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Development of an immunoassay test system for diagnostics and differential diagnosis of autoimmune motility disorders of the gastrointestinal tract

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Gastrointestinal motility disorders associated with impaired intestinal innervation have been little studied. Disruptions in the work of parasympathetic and metasympathetic structures can be caused by an autoimmune process both against the receptor apparatus and against peptides that perform mediator functions. In this regard, the development of methods for determining antibodies to the α3-acetylcholine receptor and the gonadoliberin releasing factor, which are involved in the regulation of gastrointestinal motility is relevant. As shown in this article, detection of these autoantibodies in patients with gastrointestinal motility disorders allows one to diagnose autoimmune damage to the peripheral parasympathetic and metasympathetic division of the autonomic nervous system, to conduct differential diagnosis of clinically similar pathological processes and to provide adequate timely treatment aimed at suppressing autoimmune lesions of the autoimmune nervous system and improving the quality of life of patients with peripheral autonomic insufficiency.

Keywords: autoimmune lesions, autonomic nervous system, ELISA, GnRH, α3-AchR.

The diseases characterized by impaired gastrointestinal motility are very common. The greatest difficulties brings in the diagnosis of the so-called "functional" disorders, in which many modern examination methods (ultrasonography, rectoscopy, gastroscopy, colonoscopy, irrigoscopy, biochemical and clinical blood tests, urinalysis, feces analysis, and cultures for dysbiosis, etc.) — do not reveal any abnormalities. At the same time, for example, irritable bowel syndrome (IBS) is detected in 15–20 % of the population and its incidence is 1 % [1; 2]. In addition, gastrointestinal disorders develop in patients treated with buserelin. It is especially important to establish the cause of dyspeptic disorders in this group of patients due to the insufficient effectiveness of standard symptomatic therapy. For this purpose, diet correction, various types of sorbents, enveloping agents, drugs to restore the normal intestinal flora, as well as antispasmodics (anticholinergics) and antidepressants — are used. Treatment by gastroenterologists with the participation of psychotherapists and psychiatrists is not always effective, hence a number of patients with gastrointestinal motility disorders are examined according to an extended scheme repeatedly — up to 20–30 times. Moreover, some patients (often at their urgent request)

undergo unreasonable surgical interventions. Gastrointestinal motility disorders associated with impaired intestinal innervation have been little studied. Regulation of the motor and secretory function of the intestine is carried out by the sympathetic, parasympathetic and metasympathetic divisions of the ANS. The main mediators are adrenaline, norepinephrine, acetylcholine, but some peptides can also perform neurotransmitting functions: The vasoactive intestinal peptide, the pituitary adenylate cyclase activating peptide, the gonadoliberin releasing factor (GnRH), and other parasympathetic and metasympathetic ganglia and intramural ganglia.

Disruptions in the work of parasympathetic and metasympathetic structures can be caused by an autoimmune process both against the receptor apparatus and against peptides that perform mediator functions. In this regard, the development of methods for determining antibodies to the structures of the parasympathetic intramural ganglion (α3-AChR) and the GnRH peptide involved in the regulation of gastrointestinal motility through parasympathetic and metasympathetic structures of the ANS is relevant.

Material and methods

Gonadoliberin (GnRH) autoantibodies were detected by ELISA [3]. Buserelin, a gonadoliberin drug sold through the pharmacy chain, was used as an antigen. The proposed method was examined 10 patients with myasthenia gravis, 4 patients with peripheral autonomic (vegetative) insufficiency (PVN), 1 patient with IBS with three history of surgical interventions, and 10 control donors. ELISA revealed the presence of antibodies to GnRH in a patient with IBS and gastrointestinal motility disorders. Moreover, there were no antibodies to the structures of the sympathetic (β2-adrenergic receptor) and parasympathetic (α3 AChR) divisions of the ANS. In patients with PVN, gastrointestinal motility disorders were due to the presence of antibodies to α3 AChR, but not to GnRH. Clinically similar motor impairment had a different substrate of damage. In the control sera, neither GnRH nor α3 AChR antibodies were detected. The administration of prednisone in immunosuppressive doses to a patient with autoimmune PVN led to a reduction in symptoms, the appointment of a patient with IBS neuromidine also led to a significant improvement in her condition and the abdominal pain disappeared. Thus, the detection of antibodies to 3-AChR and to GnRH ELISA allows one to diagnose autoimmune damage to the peripheral parasympathetic and metasympathetic division of the ANS. This provides adequate timely treatment aimed at suppressing autoimmune lesions of the ANS and improving the quality of life of patients with PVN. Closest to the proposed method is a technique for diagnosing autoimmune lesions of the peripheral ANS by detecting antibodies to the ganglionic subunit of the 3-acetylcholine receptor (3-AChR) by radioimmunoprecipitation, where a receptor isolated from a neuroblastoma cell culture and bound to an epibatidine labeled isotope was used as an antigen 1–125 [4] and a method for detecting antibodies to GnRH [5] by ELISA in patients treated with a synthetic analogue of gonadoliberin — buserelin. These methods allow the determination of antibodies in the blood serum, establish the lesions of the ANS and determine the target molecular target, however, it, along with high specificity, is laborious to perform, since it involves working with radioactive isotopes, requires special equipment and facilities, is more expensive. The second method — in isolation from the first one, makes it impossible to conduct differential diagnosis of clinically similar pathological processes. The proposed method is cheaper, safer and

more informative. So, to determine the antibodies in the blood serum by the method of enzyme-linked immunosorbent assay (ELISA), the extracellular domain α3 AChR and godanolin are used. In addition, this method allows for the same specificity in a simpler and more economical way (in particular, not requiring radiation protection measures) to carry out diagnostics and differential diagnosis of autoimmune lesions of parasympathetic (receptor) and metasympathetic ("mediator") intramural molecular structures of the ANS involved in the regulation of the functions of the gastrointestinal tract. The use of this diagnostic method allows one to prescribe differential adequate therapy to patients not only in neurological and gastroenterological clinics, but also in cardiological, urological and ophthalmological clinics, and also protects them from unreasonable repeated examinations and unnecessary surgical interventions.

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