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REVIEW

Adult-onset Isolated Focal Dystonia: A Comprehensive Review of the Literature

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Abstract

Dystonia is a rare movement disorder, defined by intermittent or sustained involuntary movements and/or postures. The term can refer both to a clinical syndrome and to a group of primary movement disorders in which dystonia represents the predominant manifestation. Adult-onset isolated focal dystonia is the most common form. The aim of this narrative review is to present the current understanding of adult-onset isolated focal dystonia, focusing on its recently revised classification, pathogenesis, and therapeutic approaches. The updated classification system emphasize a two-axis framework integrating clinical features and aetiology, therefore facilitating improved phenotypic characterization and differential diagnosis.

The underlying pathophysiological mechanisms of isolated focal dystonia remain incompletely understood, both genetic and environmental factors playing a role. Contemporary models conceptualise dystonia as a network disorder involving the striato–thalamo–cortical and cerebellar circuitry, with evidence supporting impaired inhibitory control, abnormal sensorimotor integration, and maladaptive neuroplasticity.

The treatment remains largely symptomatic, with botulinum toxin representing first-line therapy, although its efficacy may be limited in some cases.

Key words: blepharospasm, cervical dystonia, isolated focal dystonia, genetic

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INTRODUCTION

The term "dystonia" refers both to a clinical syndrome and to a group of primary movement disorders in which dystonia represents the predominant manifestation. From a clinical perspective, dystonia is a movement disorder characterised by intermittent or sustained involuntary movements and/or postures, usually patterned and repetitive, and frequently associated with motor overflow. It can be initiated or worsened by voluntary movements and sometimes is responsive to alleviating manoeuvres (i.e., sensory tricks or "geste antagoniste")[1].

Isolated dystonia is a clinical entity in which dystonia is the only manifestation. It can be either idiopathic or genetic[2]. It is considered a rare disorder, with an estimated prevalence of around 30 cases per 100,000 individuals[3]. Focal dystonia involves a single body region. The three most common forms of adult-onset isolated focal dystonia are cervical dystonia, blepharospasm and a particular task-specific dystonia, namely the writer's cramp[4].

The aim of this narrative review is to discuss the complexity of adult-onset isolated focal dystonia, focusing on its recently revised classification, pathogenesis, and therapeutic approaches.

CLASSIFICATION

Given the broad clinical spectrum of dystonia, multiple approaches to its classification have been proposed. In 2013, Albanese et. al. introduced the classification of dystonia on two axes: clinical characteristics (axis I) and aetiology (axis II)[5]. Subsequently, in 2025, Albanese et. al. revised and updated the classification, retaining the two-axis structure but introducing further clarifications[1] .

As mentioned above, **axis I** refers to the clinical characteristics of dystonia. It includes data emerging from the medical history and clinical examination: age at onset, family history, body distribution, temporal dimension, phenomenology and associated features[1]. The age at onset subdivision contains five groups: infancy (<= 2 years), childhood (2-12 years), adolescence (12-20 years), early adulthood (20-40 years) and late adulthood (>40 years), and can provide insight about the aetiology, prognostic factors and management[1,5]. Regarding the family history, dystonia can be classified as sporadic (in the absence of other affected relatives), familial (X-linked, autosomal dominant, autosomal recessive, or mitochondrial), or of uncertain transmission[1]. The body distribution subdivision refers to the body regions affected by dystonia: focal, segmental, multifocal or generalized[1,5]. Focal dystonia involves a single body region. It includes cervical dystonia (abnormal postures and movements of the head and neck, sometimes including the shoulders), blepharospasm (involuntary contractions of the orbicularis oculi), and the writer's cramp (a task-specific dystonia, triggered by writing)[1,4]. Segmental dystonia involves two or three contiguous body regions[1]. A representative example is Meige syndrome, characterized by blepharospasm and oromandibular dystonia involving the upper and lower face[1]. Multifocal dystonia involves noncontiguous body regions – e.g., bicrural or bibrachial dystonia[1]. Hemidystonia refers to involvement of multiple body regions on one side of the body and is typically associated with a structural brain lesion in the contralateral hemisphere[5]. The latest consensus defines generalised dystonia as „a pattern of distribution that goes beyond segmental and multifocal, and does not qualify for hemidystonia"[1]. It usually involves the trunk and two additional body regions, or at least three limbs[1]. The temporal dimension includes three main characteristics: onset of dystonia, disease course, and variability[1]. The onset refers to the time frame in which maximum symptom severity was reached: acute (minutes or hours), which may suggest a psychogenic aetiology or medication exposure (neuroleptics), subacute (days or weeks), possibly indicative of an underlying autoimmune process, or progressive (months or years), representing the most common course among people with adult-onset focal dystonia[1]. The disease course can be static (no progression over the years), progressive (worsening of signs and symptoms), or fluctuating (severity and distribution vary over time) [1]. The last characteristic of this section, variability, was introduced in the latest consensus and refers to short-lasting changes in intensity and phenomenology[1]. It can be either paroxysmal or diurnal[1]. The phenomenology refers to the relationship between dystonia and voluntary movements. Dystonia may be triggered by a specific motor activity („task-specific"), as in the case of writer's cramp, or induced by any voluntary movement involving the affected regions („action dystonia"), can persist at rest, or can be fixed, without significant improvement on passive movement[1]. Regarding additional characteristics, dystonic movements can be tremulous (rhythmic, repetitive oscillations, usually evoked by attempting to

overcome the abnormal contraction) or jerky (irregular oscillations, with a broader range, resembling myoclonic movements) [1,6]. Another characteristic is the presence of alleviating manoeuvres, also known as sensory tricks (or "geste antagoniste"), which can temporarily reduce the symptoms (e.g., slightly touching the chin can improve the cervical dystonia). These sensory tricks are most frequently observed in cervical dystonia, being present in up to 90% of cases, and serving as a supportive diagnostic criterion[1,7]. The associated feature section classifies dystonia as isolated, when no other neurological features are present, or combined, when dystonia is associated with other movement disorders (such as myoclonus or parkinsonism), additional neurological features (such as pyramidal syndrome or epileptic seizures) or systemic features (such as in Wilson's disease)[1].

Axis II of the classification includes the aetiology and pathogenesis of dystonia. It is divided into four subcategories: genetic, acquired, neuroanatomical and pathogenesis[1]. The well-established patterns of genetic inheritance are autosomal dominant (e.g., DYT1, DYT11 - myoclonus dystonia syndrome), autosomal recessive (i.e., Wilson's disease, PARK2 - juvenile Parkinson's disease), X-linked (DYT3 - Lubag syndrome, Lesch-Nyhan syndrome), and mitochondrial/maternal transmission (Leber optic atrophy and dystonia)[1,5]. Acquired dystonia can result from exposure to certain medications (levodopa or dopamine agonists, neuroleptics), toxins (manganese, cobalt, etc.), trauma (perinatal brain injury – cerebral palsy, neurosurgery) and other causes (vascular, neoplastic)[5]. Genetic and acquired aetiologies are not always mutually exclusive, as an underlying genetic predisposition may be triggered or modulated by environmental factors[1,5]. The neuroanatomical subgroup focuses on the specific type of anatomical dysfunction, which may include focal, multifocal or diffuse lesions, as assessed by neuroimaging, electrophysiological and neuropathological studies. However, in most cases, no structural abnormality is found[1]. The pathogenesis section focuses on the mechanism of the dystonia, namely developmental, degenerative, metabolic, or autoimmune/inflammatory[1].

DIFFERENTIAL DIAGNOSIS

Cervical dystonia, blepharospasm and writer's cramp are the most common forms of focal dystonia[4]. They typically have an insidious onset in late adulthood, are most often sporadic, and tend to progress over time, sometimes spreading to adjacent body regions[7]. When evaluating a patient presenting with clinical manifestations suggestive of dystonia, the broad spectrum of dystonia mimics must be considered[8].

The proposed definition for dystonia mimics (previously referred to as "pseudodystonia") is: "*abnormal postures, repetitive movements, or both, in which results of clinical, imaging, laboratory or electrophysiological investigations provide definite explanation of symptoms which is not compatible with dystonia*"[1,8].

Dystonia mimics are classified based on their pathogenesis: musculoskeletal-related disorders, impairment of sensory pathways, impairment of motor pathways and compensatory postures[8]. Psychogenic dystonia is also considered a dystonia mimic by the latest consensus[1].

Table 1. Differential diagnosis of dystonia[8].

Facial dystonia *(blepharospasm, oromandibular dystonia)*	Tics Hemifacial spasm (tonic component) Ptosis Dermatochalasia Myotonia Tetanic spasms Hypoglossal nerve damage
Cervical dystonia (head tilt)	Klippel-Feil syndrome Congenital muscular torticollis Atlanto-axial subluxation Sandifer syndrome Trochlear/abducens nerve palsy ("ocular torticollis") Space-occupying lesion in the posterior fossa Sternocleidomastoid injuries Upper spinal cord syringomyelia Dropped head syndrome in neuromuscular disease
Limb dystonia *(posturing)*	Contracture, spasticity, rigidity Trigger finger Neuropathy Dupuytren's contracture Myotonia or neuromyotonia Sensory ataxia and/or pseudoathetosis Stiff-person syndrome Tonic spasms (hypocalcaemia, hypomagnesaemia, alkalosis)

In some cases, the distinction between dystonia and dystonia mimics can be challenging. Red-flags include: 1) additional neurological signs respecting the same body distribution; 2) fixed postures which can be present at rest and during action, while characteristic abnormal postures of dystonia are usually action-induced and associated with overflow movements; 3) absence of alleviating maneuvers; 4) acute onset, rarely

seen in dystonia (apart from rapid onset dystonia-parkinsonism and dopaminergic blocking agents-induced dystonia); 5) pain is a more prominent clinical feature of dystonia mimics, although patients with several forms of dystonia also experience pain[8].

The differential diagnosis of dystonia is summarised in Table 1.

GENETICS OF ADULT-ONSET ISOLATED DYSTONIA

Adult-onset isolated focal dystonia encompasses various clinical phenotypes, the most common presentations being cervical dystonia, blepharospasm and writer's cramp[4]. Its etiology is complex and only partially understood, both genetic and environmental factors playing a role[9].

The relevance of genetic factors (i.e., pathogenic variants/mutations) in the pathogenesis of dystonia is increasingly acknowledged, particularly in monogenic familial forms, inherited through autosomal dominant, recessive, or X-linked patterns[10]. Over the past decade, major advances in molecular genetics have led to the discovery of numerous causative genes and biological pathways, including the endoplasmic reticulum stress response (e.g., EIF2AK2, PRKRA, TOR1A), calcium homeostasis (e.g., ANO3, HPCA), striatal dopamine signalling (e.g., GNAL), autophagy (e.g., VPS16), and gene transcription during neurodevelopment (e.g., KMT2B, THAP1)[10].

The genetic aspects of generalised childhood-onset dystonia have been extensively studied and are well documented. Yet, the underlying genetic predisposition of adult-onset isolated focal dystonia, by far the most common clinical form of dystonia, still lacks sufficient evidence – see Table 2 for the most robust associations. The transmission pattern, however, seems to be compatible with autosomal dominant inheritance, with a significantly lower penetrance for late-onset dystonia, of about 20%, compared to early-onset dystonia, where the penetrance is as high as 60%[2].

So far, 52 dystonia-associated genes have been identified, including 33 genes for dystonia associated with other neurological or systemic diseases, 10 genes linked to combined dystonia, and 9 genes linked to isolated dystonia[11].The list of unconfirmed dystonia candidate genes is still expanding due to ongoing sequencing efforts, bringing the total number of putative dystonia-linked genes to over 400[12].

The genes most consistently associated with isolated dystonia are THAP1, GNAL, TOR1A, and ANO3, but also KMT2B and VPS16. More genes are linked to combined forms, including PARK2, ATP1A3, and SCGE[11].

Based on the traditional DYT nomenclature, Camargos and Cardoso proposed a model of the "dystonia cell" that links dystonic genes to the functions of the proteins they encode. The causal gene is prioritised over the locus symbols in this new nomenclature, which strictly links the prefix to the predominant phenotype (e.g., DYT 1 is now designated DYT-TOR1A). When dystonia is co-dominant with another movement disorder, a dual prefix is used (e.g., DYT/PARK-ATP1A3)[11].

Generalized forms of isolated dystonia often involve DYT-TOR1A, DYT-THAP1, DYT-KMT2B, DYT-HPCA, or DYT-PRKRA. Lower-limb onset with secondary generalization is characteristic of DYT-TOR1A, DYT-HPCA, and DYT-KMT2B, while focal upper-limb onset is sometimes observed in DYT-THAP1. In contrast, DYT-GNAL and DYT-ANO3 are more likely to produce focal and segmental forms, making them core contributors to adult-onset focal dystonia[10].

One of the most extensively studied genes is TOR1A, frequently associated with early-onset generalized dystonia. However, DYT1 - TOR1A has also been implicated in focal adult-onset forms, such as writer's cramp[13].

Another key gene for dystonia is THAP, which is also predominantly associated with early-onset generalized dystonia. DYT-THAP1-associated dystonia may start in the upper body, initially affecting the upper limbs and the cranio-cervical region, with subsequent generalizations[14].

Guanine nucleotide-binding protein alpha-activating activity polypeptide (GNAL) encodes a G-protein alpha subunit, which is responsible for striatal dopamine signalling. Mutations in this gene are specifically associated with cranial or cervical adult-onset focal dystonia[15].

Alterations in lysine-specific methyltransferase 2B (KMT2B), which plays an important role in neurodevelopment, are associated with childhood-onset dystonia. This type of dystonia is distinguished by its progressive nature, usually beginning with focal dystonia in the lower limbs and progressing to generalized dystonia, with notable involvement of the larynx, cranial, and cervical regions[14].

ANO3 mutation, with an autosomal-dominant inheritance, is responsible for variable phenotypes of dystonia, most frequently manifesting as adult-onset tremulous cervical dystonia, even though childhood-onset variants have also been identified[12]. TUBB4A mutations usually result in laryngeal or cervical dystonia[16,17].

Some of the emerging candidate genes for dystonia include: KIF1A (identified mostly in spastic paraplegia), CACNA1A (frequently linked to epileptic encephalopathy, cerebellar ataxia, and episodic ataxia, generalised dystonia), NR4A2 (associated with developmental delay and levodopa-responsive dystonia) [11,18]. Notably, in one of our studies we found an association between adult-onset isolated focal dystonia and a disease-causing mutation in the CACNA1B gene[19].

Table 2. Genes associated with adult-onset isolated focal dystonia[12-17,20].

Gene	Role of the gene	Distribution of dystonia
TOR1A	Encodes TorsinA, a member of the ATPase family	Writer's Cramp
THAP1	Encodes a transcription factor involved in neurodevelopmental processes	Upper limb Cervical
KMT2B	Neurodevelopment	Lower limb focal
GNAL	Striatal dopamine signaling	Cranial Cervical
ANO3	Encodes calcium-activated chloride channel	Cervical
TUBB4A	Neurodevelopment	Laryngeal Cervical

ENVIRONMENTAL FACTORS IN ADULT-ONSET ISOLATED FOCAL DYSTONIA

Although most patients with adult-onset isolated dystonia have no known genetic abnormalities, familial aggregation suggests that hereditary factors may partially influence the disease development[2]. Whether environmental factors may play a role in reaching the threshold for disease manifestation is still under debate, particularly given that some mutation carriers remain asymptomatic, while others develop focal dystonia.

Peripheral injury and occupational exposures

Peripheral injury and occupational or task-specific exposure have been found as potential environmental triggers in many studies, supporting the theory that genetic predisposition may result in increased susceptibility to environmental factors that trigger the onset of dystonia[2]. A minor peripheral injury (e.g., by accident, surgery or chronic local diseases), as well as repetitive movements (writing, playing an instrument) or local pain, could increase the risk of developing topographically related focal dystonia[2,21]. An association between cervical dystonia and prior cervical trauma has been reported, the onset of the dystonia occurring approximately 2 to12 months after the trauma[2,22]. Using functional neuroimaging studies, a hyperactivation of the cerebellar dentate nucleus was observed, which may reflect a maladaptive neuroplasticity of cerebellar circuits[2,22].

Repetitive motor actions, such as writing, may trigger task-specific dystonia, of which writer's cramp is the most common presentation. Some studies have shown that prolonged daily writing (more than 3 hours per day, every day), and more specifically, an increase in writing time during the year preceding the onset of symptoms, may represent important triggers for writer's cramp in many patients. The same theory has been proposed in musicians as well[2]. The underlying mechanism could be explained by a possible decrease of GABAergic inhibition in the primary motor cortex, causing an abnormal sensorimotor integration, another key mechanism in the pathogenesis of dystonia[21].

Psychiatric disorders, lifestyle and stressful events

Although many dystonia patients exhibit psychiatric symptoms, such as depression, anxiety, and obsessive-compulsive traits, these are considered nonmotor features of dystonia, rather than triggers of disease onset[2]. Available evidence does not support an association between the onset of dystonia and prior psychiatric disorders or stressful life events[2]. Controversial correlations were found between caffeine and nicotine consumption and dystonia, showing that caffeine intake and cigarette-smoking may exert a protective effect against the development of blepharospasm. Nevertheless, the underlying mechanisms are not fully understood, and these hypotheses needs to be further studied[2,21].

RELEVANT NEUROCIRCUITRY AND THE PATHOGENESIS OF ADULT-ONSET ISOLATED FOCAL DYSTONIA

Initially, the pathogenesis of adult-onset focal dystonia was thought to be exclusively related to basal ganglia

dysfunction, given that strategic lesions in the basal ganglia could cause contralateral dystonia (secondary dystonia)[10]. In contrast, idiopathic dystonia was, for decades, considered a psychiatric condition, mainly because conventional neuroimaging studies were unable to identify a specific structural lesion[10]. More recently, dystonia is viewed as a network disorder rather than a single anatomical structure dysfunction. Current models propose a distributed network model encompassing impaired inhibitory control, abnormal sensorimotor integration and neuroplasticity[23]. Key aspects of the pathogenesis of adult-onset isolated dystonia include dopaminergic and GABAergic neurotransmission, and potentially the cerebellum[10,24].

Basal ganglia dysfunction

Earlier studies focused primarily on secondary dystonia, for which an organic basis could be identified. Using the neuroimaging studies available at the time (mostly computed tomography), investigators identified lesions involving the caudate nucleus, lentiform nucleus and thalamus, often in combination, responsible for secondary hemidystonia or isolated limb dystonia[25,26].

Subsequent research on idiopathic dystonia led to the hypothesis that this disorder arises from abnormal basal ganglia circuitry, consisting mainly of an imbalance between the activation of the direct and indirect pathways[23,24]. The direct pathway reduces the activity of globus pallidus internus (GPi), thereby facilitating voluntary movements. In contrast, the indirect pathway increases the GPi inhibitory output, thereby suppressing voluntary movements. It was initially hypothesized that dystonia results from an overactivation of the direct pathway and a decreased activation of the indirect pathway, leading to thalamic disinhibition and, consequently, increased cortical excitability[24]. This theory was further refined to emphasize a disruption in the precise temporal and spatial pattern regulation of these pathways for agonist and antagonist muscles, which is necessary for normal movement execution[24]. Modern neuroimaging studies have highlighted abnormal findings in multiple regions, including the cerebral cortex, thalamus, cerebellum, midbrain and brainstem in patients with dystonia, suggesting this disorder cannot be exclusively attributed to basal ganglia dysfunction, therefore enforcing the network dysfunction theory (possibly involving a basal ganglia-cerebello-thalamo-cortical circuit)[23].

Loss of inhibition

As previously mentioned, dystonia may arise from abnormal co-contraction of agonist and antagonist muscles. In addition to excessive contraction of the primary involved muscle, this phenomenon implies overflow contraction of adjacent, sometimes antagonistic, muscles, potentially related to deficient reciprocal inhibition within the spinal cord circuitry[23]. Alongside basal ganglia dysfunction leading to loss of cortical inhibition, accumulating evidence suggests that the cerebellum plays an important role in modulating cortical excitability[27]. It has been proposed that changes in cortical excitability induced by repetitive somatosensory stimulation could be modulated by the cerebellum. However, there is currently insufficient evidence to determine whether the loss of inhibition in dystonia specifically is linked to the basal ganglia and/or the cerebellum[23].

Maladaptive neuroplasticity

Neuroplasticity refers to the brain's capacity to reorganize and remodel neural connections in response to multiple internal, as well as external, stimuli. Although this remarkable adaptive characteristic underlies learning and functional recovery, maladaptive neuroplasticity may contribute to a range of pathological states, such as addiction, psychiatric conditions, chronic pain and movement disorders. The mechanisms underlying this dual role remain incompletely understood[28]. In this regard, it was proposed that abnormal muscle contraction patterns could be incorporated as learned actions through a maladaptive process, leading to dystonia. Several studies, conducted both in mice and in humans, have demonstrated alterations in long-term potentiation (LTP) and long-term depression (LTD) of corticospinal projections, along with impaired synaptic depotentiation, suggesting reduced reversibility of the neuroplastic changes[24]. Interestingly, these changes in neuroplasticity could be reversed by deep-brain stimulation of the GPi[24].

Cerebellar involvement

The cerebellum plays a crucial role in motor learning, coordination, muscle tone regulation and sensory integration, contributing to the complexity of the motor circuit, along with the basal ganglia, thalamus and cerebral cortex[24].

It is well established that the cerebellum has both direct and indirect connections with the basal ganglia, thereby providing feedback and modulating motor

processing within these circuits. Purkinje cells, which are GABAergic inhibitory neurons located in the cerebellar cortex, represent the sole output of the cerebellar cortex to the deep cerebellar nuclei[29]. Consequently, abnormal function of these cells could impair excitability in the basal ganglia and cerebral cortex, supporting the "loss of inhibition" theory that we previously mentioned[23].

Several studies have investigated the cerebellar involvement in dystonia. In a neuropathological examination of post-mortem brain tissue from patients with cervical dystonia, one study reported scattered Purkinje cell loss along with axonal swelling[30]. Recent studies have explored the role of the cerebellum by using the eye-blink classical conditioning (EBCC) paradigm. EBCC is a learning process associated with the cerebellar cortex, in which an unconditioned stimulus of the eyeblink response is repeatedly associated with a conditioned stimulus, such as an auditory stimulus. After multiple associations, the conditioned stimulus will produce the blink response on its own[31]. Studies have shown that EBCC is significantly reduced in patients with idiopathic focal hand dystonia and cervical dystonia[24]. However, these findings have not been replicated in other forms of dystonia, suggesting that cerebellar involvement may vary across different dystonia phenotypes[24]. The cerebellum's crucial role in sensory processing further supports its involvement in the pathogenesis of dystonia[23].

Notably, several studies have reported promising outcomes with cerebellum deep brain stimulation (DBS) in patients with different dystonia phenotypes[29].

Sensorimotor integration

Patients with various forms of idiopathic focal dystonia exhibit altered spatial and temporal discrimination, as well as abnormal processing of sensory stimuli[23]. Neuroimaging studies using functional MRI (fMRI), as well as {^{18}F}-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET), have shown altered activation pattern across multiple areas, including primary sensorimotor cortex, medial and lateral premotor areas, parietal cortex, as well as basal ganglia, thalamus and cerebellum, some of them specifically identifying particularities in the somatotopy of somatosensory cortex in patients with dystonia[24,32]. Additionally, spatial and temporal discrimination (i.e., the ability to distinguish two stimuli as separate in space or time) is impaired in individuals with focal dystonia. This could help explain the beneficial effects of "geste antagoniste" or sensory tricks in some patients[24].

Another important aspect of sensorimotor integration concerns sensorimotor gating mechanisms. During voluntary movement, the initial input, or the expected sensory input, is reduced, allowing the motor system to adapt to unexpected stimuli that could otherwise affect the movement. In dystonia patients, electrophysiological studies have demonstrated that this gating mechanism is impaired or even abolished, potentially leading to a compensatory exacerbation of movement if initial sensory transmission is not adequately suppressed[24].

Dopaminergic neurotransmission

The involvement of dopaminergic transmission in the pathogenesis of dystonia is supported by the well-documented occurrence of dystonia as a side effect of dopamine receptor blockers. Moreover, dopa-responsive dystonia syndromes, usually attributed to genetic mutations involving genes responsible for dopamine synthesis (GCH1, TH, SPR), further highlight the importance of the dopaminergic pathways[24].

The imbalance between the direct and indirect pathways, discussed earlier, may be related to altered dopaminergic receptor availability, particularly an increase in D1 striatal receptors, concomitant with a decrease in D2 receptors in various forms of dystonia, including focal dystonia such as writer's cramp or cervical dystonia. Moreover, a drop-in phasic dopaminergic activity has been described in patients with focal hand dystonia and laryngeal spasm during symptomatic tasks, further emphasizing the complex disorganization of dopaminergic neurotransmission[32].

Another important aspect involves loss of inhibition of striatal cholinergic transmission due to decreased activity of D2 striatal receptors. This mechanism has been implicated in both dystonia and Parkinson's disease. Notably, anticholinergic agents remain one of the few symptomatic pharmacological treatments for dystonia[24].

THERAPEUTIC APPROACH

Currently, botulinum toxin (BT) injections represent the first-line therapy in focal dystonia. Several investigations can be used to localize the dystonic muscles and guide the BT administration, such as electromyography (EMG) (with or without electric stimulation) and ultrasound (US)[33,34]. A randomized clinical trial

on 40 idiopathic cervical dystonia patients found similar outcomes for US and EMG-guided injections[35]. However, BT injections have a relatively short duration of beneficial effects, implying repeated visits for injection administration[36].

Several pharmacological classes may be used as symptomatic therapies in dystonia - particularly when BT injections are not feasible or may result in functional impairment. A trial of levodopa should be considered in focal limb dystonia if dopamine-responsive dystonia cannot be excluded. Among pharmacological therapies, anticholinergics, primarily trihexyphenidyl, are considered first-line. The general principle in the medical treatment of dystonia is to "start low and go slow", with titrations every 3-4 days up to one week and dose decrements or association of new agents if adverse effects occur[37]. Notably, a prospective, randomized, double-blind controlled trial on 66 patients with idiopathic cervical dystonia found greater dystonia improvement and fewer side effects for BT injections compared to trihexyphenidyl[38].

Baclofen and benzodiazepines are generally used as second-line medications, but they have not been investigated in any controlled trials in dystonia so far[39]. Baclofen might be preferred for oromandibular dystonia, and clonazepam for blepharospasm[40]. Interestingly, in a case report, two patients with cervical dystonia (one of them with simultaneous writer's cramp), who had become resistant to BT injections, responded very well to continuous cervical intrathecal baclofen[41].

Regarding therapeutic agents such as amantadine, amphetamine, bromocriptine or lisuride, there is evidence from randomized controlled trials in favour of a mild to moderate benefit in cervical dystonia[40]. There is a number of drugs that yielded positive results in small trials, like sodium oxybate (particularly in laryngeal dystonia) and zolpidem[37].

DBS has been successfully used in focal dystonia patients who did not respond properly to BT therapy, with benefits persisting for several years of follow-up[42,43]. This approach has replaced lesional neurosurgery techniques (targeting regions such as the medial thalamus, the dentate nucleus and the basal ganglia), which were associated with significant adverse effects[44]. The most common DBS target areas in dystonia are the GPi and the subthalamic nucleus (STN). A 2021 systematic review concluded that stimulation in these two regions led to similar outcomes in terms of efficacy, quality of life, and adverse reactions. Moreover, patients with focal and primary dystonias had superior results compared to the segmental/generalized and secondary subtypes (except for quality of life, which was less improved in focal than segmental dystonia)[45]. Unfortunately, they can have significant side effects, such as dysarthria and parkinsonism for GPi stimulation, and chorea for the STN[24].

CONCLUSION

Adult-onset isolated focal dystonia, despite being the most common form of dystonia, remains the least understood in terms of its underlying pathophysiological mechanisms. The theory of network dysfunction proposed for its pathogenesis provides a better understanding of its mechanisms and is supported by evidence from neuroimaging and neurophysiological studies. However, whether these abnormalities represent the primary pathogenic mechanism or compensatory changes, resulting from the prolonged abnormal movements and postures, remains to be elucidated. The relation between genetic and environmental factors also needs further clarification. Given a much lower penetrance in adult-onset isolated focal dystonia, it is currently considered that genetic predisposition may require the presence of certain environmental factors to reach the disease threshold. The treatment remains symptomatic, with limited efficacy in some cases.

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