with myasthenia gravis in selected countries and regions of the world also contributed to a more complete inclusion of patients in studies and an increase in epidemiological indicators. A number of authors used an original method for selecting patients with myasthenia gravis and studied databases of prescriptions for the prescription of pyridostigmine [13-15, 19], for which myasthenia is the only approved indication in these countries. This method was used by researchers from Denmark, Australia, Portugal and Canada, and data on the incidence of myasthenia gravis in these countries was slightly higher.

Thus, despite the diversity of epidemiological data on the problem of myasthenia gravis, most scientific papers clearly show the following trends: an increase in the incidence of myasthenia gravis over the past 10–15 years, an increase in the number of patients over 40 years of age, which, according to most researchers, is associated with an increase in the duration of life and access to medical care in general, as well as with improved diagnosis of myasthenia gravis in particular. Myasthenia gravis is a chronic autoimmune disease characterized by impaired neuromuscular transmission due to the formation of autoantibodies to various autoantigenic epitopes of the peripheral neuromuscular apparatus, clinically manifested by weakness and pathological muscle fatigue [1]. The prevalence of myasthenia gravis ranges from 4.8 to 20.0 per 100,000 people [1–5]. The severity of the disease, leading to disability of patients, and the frequency of deaths determine the high relevance of the search for the most effective methods of treating this pathology. According to domestic scientists, an important link in the pathogenesis of a number of autoimmune diseases, including myasthenia gravis, is the activation of free radical oxidation as a typical pathological immune complex (CIC), due to an excess of autoantibodies and a violation of their elimination processes, leads to the activation of free radical processes, and primarily peroxide lipid oxidation, due to the interaction of the CEC with the cell membrane apparatus, which aggravates the course of the disease [6].

The key symptoms in all forms of myasthenia gravis are weakness and pathological muscle fatigue, which increase during exercise and decrease after rest or taking anticholinesterase drugs [7]. The consequence of the development of myasthenia gravis is disability and often disability of patients, a decrease in their quality of life, which determines the high medical and social significance of the problem [2, 8, 9]. The presence of a large number of various antigenic determinants and autoantibodies formed to them in myasthenia gravis allows us to conclude that this disease is heterogeneous, which should be taken into account when developing new diagnostic and treatment methods [1, 4, 10].

Often there is an erroneous or late diagnosis of myasthenia gravis, despite the simplicity of the clinical manifestations of this disease and the general availability of diagnostic tests confirming this diagnosis. Our data indicate that during the initial visit of patients to medical institutions, the correct diagnosis was made only in 30.0–33.0% of cases [10,11,13]. Most of the patients in the first months or years from the onset of the disease were treated with other diagnoses, and, therefore, did not receive adequate treatment for a long time [3,11,12.]. The reason is probably the lack of clear knowledge of the pathognomonic symptoms of the manifestation of this disease by doctors (general practitioners, ophthalmologists, otolaryngologists), who often turn to patients for medical help at the onset of myasthenia gravis. Neurologists do not always know the clinical criteria for early diagnosis of myasthenia gravis well enough, which also leads to erroneous diagnosis.

In addition, diagnostic errors are sometimes associated with the similarity of myasthenia gravis in the early stages of its development with other diseases of the nervous system and muscles [7,10,16]. The prognosis of myasthenia gravis, in relation to both life and recovery, if pathogenetic therapy is not carried out in a timely manner, is very unfavorable.

Myasthenia gravis with an early onset of the disease is characterized by frequent involvement of extraocular (80%), mimic (92%) and bulbar (65%) muscles, relatively rare lesions of masticatory (40%) and respiratory (20%) muscles, as well as neck muscles (30 %). Most patients showed weakness of the muscles of the trunk and limbs, and the decrease in strength in the triceps muscle was more pronounced (60%) than in the deltoid muscle (35%). In patients with myasthenia associated with thymoma, damage to the respiratory and masticatory muscles, neck muscles and deltoid muscle is significantly more often detected compared to the triceps muscle of the shoulder. The clinical pattern of late-onset myasthenia is

similar to that of patients with myasthenia gravis associated with thymoma [7]. The disease has a progressive character, quickly leads to disability and disability, which explains the high medical and social significance of the problem.

It was believed that only movement disorders were characteristic of myasthenia gravis. However, in the future, cognitive impairments, in particular memory impairments associated with central cholinergic deficiency, began to be detected [8,9]. Dysfunction of the basal cholinergic system leads to increased distractibility, reduced concentration of attention and, as a result, a rapid loss of acquired information [10]. Acetylcholine is the main neurotransmitter regulating the activity of the basal cholinergic system. The main role of acetylcholine is associated with ensuring the memorization of new information. Acetylcholine plays a key role in sustaining attention through an activating effect on the cerebral cortex [11]. It is known that in the hypothalamus, hippocampal gyrus, midbrain, and cerebral cortex there are acetylcholine receptors structurally and genetically similar to receptors on the postsynaptic membrane of the neuromuscular synapse. Cross-reaction of antibodies between these receptors can cause the formation of cognitive impairment in myasthenia gravis [12]. Regardless of the predominance of the primary neurodegenerative process or vascular lesions of the brain, a common pathogenetic mechanism in the development of cognitive impairment and dementia is a deficiency of acetylcholine in the structures responsible for cognitive functions.

More recently, small studies have begun to evaluate the impact of myasthenia gravis on cognition [13, 20]. These studies were limited by small sample sizes and were complicated by various factors. For example, some of these studies did not reliably take into account the dosage and duration of corticosteroid therapy. This is an urgent problem, since there were works in which the possible consequences of long-term use of corticosteroids on memory were determined [14]. Understanding the issue of cognitive changes in patients with myasthenia gravis has not yet been achieved.

According to a study by Y. Iwasaki. et al., 1990, 27 patients (19 women, 8 men) with generalized myasthenia were examined. Age ranged from 19 to 82 years. The duration of the disease is from 3 months to 8 years. For neuropsychological testing, the Mini Mental Status Assessment Scale (MMSE) was used, and the Zung Depression Self-Assessment Scale (SDS) was used to assess the severity of depression. A decrease in intellectual function was found in patients with myasthenia gravis, as well as a decrease in memory. But the authors expressed caution about interpreting memory tests. First, the patients had moderate to severe depression, which could affect their performance. Secondly, in patients with myasthenia, the reproduction of the material was delayed, this reflects

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