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HISTOLOGICAL PREPARATIONS IN THE PREVENTION OF DYSTONIA

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Annotation: This article analyzes the role and effectiveness of histological (histological) preparations used in the prevention of dystonia. The diagnostic and prophylactic value of these preparations in reducing neuromuscular dysfunctions and detecting pathological changes in the central nervous system at an early stage is highlighted. Also, the possibilities of histological methods in assessing morphological changes in muscle fibers and nerve cells in the pathogenesis of dystonia are considered on a scientific basis. The results of the study serve to improve strategies for the early detection and prevention of dystonia.

Abstract: This article analyzes the role and effectiveness of histological (histological) drugs used in the prevention of dystonia. The diagnostic and prophylactic value of these drugs in reducing neuromuscular dysfunctions and detecting pathological changes in the central nervous system at an early stage is highlighted. Also, the possibilities of histological methods in assessing morphological changes in muscle fibers and nerve cells in the pathogenesis of dystonia are scientifically considered. The results of the study serve to improve strategies for early detection and prevention of dystonia.

Keywords: *Neurohistology, muscle tissue morphology, neuronal plasticity, synaptic transmission, histological preparations, immunohistochemistry, hematoxylin-eosin staining (H&E staining), nerve fiber degeneration, neurotransmitters*

(acetylcholine, dopamine), glial cell activity, microcirculation disorders, tissue regeneration, dystrophic changes in muscle fibers, morphometric analysis, biomarkers (histological indicators), neurohumoral system, cell nucleus and cytoplasmic structures, histochemical reactions, preventive histological monitoring Dystonia is a heterogeneous disease with many causes, diverse clinical manifestations, and varying responses to treatment.

Although significant progress has been made in understanding this condition, disease-modifying (i.e., pathogenesis-directed) therapies are not yet available for most types of dystonia. However, with the introduction of techniques such as botulinum toxin (BoNT) and deep brain stimulation (DBS), there has been significant progress in the symptomatic treatment of dystonia. Treatment of dystonia requires an individualized approach for each patient. Treatment options are selected based on the patient's age, the anatomical distribution of dystonic symptoms, and the risk of side effects. The goal is to correct abnormal movements and postures, reduce pain, and manage comorbid conditions such as mood disorders, contractures, and orthopedic complications. In recent years, the scientific evidence base for dystonia therapy, particularly deep brain stimulation and neurotoxins, has been expanding. However, in some areas, there is still a lack of fully controlled and well-designed clinical trials. One of the main problems in this regard is that clinical scales cannot fully reflect the true functional changes in some types of dystonia and that dystonia forms are very diverse in etiology and clinical manifestations. Many studies have been conducted without control groups, with short follow-up periods and with small sample sizes, which limits the reliability of the results. In this review, we review the pathogenesis-oriented therapies used in some types of dystonia and describe the methods of treating dystonia with symptomatic drugs. We also review the current status of botulinum toxin (BoNT) therapy, which has revolutionized the treatment of dystonia since its introduction into clinical practice in the late 1980s. We also review the evidence from studies on ablative surgery and deep brain stimulation (DBS), as advances in functional stereotactic neurosurgery over the past three decades have significantly expanded the options for

treating dystonia. Finally, we review the evidence for other therapeutic approaches, such as rehabilitation paradigms and noninvasive stimulation techniques. Pathogenesis-directed therapies. Mechanism-based therapies that can modify the course of the disease and improve outcomes are currently available only for a few rare inherited neurological diseases that occur in children. Movement disorders, particularly complex dystonia, are common in these diseases. The two best-studied examples are dopa-responsive dystonia (DRD) and Wilson disease. Because these diseases are so rare, evidence for their treatment comes mainly from small studies, often single-center, unblinded, and nonrandomized. For example, levodopa has become the standard of care in DRD, although it is not approved by regulatory authorities. Treatment recommendations are largely based on expert consensus and good clinical practice. In many of these diseases, early diagnosis and treatment are crucial to prevent disease progression and permanent neurological damage. A 2018 review by Jinnah et al. provides a detailed overview of many of these disorders, along with their treatment options, including enzyme replacement therapy, dietary changes, and other targeted therapies.

While detailed treatment algorithms for these disorders are not provided in this article, a brief overview of the most common disorders presenting with dystonia is provided. Below, we briefly review Wilson's disease and dopa-responsive dystonia (DRD). Dopa-responsive dystonia (DRD) is the best example of a targeted (pathogenesis-directed) therapy for dystonia. DRD encompasses several clinically and genetically heterogeneous conditions that are caused by various disorders of dopamine biosynthesis. These conditions typically present with progressive dystonia, parkinsonism, and spasticity, with onset in childhood or early adolescence, and respond remarkably well to levodopa treatment . One form of DRD, Segawa disease, is associated with a deficiency of the enzyme GTP-cyclohydrolase I (GTP-CH-I), which is caused by autosomal dominant or recessive mutations in the GCH1 gene. The second form is characterized by sepiapterin reductase deficiency, in which autosomal recessive mutations in the SPR gene impair the biosynthesis of tetrahydrobiopterin (BH_4). BH_4

is an essential cofactor for the enzymes tryptophan hydroxylase and phenylalanine hydroxylase [23]. The third form is associated with a deficiency of tyrosine hydroxylase (TH), which is caused by autosomal recessive mutations in the TH gene, which impair the initial and rate-limiting step of dopamine synthesis. In addition, 6-pyruvoyl-tetrahydropeptoridine (PTP) synthase (encoded by the PTS gene) and dihydropteridine reductase (DHPR) (encoded by the QDPR gene) are also involved in the synthesis and regeneration of BH_4; their rare deficiency causes the DRD phenotype, in which neurological symptoms other than dystonia are also observed. Aromatic L-amino acid decarboxylase (AADC) is the final enzyme in the biosynthesis of dopamine and serotonin, and its deficiency leads to a rare autosomal recessive neurometabolic disorder characterized by a combined deficiency of serotonin, dopamine, norepinephrine, and epinephrine; this condition manifests as generalized dystonia in childhood. Treatment and clinical outcomes: If treatment is started early, the combination of levodopa and peripheral decarboxylase inhibitors (in some cases in combination with BH_4) can prevent the onset and progression of DRD-like symptoms. Patients with autosomal dominant GTP-CH-I deficiency usually have a very good and long-lasting response to low doses of levodopa, with little or no “levodopa-induced dyskinesia” or “levodopa-induced dyskinesia.” Patients with autosomal recessive or compound heterozygous GTP-CH-I deficiency often require higher doses, but have a stable and adequate clinical response. These patients may require additional treatment with BH_4 and 5-hydroxytryptophan (5-HT). Despite significant improvement with levodopa, patients with autosomal dominant GTP-CH-I deficiency may still have residual symptoms. In these cases, additional treatments such as anticholinergic drugs, dopamine agonists, botulinum toxin injections, or even deep brain stimulation (DBS) are used. Patients with tyrosine hydroxylase and sepiapterin reductase deficiencies may also respond to levodopa, but the response is likely to be delayed or incomplete. Levodopa-induced dyskinesia is particularly common in TH deficiency. The mechanism of dyskinesia in DRD is unclear, but it is not thought to be related to neuronal degeneration or striatal denervation (in this respect, it differs from Parkinson's

disease). Patients with PTP synthase deficiency have a significant and sustained positive response to levodopa, although this treatment is usually given in combination with BH_4 and 5-HT. These patients also have other neurological symptoms, such as seizures, spasticity, and cognitive deficits, in childhood. Motor outcomes are generally worse in TH, PTP synthase, DHPR, and autosomal recessive GTP-CH-I deficiencies than in sepiapterin or autosomal dominant GTP-CH-I deficiencies. The most widely used treatment for patients with AADC deficiency is a combination of dopamine agonists and monoamine oxidase inhibitors (MAOIs); levodopa is rarely used. The success rate of treatment for these patients is generally very low, but in recent years there has been promising results in the direction of gene therapy. Interestingly, there is evidence that some AADC gene variants affect levodopa binding sites, which may make them more responsive to treatment. Wilson's disease is caused by autosomal recessive pathogenic variants in the ATP7B gene. This gene encodes a copper-transporting P-type ATPase protein. The disease is often accompanied by various movement disorders, including dystonia. The main goal of Wilson's disease treatment is to eliminate excess copper in the body and reduce its absorption from the intestine. The following methods are used for this: Copper chelating drugs (penicillamine, trientine, or tetrathiomolybdate), Zinc preparations - they reduce the absorption of copper in the intestine, Following a low-copper diet. Early diagnosis and treatment are important in preventing neurological damage. Intravenous disodium calcium edetate (EDTA) is also used to chelate heavy metals. This method is used in hereditary manganese transport diseases (i.e., hypermanganemic dystonia 1 and 2). These conditions are associated with defects in the SLC30A10 and SLC39A14 genes, respectively, and are characterized by progressive complex dystonia. Top of form Dopaminergic and antidopaminergic drugs: In addition to dopa-responsive dystonia (DRD), levodopa and other dopaminergic drugs are used symptomatically in other forms of dystonia, including acquired dystonia, myoclonus–dystonia, and rapidly progressive dystonia–parkinsonism (RPD). However, the mechanism of action of levodopa in conditions other than DRD is not fully understood, and the response rate

is usually much lower. Myoclonus–dystonia: This condition is characterized by dystonia and myoclonus with an early onset and is characterized by alcohol sensitivity (i.e., temporary relief of symptoms). Most cases are associated with mutations in the epsilon-sarcoglycan gene (SCGE). This condition has been reported to have a stable and positive response to levodopa, but effective treatment usually includes other drugs such as benzodiazepines, valproate, levetiracetam, L-5-hydroxytryptophan, and, rarely, sodium oxybate. Significant clinical improvement has also been reported with deep brain stimulation (DBS). Rapidly progressive dystonia–parkinsonism (RDP, DYT12) RDP is a disease characterized by rapidly progressive focal, segmental, or hemicorpus dystonia, primarily affecting the head and neck and upper arms. The disease is caused by defects in the Na^+/K^+-ATPase α3 gene, ATP1A3. Defects in the ATP1A3 gene have a wide phenotypic spectrum and can manifest with bulbar symptoms, parkinsonism, epilepsy, alternating hemiplegia, and psychiatric disorders. Most patients do not respond or respond minimally to levodopa, with very few exceptions. Side effects of levodopa include nausea, vomiting, orthostatic hypotension, and psychosis. First-generation dopamine agonists: For example, drugs such as apomorphine, bromocriptine, and lisuride are currently rarely used in practice, but small clinical trials have shown positive results. Recent studies in animal models suggest that enhancing dopamine neurotransmission by co-activating D1 and D2 receptors may be a promising approach for the treatment of dystonia. Antidopaminergic agents: In the past, dopamine receptor blocking drugs were widely used in the treatment of dystonia. However, their efficacy is currently questionable and their use is not recommended due to the high risk of side effects, including tardive dyskinesia (i.e., late-onset movement disorders). One exception is clozapine, which is a D4 receptor antagonist but has relatively little effect on D2 receptors. Therefore, it is considered to have a low risk of inducing parkinsonism or tardive dyskinesia. Regular blood monitoring is required in patients taking clozapine due to the risk of agranulocytosis, but it has been shown to be effective in reducing symptoms of tardive dyskinesia. VMAT-2 inhibitors for tardive dystonia. The approach to the treatment of tardive dyskinesia has changed dramatically with the

introduction and widespread use of vesicular monoamine transporter-2 (VMAT-2) inhibitors. Tetrabenazine (TBZ) was first used in the 1970s to treat dystonia and other hyperkinetic movement disorders. Currently, TBZ is rarely used as a first-line treatment for dystonia, mainly in tardive formsAvailable in the United States since 2008, TBZ is FDA-approved only for the treatment of Huntington's chorea, but its use in tardive dystonia is considered off-label. Small clinical observations and trials have shown that TBZ has a positive effect in cases of tardive dystonia. Reserpine, which has a similar effect, was previously used to treat tardive syndromes, but is currently not used in the United States due to its high risk of hypotension and depression. Two new VMAT-2 inhibitors, deutetrabenazine and valbenazine, have been developed in recent years. They have improved pharmacodynamic and pharmacokinetic properties compared to TBZ. Both drugs have shown efficacy in double-blind, randomized, placebo-controlled clinical trials (DBRPCTs) and were approved by the FDA for the treatment of tardive dyskinesia in 2017. Deutetrabenazine is a deuterated form of TBZ and has been evaluated in 2 DBRPCTs and 1 open-label study. Valbenazine is a highly selective reversible VMAT-2 inhibitor consisting of three oxidative metabolites of TBZ and has been evaluated in 4 DBRPCTs and 1 open-label study. Overall, the trials of these two drugs have included more than 1000 patients, including those with tardive dystonia. This is the largest controlled clinical trial to date in tardive hyperkinetic movement disorders. A recent meta-analysis, summarizing the results of all DBRPCTs, confirmed the efficacy of VMAT-2 inhibitors and showed no increased risk of adverse events compared to placebo. However, no clinical trials have yet been conducted directly comparing VMAT-2 inhibitors with other drugs. An open-label trial is currently underway to evaluate the efficacy of deutetrabenazine in dystonia. Anticholinergic drugs: These drugs are among the most effective pharmacological agents in the treatment of dystonia. They are mainly used to treat generalized dystonia, but they are also useful in other types. The most commonly prescribed anticholinergic drug is trihexyphenidyl, but benztropine, ethopropazine, procyclidine, and biperiden have also been used in clinical practice. Diphenhydramine is an H1-type histamine

receptor antagonist that has shown antidystonic effects in small trials due to its anticholinergic properties. The efficacy of anticholinergic drugs is explained by the mechanism of reducing the hyperactivity of cholinergic interneurons in the striatum.

Conclusion: Dystonia is a very heterogeneous group of disorders in terms of etiology, clinical manifestations, and response to treatment. Although disease-modifying (pathogenesis-directed) therapies are somewhat limited in most cases, significant progress has been made in the area of symptomatic treatment. In particular, in the management of tardive dystonia and tardive dyskinesia, VMAT-2 inhibitors (deutetrabenazine and valbenazine) have made clinically important changes, and large randomized trials and meta-analyses have confirmed their efficacy; therefore, these drug classes occupy a central place in modern practice. Anticholinergic drugs (especially trihexyphenidyl) can be effective in high doses in generalized and some other types of dystonia, especially in children, where efficacy and tolerability have been shown to be better than in adults; however, central and peripheral antimuscarinic side effects limit high doses, so gradual titration and careful monitoring are required. Baclofen (oral) and intrathecal baclofen (ITB) may be useful in severe, refractory segmental/generalized dystonia with spasticity. Published series regarding ITB indicate long-term benefit in a significant proportion of patients, but there are also procedural and device complications. Tetrabenazine (TBZ) has been used as a traditional VMAT-2 inhibitor since the 1970s; in the US, TBZ was approved by the FDA in 2008 for chorea associated with Huntington's disease, but its use for tardive dystonia is often considered off-label. Newer-generation VMAT-2 inhibitors have improved pharmacokinetic and safety profiles and are preferred in clinical practice. In general, dystonia therapy should be individualized, taking into account the patient's age, clinical presentation, etiology, and risk of side effects. Because many therapeutic studies have been small, uncontrolled, or short-term, additional well-designed randomized trials, long-term follow-up, and subtype-specific functional assessment tools are needed in dystonia.

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