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Autoimmune Diseases of the Nervous System: Problem Statement and Prospects

This review highlights the achievements in the field of autoimmune diseases of the nervous system over the last 15 years. It became possible to deepen the understanding of medical and social significance of these diseases, form the concept of nosologic unit heterogeneity, describe new and atypical forms of demyelinating diseases of the central and peripheral nervous system, autoimmune diseases of the neuromuscular synapse. Also, it is important to mention, that the new antigens were identified, the diagnostic panel of autoantibodies was developed and put into practice. Furthermore, the clinical practice guidelines for the diagnosis and management of patients were developed, the new drugs were tested and included in these guidelines. The scientists of the biggest Russian neurological center, Research Center of Neurology (Moscow), developed a «vaccine» for immunotherapy of multiple sclerosis, studied pathomorphosis of Guillain–Barre syndrome, specified the components of its pathogenesis, improved the programs of pathogenetic therapy, which led to the decrease in mortality from 30 to 3%, helped to decrease the AVL period by 2 times, hasten the recovery of independent walking by 2.5 times. Nowadays different biomarkers of diseases of the central and peripheral nervous system are studied and modern technologies in neurorehabilitation are applied.

Key words: *neuroimmunology, autoimmune diseases of the nervous system, multiple sclerosis, Guillain–Barre syndrome.*

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Autoimmune diseases of the nervous system have many common features which makes it possible to treat them as pathological phenomena with a similar mechanism of development. They include: genetic predisposition, young age, female gender, reoccurring and progression, and at the same time – spontaneous remission; high frequency of a number of autoimmune diseases in one and the same patient; evident efficacy of immunosuppressive and immunomodulation therapy.

Nowadays there are over 30 autoimmune diseases of the nervous system known. The most common among them are multiple sclerosis (MS), Guillain-Barre syndrome (GBS), myelitis, acute and chronic polyneuropathies, myasthenia gravis, polymyositis and dermatomyositis[4,5]. Almost each structure of the central or peripheral nervous system can be a target for an autoimmune attack. Some of them are related to a certain infection agent (ppostpoliyo syndrome, campylobacter- or CMV-associated Guillain-Barre syndrome, Sydenham's chorea) and tumors (paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS), opsoclonus-myoclonus etc.) [6,7]. Nevertheless, disease triggers in most of the cases still remain unclear. This statement is true for instance, in neurosarcoidosis, Tolosa-Hunt syndrome, multifocal motor neuropathy with conduction blocks (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP) etc.[8]. So, there is a need in further research in this field.

There have been only a few models for autoimmune diseases of the nervous system used for a long time, but over the last few years a big step forward was done in this direction. Apart from classical experimental autoimmune neuritis in rats and mice (active and passive model) there were Tx9, P0- associated neuritis, transgene models and, a model with a passive antibody transmission [9] developed. Recently a chronic polyneuritis model has been created, which discovered a big prospective to explore the pathogenesis of the diseases and efficacy of drugs in chronic conditions [10].

A great progress in neuroimmunology appeared with an identification of new earlier unknown antigens. For example, myasthenia gravis was traditionally associated with antibodies to acetylcholine receptors, but an identification of MuSKusk (muscle-specific tyrosine kinase) and LRP4 that lie on postsynaptic membrane and take part in ACR-complex building suggests another pathogenesis pathway [11]. Many types of gangliosides with specific localization and clinical pattern of the disease were identified for a big group of acute and chronic polyneuropathies. So, neuropathies associated with GM1 antibodies have isolated motor deficit (motor form of GBS, MMN) [12].

All mentioned above results in understanding that each disease is made up of a group of syndromes. Deep exploration of multiple sclerosis, myasthenia, GBS [13], chronic polyneuropathies has shown their heterogeneity. Nowadays there are seropositive and seronegative forms of myasthenia known, and a seronegative form includes an anti-MuSK form [14]. Also there are descriptions of neonatal and congenital myasthenia. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) before was considered to be synonymous to GBS, but then it appeared to be just one of its four basic and four additional forms. CIDP includes 7 atypical forms. Finally, there are 8 forms of MS, including atypical forms, described [15-17].

Antibodies verification and new diagnostic arrays development for using in everyday clinical practice is another perspective trend of neuroimmunology. Nowadays there is a possibility to investigate oligoclonal bands of IgG in blood and CSF for MS diagnosis, aquaporin 4 antibodies for opticomyelitis, to determine antiganglioside antibodies in autoimmune polyneuropathies, to define pathologic immunoglobulines (paraproteins), glutamate decarboxylase antibodies (GAD) in stiff-man syndrome [18-20]. These tests have found place in autoimmune diseases of nervous system routine practice.

Most of the neurologists follow the guidelines that were developed by professional neurological associations according to many high evidentiary trials. Diagnostic criteria for MS and associated conditions, some of polyneuropathies, such as CIDP [21], MMN [22], paraproteinemic demyelinating polyneuropathies [23], myasthenia gravis [24] were improved. But there is a wide variety of diseases that wait for it. The main problems are low prevalence of these diseases and their clinical polymorphism, which makes it difficult to include patients in trials and collect data. Over the last few years we observed a fast development of new therapeutic approaches for autoimmune nervous system diseases and their practical use. "Ex juvantibus" therapy (corticosteroids, plasmapheresis, intravenous immunotherapy, sometimes cytostatics) is replaced by new targeting strategy [24-26]. First of all it refers to pharmaceutical innovations. Monoclonal antibodies, fusion proteins are now used in neurology as well as it was made before in rheumatology. Rituximab (anti-CD20), Natalisumab and Fingolimod are the most promising medications among the others. Their efficacy has been proved in MS trials, including Research center of neurology trials [27,28], which allowed us to include these medicines into therapeutic protocols. Their implication gets even wider. One of the most expensive drugs in the

world, Eculizumab, is now on the clinical trial phase (<https://www.clinicaltrials.gov/ct2/show/NCT02029378>) and it's expected to be effective in treatment of GBS axonal forms characterized by long term course and bad prognosis. For several years the Research center of neurology team has been focusing on the most common demyelinating disease of the central nervous system –MS, and the most severe condition of peripheral nervous system - GBS.

Conducted trials [29] have revealed clinical polymorphism of MS (atypical forms – pseudotumorous, Balo-like, isolated optic neuritis and myelitis); imaging and biochemical methods for the diagnosis of ADEM, opticomyelitis and aquaporine-associated syndromes in systemic inflammatory diseases (lupus, Behcet disease) have been improved; the role of T-regulatory cells (T_{per}) in MS pathogenesis has been determined; a role of lipids in MS immune response is being actively studied: the interaction with Toll-like receptors, antibody production to different types of myeline lipids; neurodegeneration biomarkers evaluation methods in MS, including neuroimaging (MRI, MR-spectroscopy), biochemical (neurotransmitters, neurofilaments – heavy and light chains, beta-amyloid in biological liquids), neurophysiological (evoked potentials, optic coherent tomography, electrophysiological study of retina) have been developed; neuroplasticity mechanisms in MS – related motor disorders are being studied using the most modern technologies – functional MRI and navigational transcranial magnetic stimulation (TMS) [30].

Autologous cell vaccine T_{per} CD4+CD25Foxp3+ made for MS immune therapy is a significant achievement of the Russian science and it doesn't have any analogues abroad. The Research was conducted together with the Cell technology and regenerative medicine group of Pirogov Russian National Research Medical University (RNRMU) with the financial support of "Scolcovo" foundation. Immune and clinical markers of T_{per} vaccine used in 14 MS patients (1,5 years of observation) showed exacerbation rate reduction from 1-2 in all patients to 1 in 3 patients, EDSS rate stabilization from 3,7 in the beginning till 3,3 during the same period of time with reliable increase of T_{per} blood level [31]. Vaccine producing technique has been patented in Russia and USA in 2014.

Navigated TMS has become another prior technology developed in Research center of neurology. It was shown that magnetic stimulation of the leg area in motor cortex reliably decreased spasticity in patients with progredient course of MS [32]. Now stimulation protocols are being refined, a group of patients in which this kind of therapy may be most effective in decrease of spasticity and improving of leg function is being allocated. Navigated TMS is one of the most popular and perspective methods of neuroplasticity modulation that allows reliable rehabilitation and compensation of lost functions after brain lesion.

The Research center of neurology is one of the biggest centers in the world with a great experience in diagnostics and management of over 400 patients with GBS, and the only center in Russia specialized in this field. GBS is the most common cause of acute paralysis in the world. One in four cases requires full-scale resuscitation measures, including prolonged artificial lung ventilation. It is based on autoimmune attack against the myelin and axons of peripheral nerves in particularly severe forms. Recently the prevalence data has been obtained in Russia (1,8 in 100.000 per year) that allows relevant treatment and rehabilitation in patients with determined diagnosis (or suspicion of it) in every region [33,34]. We have developed an algorithm for acute flaccid paralysis differential diagnosis, adapted for Russian population. GBS is proved to be the main cause of acute flaccid paralysis for now (before that it used to

be polyomyelitis). Obtained data helps practitioners to act according to the plan and choose optimal set of diagnostic tests. In the last few years we succeeded in decreasing mortality from 30 to 3%, halving artificial ventilation period and speeding up walking recovery time for 2,5 times by improving a diagnostic algorithm, control and optimization of treatment protocols.

Establishment of GBS and its pathomorphosis description have become the result of 10 year fundamental research first time in the world literature. For instance, the elevation of axonal forms for 4 times has been shown, many of them require providing of artificial lung ventilation 5 times longer than in demyelinating forms. Apart from this, disease triggers have changed: acute respiratory infections appear less frequent in demyelinating forms, and diarrhea as a trigger of Guillain-Barre syndrome is not rare now. The pathogenesis links have been clarified: the main role of *Campylobacter jejuni*, GM1 gangliosides antibodies participation. Biomarkers associated with severe course of the disease and residual paresis have been defined: 2 types of antibodies – anti GM1 and anti GD1a, also heavy chains of neurofilaments revealing in blood serum first 2 weeks from the beginning. Anti-GM1 and anti-GD1 are associated with severe course of the disease, artificial lung ventilation supply and resistant residual paresis; heavy chains of neurofilaments concentration in the serum of the patients $> 0,144$ ng/ml considers high risk of respiratory disorders, $> 0,094$ ng/ml – high probability of dysphagia with tube feeding [35].

We provide research to reveal molecular mechanisms of Guillain-Barre syndrome pathogenesis together with M.M. Shemyakin and Yu.A. Ovchinnikov Institute of bioorganic chemistry of the Russian Academy of Sciences and SRI of Physical-Chemical Medicine. After few pilot studies dedicated to profiling of the serum in patients with Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and comparing with control group [36], further work was focused on CSF studying. Data of CSF proteomic and peptidomic spectrum in patients with demyelinating form of Guillain-Barre syndrome and healthy controls were obtained. It was shown that amount of proteins, which were found in the form of degradation products in CSF samples of GBS patients, was 4 times higher than in a group of controls. Significant part is presented with immunoglobulin fragments that consider more intense immune status of CSF in GBS. Furthermore, adhesion protein fragments, which take part in myelin cover organization of peripheral nerve in paranodal areas, are identified among specific for Guillain-Barre syndrome proteins, and it can indicate possible mechanism of nerve demyelization by proteolytic degradation of these proteins. Blood analysis in patients with Guillain-Barre syndrome and healthy controls was performed to reveal antibodies to different herpes virus subtypes. In blood samples of patients with Guillain-Barre syndrome there are antibodies against few different types of herpes virus at the same time unlike control group. The transcript of lymphocytes from peripheral blood in patients with GBS has been obtained: analysis of these data is going on now. There is a plan for future not only to clarify some of pathogenesis links but to improve diagnostic tests and include them into clinical practice.

Finally, it is worth saying that neuroimmunology in all its aspects is a quite young, relevant and intensively developing direction of medical science. Deep studying of GBS as a unique severe, but self-limiting condition with proved autoimmune mechanism is especially important. If we clarify its pathogenesis, we will be able to find a clue to treatment of autoimmune diseases which nowadays are the most complicated aspect of modern medicine.

Conflicts of interest

The authors have indicated they have no financial or any other relationships relevant to this article to disclose.

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