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MODERN CONCEPTS OF MUSCULAR DYSTONIA

This study presents a comprehensive analysis of the genetic, clinical, and therapeutic aspects of muscular dystonias — a heterogeneous group of neurological disorders characterized by pathological postures and disabling hyperkinesias. Based on a synthesis of data from recent decades, the authors highlight key advancements: the identification of 25 hereditary forms (DYT1–DYT25), the role of mutations in the TOR1A gene (DYT1) in disrupting intracellular transport, and progress in symptomatic treatments such as botulinum toxin therapy, deep brain stimulation, and MR-guided focused ultrasound (MRgFUS). Special attention is given to the limitations of current approaches, including an incomplete understanding of pathogenesis and therapeutic resistance observed in 30–40% of patients. The necessity of integrating genetic testing, neuroimaging, and emerging biotechnologies (e.g., CRISPR, recombinant toxins) is emphasized as a pathway toward developing targeted treatment strategies. The paper also summarizes epidemiological data (prevalence: 3–60 cases per 100,000), presents the current classification framework, and outlines prospects for personalized medicine – offering a roadmap for future research.

Keywords: dystonia, hyperkinesis, genetics, torsion dystonia, cervical dystonia.

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Introduction. Dystonia is a neurological disorder characterized by impaired motor functions, persistent muscle contractions, and abnormal violent movements that lead to the formation of unnatural postures and disability [1, 2]. The study of dystonia as a nosological entity has a history of more than a century. The first systematic observations were made by A. Schwalbe (1908), who recorded a chronic syndrome combining muscle spasms with psychoneurological symptoms. A significant contribution to the nosological differentiation of the pathology was made by G. Oppenheim (1911), who introduced the terms "deforming muscular dystonia" and detailed the key clinical markers of the disease, including muscle tone disorders and the formation of abnormal postural settings. These works laid the foundation for understanding the pathogenesis and clinical identification of dystonic disorders [3]. Dystonia is the third most common movement disorder after Parkinson's disease and tremor, which emphasizes the need to improve diagnostic algorithms and expand the availability of genetic testing [50]. Different types of dystonia can occur in people of any age, leading to serious disorders and a significant deterioration in the quality of life [10]. In ICD-10 (International Classification of Diseases, 10th revision), dystonia is included under the code G24 [6]. According to estimates, the prevalence of dystonia may be: 3-11 cases per 100,000 population for generalized forms (most often beginning in the 1st or 2nd decade of life and often having a hereditary nature); 30-60 cases per 100,000 population for focal forms, which usually manifest at a later age [7]. There are also statistics on the types of dystonia: Primary dystonia accounts for 60%; of all cases of dystonia. Secondary dystonia - 40% of all cases of dystonia [8].

A variety of heterogeneous movement disorders are grouped under the general term – dystonia. The clinical picture ranges from isolated dystonia to multisystem disorders where dystonia is only an accompanying feature [9]. The pathophysiology of dystonias is still poorly understood. However, over the last two decades, many models have been developed that improve our knowledge of the molecular and cellular basis of this heterogeneous group of movement disorders [10]. Recently, a number of innovative genetic and molecular findings have been obtained. Although these allow for genetic testing and counseling, their translation into new treatments is still limited. Nevertheless, it is worth noting that the road to understanding common pathophysiological and molecular mechanisms has begun [12].

Epidemiology and genetic classification of primary dystonia. The ratio between cases of primary and secondary (degenerative) dystonia is estimated to be approximately 2:1. At the same time, dystonia-plus syndromes are much less common than these two types of dystonia. [37]. Estimates of the prevalence of primary dystonia range from 2 to 50 cases per million for the early form and from 30 to 7320 for the late form, although researchers question the results of statistical analysis. Based on more reliable studies, the following estimates can be distinguished: 111 cases per million for early dystonia in Ashkenazi Jews in New York, 600 for late dystonia in the north of England, and 3000 in Italy among people over 50 years of age [36].

Primary dystonia includes syndromes in which dystonia is the only phenotypic manifestation, except that tremor may also be present. Most cases of primary dystonia have adult onset, and approximately 10% of probands report one or more affected family members [26]. Pathogenic variations in several genes can cause isolated dystonia, and the number of dystonia genes identified is increasing [50]. Hereditary dystonia, denoted by the *DYT* locus symbols, can be divided into three broad phenotypic categories: primary torsion dystonia, where dystonia is the only clinical feature (except tremor) (*DYT1, 2, 4, 6, 7, 13, 17,* and *21*); dystonia plus, where other phenotypes in addition to dystonia are present, including parkinsonism or myoclonism (*DYT3, 5/14, 11, 12, 15,* and *16*); and paroxysmal forms of dystonia/dyskinesia (*DYT8, 9, 10, 18, 19,* and *20*) (Table) [32, 49].

Early-onset dystonia type *DYT1* is the most common form of primary dystonia. In non-Jewish populations, it accounts for about 50% of cases of early-onset generalized dystonia, while in the Ashkenazi Jewish population this figure reaches 80–90% [37]. The *DYT1/TOR1A* gene is located on the long arm of chromosome 9 at locus 9q34.11 (Figure 1). The pathogenesis of *DYT1* also involves autosomal dominant inheritance, but with low pen-

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etrance (about 30%), meaning that not all mutation carriers will exhibit clinical symptoms [39].

Most patients with *DYT1* have a heterozygous mutation representing a deletion of the GAG trinucleotide in the *DYT1/TOR1A* gene, which leads to the formation of an abnormal torsin A protein with the loss of one glutamine residue in its structure [38]. Torsin A is a member of the AAA+ adenosine triphosphatase family and is involved in intracellular transport, vesicular element fusion, formation of tertiary and quaternary protein structure, protein degradation, and organelle biogenesis. Abnormal torsin A promotes the formation of spherical inclusions near neuronal nuclei, which can destabilize the functional form of the protein and lead to its rapid degradation. Dysfunction of torsin A and the widespread distribution of this protein in the extrapyramidal system lead to the characteristic symptoms of primary dystonia type 1, including involuntary muscle contractions and the formation of pathological postures [39].

Therapeutic strategies for dystonia. Treatment of dystonia primarily involves agents targeting dopamine and acetylcholine receptors [8]. Pharmacological agents used include muscle relaxants, benzodiazepines, antiepileptic and certain antipsychotic drugs, as well as antihistamines, the effectiveness of which is supported by evidence at various levels. However, their use is associated with a number of limitations, including side effects, moderate therapeutic efficacy, and the requirement for long-term treatment [16]. Oral medications and botulinum toxin injections are the first-line treatments and play an important role in the initial therapy of patients with dystonia. In cases where the disease is more severe or refractory to treatment, neurosurgical interventions are used to improve the quality of life of patients [51].

Deep brain stimulation (DBS) is the most common surgical approach for the treatment of drug-resistant movement disorders such as tremor and dystonia [40]. It can alleviate the symptoms of genetic and primary dystonia by suppressing abnormal neuronal activity in the motor loop network [41]. Modern DBS systems, adapted from cardiology, included an intracranial electrode, an extension wire, and a pulse generator and have been gradually improved over the past two decades. Improvements in electrode systems and battery cells, the introduction of innovative approaches to neurostimulation, including closed-loop feedback systems and adaptive activation modes, and the development of neuromonitoring methods will significantly improve the therapeutic efficacy and safety profile of DBS methods [42]. In a meta-analysis by *Wang et al. (2021)*, which included data from 71 patients from 31 studies, DBS demonstrated a significant reduction in the severity of myoclonus and dystonia symptoms. The average improvement on the Unified Myoclonus Rating Scale was 79.5% (±18.2), with 94.1% of patients showing a motor function improvement of more than 50% [51]. However, a number of limitations should be taken into account: the risk of postoperative complications, adverse effects during stimulation (dysarthria, paresthesia, cognitive changes), the need for repeated surgical interventions to replace the pulse generator [52].

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive treatment method that uses focused ultrasound waves to heat specific tissue targets in the brain [43]. It is widely recognized as an effective treatment for both essential and parkinsonian tremors [44].

In Russia, this treatment method was approved in 2017. The first experience in Russia using MR-FUS for the treatment of essential tremor demonstrated 96% efficacy with no long-term complications, which confirms the promise of the method [4]. MR-FUS also demonstrated high efficacy in the treatment of refractory cervical dystonia, providing a 70% reduction in symptoms according to the TWSTRS scale, which is comparable to the results of invasive methods [5]. It should be noted that the study by Singh et al. (2020) obtained encouraging preliminary results when studying new indications, including focal dystonia and neurological conditions such as obsessive-compulsive disorder and depression [46]. This innovative technology is characterized by its precision and potential advantages over traditional surgical methods [45]. Importantly, the lesion formation process is closely monitored in real time using both neuroimaging and clinical methods [47]. This technology is characterized by high accuracy and has allowed the development of minimally invasive treatments with results comparable to traditional brain surgery [14]. However, the current level of evidence remains insufficiently high, and limited efficacy, thermal tissue damage, and lack of long-term effect require further study [48].

Botulinum toxin (BT) is used to treat a wide range of muscle hyperactivity syn-

Classification of dystonias

By type of inheritance / By etiology	Autosomal dominant	Autosomal recessive	X-linked
Primary dystonia	*DYT1, DYT4, DYT6, DYT7, DYT13, DYT21*	*DYT2, DYT17*	-
Dystonia-plus	*DYT5/14, DYT11, DYT12, DYT15*	*DYT16*	*DYT3*
Paroxysmal dystonia	*DYT8, DYT9, DYT10, DYT18, DYT19, DYT20, DYT23, DYT24, DYT25*	-	-

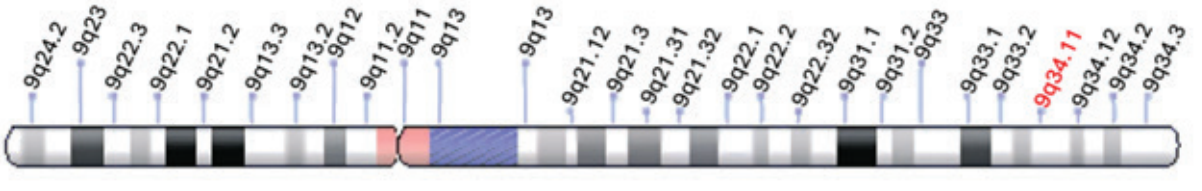

Fig. 1. Schematic representation of chromosome 9 indicating the locus 9q34.11 (highlighted in red), where the *TOR1A* gene associated with the hereditary form of dystonia *DYT1* is located.

dromes. One of the key indications for its use remains dystonia, which is confirmed by numerous studies demonstrating the effectiveness of BT in the symptomatic treatment of this disease [13, 18]. Clinical use of botulinum toxin is highly effective in focal dystonias (improvement in 70-90% of patients with cervical dystonia), low invasiveness (outpatient administration) and rapid action (initial effect - 3-7 days, maximum - 2-4 weeks). Advantages include complete reversibility of the effect, minimal risk of systemic complications due to the local mechanism of action and no need for surgical intervention [36, 44]. However, there are a number of limitations to the method: the transient nature of the therapeutic effect, the need for repeated injections every 3–6 months, the development of secondary resistance in 5–15% of patients, local adverse effects (muscle weakness, dysphagia, xerostomia), high pharmacoeconomic costs and the absence of a significant effect in generalized forms of dystonia [12, 25].

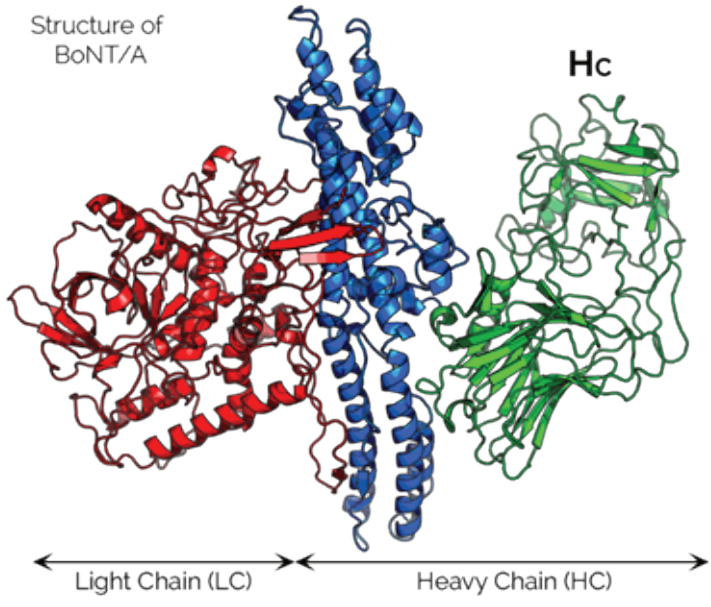

Fig. 2. Crystal structure of botulinum toxin type A (Structure of BoNT/A): binding domain (Heavy Chain (HC) - heavy chain, 100 kDa), translocation domain and catalytic domain (Light Chain (LC) - light chain, 50 kDa) [*Lacy D.B. et al., 1998*].

Botulinum toxin: molecular mechanism. The use of botulinum toxin in medicine demonstrates a paradoxical phenomenon: a substance that causes fatal botulism poisoning has become the basis for innovative therapeutic agents for the correction of neurological pathologies [22]. Botulinum toxins are natural origin toxins produced by the bacteria Clostridium botulinum, Clostridium butyricum and Clostridium baratii. Of the eight (A, B, C1, C2, D, E, F, G) serologically active types of botulinum toxins, only one (C2) does not have tropism for the nervous system [19]. The mechanism of action of all botulinum toxin serotypes, regardless of type, is the presynaptic blockade of SNARE (Soluble N-ethylmaleimide-sensitive factor (NSF Attachment Protein Receptor) transport proteins, which results in the suppression of acetylcholine release into the synaptic cleft and a reversible block of neuromuscular transmission [20, 21].

The chronometry of the therapeutic effect of different botulinum toxin serotypes demonstrates marked heterogeneity due to the molecular features of their protease activity [27]. Clinical observations show that serotype A-based drugs provide neuromuscular blockade lasting 6–9 months, while serotype B exhibits a pharmacodynamic effect for 3–4 months [28, 30]. This dissociation of time parameters correlates with the differential kinetics of SNARE complex regeneration: SNAP-25, a serotype A substrate, undergoes slower intracellular renewal via neuronal protease systems (calpain, cathepsin L), while synaptobrevin, a serotype B target, is resynthesized at an accelerated rate due to the activation of vesicular recycling mechanisms [28, 29]. An additional factor is the structural resistance of proteolytic fragments to degradation: tryptic cleavage of SNAP-25 in the Gln197-Arg198 region creates a more stable product complex compared to the modification of synaptobrevin in the Gln76-Phe77 region [17, 32]. The heavy chain of botulinum toxin has a high affinity for specific receptors on the presynaptic membrane of cholinergic terminals of motor neurons, which facilitates the binding of the toxin to the target cell. The light chain, possessing zinc-dependent protease activity, destroys synaptosomal associated protein 25 (SNAP-25) in the cytoplasm of neurons. This prevents the exocytosis of acetylcholine, which makes it impossible to release it into the synaptic cleft and disrupts neuromuscular transmission [23, 24].

Bacteria produce botulinum neurotoxins in the form of complexes. Their structure contains a non-toxic polypeptide precursor of the neurotoxin, as well as a set of accompanying proteins that do not exhibit a toxic effect. [15, 23]. Endopeptidases break the polypeptide chain, forming a light (50 kDa) and heavy (100 kDa) chains, which are linked by a disulfide bond (Figure 2). Thus, the active toxin is created as a result of changes that occur with the protein after its synthesis (post-translational modifications) [24].

Modern biotechnological modifications have made it possible to create recombinant forms of the toxin with altered properties. Using site-directed mutagenesis, it was possible to obtain variants with a controlled duration of action and an extended temperature range of stability. These achievements have opened up new prospects for the treatment of diseases requiring long-term modulation of neuromuscular activity, such as spasticity in cerebral palsy or post-traumatic muscle contracture [33, 34].

Conclusion. Modern studies of muscular dystonias, despite the identification of 25 genetic loci (*DYT1–DYT25*), have revealed their significant heterogeneity, which limits the effectiveness of therapy. Symptomatic treatment, including botulinum therapy, deep brain stimulation and MRgFUS, demonstrates success mainly in focal forms, but the lack of etiotropic methods and the resistance of some patients require a deeper understanding of the molecular mechanisms (the role of torsin A, SNARE complexes) and the introduction of genetically oriented approaches (CRISPR, AI). The integration of neurology, genetics and biotechnology will be the key to the transition from palliative care to targeted correction of pathogenesis, especially given the high prevalence and disabling nature of the disease.

The authors declare no conflict of interest in the submitted article.

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