Dystonia: A Leading Neurological Movement Disorder

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Abstract: Dystonia is the third leading movement disorder arising mainly from the damage of basal ganglia or other parts of the brain that control movements. The objective of this review is to represent the detailed profile of dystonia. A computerized literature review was conducted in authentic scientific databases including PubMed, Google Scholar, Scopus, Science Direct and National Institutes of Health (NIH) etc. Terms searched included dystonia, risk factors, etiologies, clinical features, classification, pathology, guidelines, treatment strategies, primary and secondary dystonia. Initially, 97 articles and 9 books were extracted but finally, 64 articles and 7 books were used. After analysis, we found that causes of dystonia could be acquired or inherited and dystonia can be classified based on age at onset, etiology, and distribution of the affected body parts. The risk factors of this heterogeneous disorder could be trauma, thyroid disorder, hypertension, life habits, occupation, use of drugs and genetics. A significant number of articles were found which signify the ability of brainstem and cerebellar pathology to trigger the symptoms of dystonia. Since antipsychotic drugs are the most commonly prescribed among the people with intellectual disability (ID), therefore they possess a greater risk to experience antipsychotic drugs-induced movement side effects including acute dystonia, parkinsonism, tardive dyskinesia, and akathisia. Depending on various manifestations and causes, there are several treatment options including oral medications, intramuscular injection of botulinum toxin, neurosurgical procedures and occupational therapy.

Keywords: Dystonia, Movement disorder, Intellectual disability, Antipsychotic drugs, Oral medications.

INTRODUCTION

The word athetosis describes the movements which are not normal including low speed, twisting, anfractuous in features and if the condition persists for a long time then it is more appropriate to denote as dystonia [1]. Dystonia is a heterogeneous neurology related condition of uncontrollable muscle contraction. It could affect one or more parts of the body [2]. It also could be occurred due to the negative observable condition of many others diseases [3]. Earlier, dystonia was not considered as an observable condition of psychiatric imbalance or illness and more than 40 years have been taken to identify that this abnormal movement propagates from impairment in the function within the circuits of basal ganglia. Physiological investigations and neuroimaging studies refer clearly that dystonia is connected with alleviated repellent basal ganglia output, unnatural sensory-motor integration, failure of cortical restriction and maladaptive plasticity. Over the past 20 years, an adequate number of imaging studies had been performed by using functional magnetic resonance imaging, positron emission tomography with fluorine-18 fluorodeoxyglucose, positron emission tomography with $H_2{}^{15}O$ for in-patients with various forms of dystonia which are the evidence of rapid changes in cortical and subcortical activity [2].

Dystonia is a non-frequently occurring disorder and mortality and morbidity rate due to this disorder is too low and it can be considered as non-fatal. The prevalence rate of dystonia has been found 30 to 7320 per million of cases [4]. Another study revealed that an outbreak of primary dystonia was 16.43 per 100,000 patients where the confidence interval was 95% [5].

After Parkinson's disease, it is the second leading movement disorder [6] and another study indicates it as the third leading movement disorder after essential tremor and Parkinson's [7]. This movement disorder is featured by co-contracting simultaneous manifestations of agonist and antagonist muscle groups. The loss of inhibition at multiple levels of the nervous system as well as elevated cortical excitability and its rearrangement, all these features are associated with dystonia. Basal ganglia as the site of origin are one of the main focus for an adequate number of dystonia [8]. Limb, cranial voluntary muscle and axial could also become the victim of this disorder.

Among all the movement disorder, dystonia is recognized very poorly as it is non-frequent and non-fatal. An experienced physician could make a

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provisional diagnosis quite quickly but an adequate number of patients made a long delay to visit the physician after the onset of symptoms. A recent study of 107 patients of laryngeal dystonia found out the average time delay of 4.43 years between symptoms onset and diagnosis [9]. Another study on146 sequent patient of cervical dystonia (arising from neck region) who were admitted at a tertiary care center of the United States revealed that the average duration from the initial existence of symptoms to diagnosis was about 3.7 years [10]. Another study conducted in Italian movement disorder center showed that time lapse between symptom onset and diagnosis was very long before 1980 and in recent years to reach a correct diagnosis, one year delay was found in half of the cases in adult-onset dystonia (cervical dystonia, laryngeal dystonia, blepharospasm and oromandibular dystonia or focal dystonia) [11]. The delay of treatment procedures is the evidence of the necessity of better education, training, and awareness among the neurologists [12]. Therefore, the aim of this paper is to characterize the details outline of dystonia and with respect to what sustained or repetitive muscle contractions result in twisting and repetitive movements or abnormal fixed postures.

CLASSIFICATION OF DYSTONIA

Dystonia is classified based on four major variables which are the age at onset, the underlying reasons, special clinical features and distribution of affected body parts (Figure **1**). Based on these four variables the current European Federation of Neurological Societies (EFNS) put forward a classification scheme. They classified dystonia based on the age of onset, etiology, and distribution of affected body parts [13].

Based on Age at Onset

1. Early-Onset Generalized Dystonia

At early age onset (onset before age 30), dystonia develops to arm or leg and frequently to other limbs or trunk [13].

2. Adult-Onset Dystonia

At late age or adult onset (onset after age 30), it begins in neck including larynx, one arm or the cranial muscles [13].

Based on Etiology

1. Primary Dystonia

Primary dystonia is denoted as a disorder in which dystonic movement happen as an isolated sign. There is no existence of recognizable neuropathological damage or external causes in primary dystonia [14]. Primary dystonia can be sub-classified into primary pure dystonia, primary plus dystonia and primary paroxysmal dystonia [13, 14].

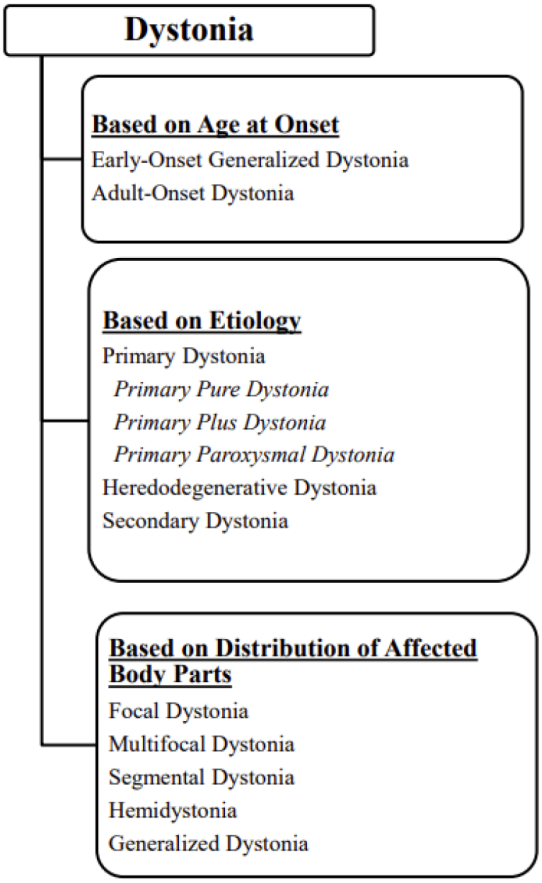

Figure 1: The classification of dystonia.

1.1. Primary Pure Dystonia

Primary pure dystonia happens in patients who don't have any structurally abnormal signs in the central nervous system (CNS). Tremor might or might not be present [16]. Twisting state is the only clinical symptoms excluding involuntary quivering movement in the absence of neurologic abnormalities or exogenous cause [13]. Example of primary pure dystonia is focal dystonia (cervical, writer's cramp, and blepharospasm), genetic dystonia (DYT1 and DYT6 dystonia) [17].

1.2. Primary Plus Dystonia

When dystonia is combined with other pathologic changes is known as primary plus dystonia [13, 16]. In primary plus dystonia, there is no existence of neurodegeneration. Examples are dopa-responsive dystonia, myoclonus dystonia syndrome and rapid-onset dystonia parkinsonism [17].

1.3. Primary Paroxysmal Dystonia

Paroxysmal dyskinesia (POD), a movement disease where abnormal movements are found during the attack. The term proximal reveals that symptoms are only observable for a certain time. This movement could be choreic, dystonic, ballistic or a combination. Dystonic forms of POD could be paroxysmal exercise-induced dystonia, paroxysmal non-kinesigenic dystonia (DYT8) and paroxysmal kinesigenic dystonia (DYT9) [17].

2. Heredodegenerative Dystonia

Heredodegenerative dystonia is dystonic movements occurring in the association of other heredodegenerative disorders with additional clinical features [17, 18]. Heterogenerative dystonia is seen in mitochondrial diseases, metabolism disorders, disorders of parkinsonian, trinucleotide repeat disorders as well as other neurologic abnormalities with an unknown cause [18].

3. Secondary Dystonia

Dystonic movements which are arising from a lesion or injury to the motor system are known as secondary dystonia. Neurological abnormalities are found to be accompanied in the secondary dystonia [15]. Secondary dystonia is also known as symptomatic dystonia. There are some features that suggest symptomatic dystonia; perinatal history or abnormal birth, developmental lateness, atypical site for age at onset (eg, leg onset in late age onset or cranial onset in early age onset), dystonia at rest (rather than with action) at onset, seizures, continuous progression of symptoms, exposure to drugs, prominent bulbar involvement, hemidystonia (dystonia of ipsilateral face, arm and leg), additional neurological symptoms except tremor, or multisystem involvement [17].

Based on Distribution of Affected Body Parts

1. Focal Dystonia

When dystonic movements affect only a single part of the body is known as focal dystonia. Examples of focal dystonia could be blepharospasm when affecting eyelids, dystonic adductor dysphonia by affecting larynx, writer's cramp or abnormal clenching of fingers of hand and arm, cervical dystonia of neck and musician's dystonia, oromandibular dystonia of mouth [19].

2. Multifocal Dystonia

When dystonic movements have an effect on two or more parts of the body which are not connected to each other like the right arm and right leg is known as multifocal dystonia [19].

3. Segmental Dystonia

If two or more connected parts of the body are affected, it will be known as segmental dystonia. Cranial dystonia affecting two or more parts of cranial and neck musculature, axial dystonia affecting neck and trunk, crural dystonia affecting one leg and trunk; two legs with or without trunk are the examples of segmental dystonia [19, 20].

4. Hemidystonia

Dystonia which occurs on the same sides of the face, arm, and leg. Mostly, contralateral structural damage or lesion of the basal ganglia or thalamus could be disclosed by neuroimaging. Stroke and trauma are the common etiologies and younger patients have many possibilities of developing hemidystonia after cerebral injury [21].

5. Generalized Dystonia

Generalized dystonia is one type of dystonia that is not limited to a single region of the body. It affects multiple muscle groups in the whole body. Both legs and minimum one other body part (normally one or both arms) [13].

ETIOLOGIES OF DYSTONIA

Researchers believe that this movement disorder arises from an abnormality in or injury to the basal ganglia or any other parts of the brain that controls movements. The causes of dystonia can be divided into two groups including inherited and acquired.

1. Inherited

The causes which can be passed down from parent to child are known as inherited causes. The causes that lead to inherited dystonia are also known as primary dystonia. Inherited causes of dystonia can be sub-divided into following sections:

2. Amino Acid Metabolism

Amino acid metabolism disorders are the most frequently occurring inborn errors of metabolism in humans. Amino acids are important molecules associated with various complex metabolic pathways like neurotransmission. As a result, disorders of amino acid metabolism have an effect on neurological activities in human. They could affect sulfur-containing

amino acids, aromatic amino acids, and branched-chain amino acids [22]. Patients could be affected by the disorders of amino acid metabolism in the forms of glutaric academia (GA), Hartnup disease, homocystinuria, guanidinoacetate methyltransferase (GAMT) deficiency, methylmalonic academia, sulfite oxidase deficiency, propionic academia which could ultimately lead to dystonia as dystonia is originated neural dysfunction specifically basal ganglia and thalamus [23].

3. Lipid Metabolism or Storage

Lipids and lipid intermediates act as essential components for the composition and functional activities of the brain. After adipose tissue, the brain has the maximum lipid content which is about 50% of the dry brain weight. The brain is thought to mainly exploit acylated lipids to produce phospholipids for the cell membrane [24]. So, disorders of lipid metabolism like metachromatic leukodystrophy (MLD), Krabbe's disease, neuronal ceroid lipofuscinosis, GM1 or GM2 gangliosidosis could affect structure and functions of the brain specifically basal ganglia and thalamus which could induce dystonia [23].

4. Ion or Metal Homeostasis

Wilson's disease, neuroferritinopathy, Fahr's disease, aceruloplasminemia, rapid onset dystonia-parkinsonism, cav2.1 calcium channel defects [23] are the ion or metal homeostasis disorder which is associated with neurodegeneration with brain iron accumulation which induces dystonia [25].

5. Polyglutamine Expansions

Polyglutamine (polyQ) diseases are a group of neurodegenerative disorders resulted from cytosine-adenine-guanine (CAG) expansion which repeats encoding of continuous glutamines tract in the respective proteins. Nine genetic neurodegenerative disorders are resulted from ployQ and have an effect on the basal ganglia, cerebellum, striatum, and other brain regions [26]. PolyQ diseases like spinocerebellar ataxias, lubag, Rett's syndrome, xeroderma pigmentosum, Cockayne's disease and ataxia telangiectasia are the contributors of dystonia [23].

6. Neurotransmitter Metabolism

Neurotransmitter abnormalities have an effect on different parts of the brain which could lead to movement disorders like dystonia. The mechanisms behind these abnormalities could be receptor antagonism, receptor stimulation, neurotransmitter reuptake inhibition, neurotransmitter depletion and altered neurotransmitter turnover [27]. Neurotransmitter abnormalities associated with tyrosine hydroxylase deficiency, 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, guanosine triphosphate (GTP) cyclohydrolase deficiency, aromatic L-amino acid decarboxylase (AADC) deficiency which are the contributors of dystonia [23].

7. Mitochondrial Function

Mitochondrial dysfunction leads to dystonia by affecting the nervous system by mutation in the *FH* genes (Fumarase deficiency), degeneration of CNS (Leigh's deficiency), causing neuronal dysfunction by mutations in the genetic materials like nuclear deoxyribonucleic acid or mitochondrial deoxyribonucleic acid (mitochondrial encephalopathy with lactic acidosis and stroke (MELAS) like episodes, mitochondrial encephalopathy with ragged red fibers (MERRF) [23].

8. Acquired

When a dystonia results from environmental factors or due to disease-related factors it is known as acquired dystonia. Acquired dystonia is also known as secondary dystonia. Mostly acquired dystonia presents with other neurologic findings. Acquired causes of dystonia can be sub-divided into following sections:

I. Medications

Dystonia could be induced due to a wide variety of drugs like carbamazepine, cinnarizine, fenfluramine, dopamine agonist and antagonist, levodopa, phenytoin, cyanide, disulfiram, metoclopramide, methanol, manganese, serotonin uptake inhibitors, tiagabine, and toxins are the contributors to dystonia. Patients who are developing abnormal positioning or muscle spasms within seven days of starting medicine or a quick increase in the dose of a drug may be growing acute dystonia [28].

II. Vascular

Movement disorders like dystonia is primarily associated with basal ganglia and thalamus. So, the possibility of having a movement disorder after deep nuclei infraction is three times greater than a surface infraction. Movement disorders like dystonia could follow cerebrovascular lesion in the basal ganglia and thalamus after ischemic and hemorrhagic stroke [29].

Vascular malformation, inflammation in the blood vessels of the brain could also be the contributors of dystonia by developing lesion in the brain [23].

III. Infection

Bacteria, viral and fungal infections of the brain caused meningitis and encephalitis which is associated with movement disorders like dystonia, Movement abnormalities normally arise at the acute phase of disease and transient. The reasons could be vasculopathy (capillary and vascular injury) due to antibodies or organism, direct basal ganglia attack or invasion by the organism and neuronal lesion or injury by the organism and toxin [27].

IV. Autoimmune Disorders

Movement disorders are known to be associated with wide varieties of autoimmune disorders. The striatal function of basal ganglia is altered by creating vascular abnormalities in the brain, stimulating inflammatory reaction the direct response of antibodies with basal ganglia [27]. Dystonia could be the initial or even only clinical presentation of these autoimmune diseases like Hymenoptera stings, multiple sclerosis, dystonia gravidarum, Reye's syndrome, sub-acute sclerosis panencephalitis, Sjogren's syndrome, antiphospholipid syndrome and systemic lupus erythematosus [23].

V. Trauma

By developing acute brain lesion or injury, trauma (head, neck and spinal) could also be the contributor of dystonia [23].

VI. Others

Tic disorder, multiple system atrophy, progressive supranuclear palsy, cerebral palsy etc. [23].

Among them birth trauma, perinatal ataxia, and hyperbilirubinemia are the most frequent reasons of dystonia. These abnormal movements could develop before 5 years old. Dystonic movements and postures could be the principle characteristics of isolated torsion dystonia. It could also be occurred due to the manifestation of Wilson disease or Huntington's disease or due to the sequel of encephalitis [1].

PATHOLOGY OF DYSTONIA

Dystonia is a clinical syndrome with twisting, sustained muscle contraction, and abnormal postures [24]. Dystonia was initially regarded as a disease of basal ganglia. Dystonia is now considered as a 'network' disorder counting the cerebellum. However, the precise pathogenesis is yet to be determined [25]. A range of various genetic forms has been reported. Nevertheless, most cases are intermittent in nature and take place due to indefinite cause [25]. In terms of etiology, the dystonias are often broadly classified as primary or secondary [24].

Pathology of Primary Dystonia

In case of primary dystonia, in the CNS, no significant signs of structural abnormality are noticed; in addition, tremor may or may not be present. On the other hand, this disorder is synonymous with idiopathic torsion dystonia, when generalized [26]. The most commonly noticed forms of primary dystonia are focal, in which single body part, for example, the neck is affected, and come on in the course of adult life. In most of the cases, these are sporadic in nature, which means that they are not triggered by any known dystonia genes and there is no definite family history. However, in a few cases, primary focal dystonia will have an association of genes or family history [24]. Most recently it has been found that DYT6 primary dystonia is caused by mutations in the THAP1 Gene [27]. Rather than cervical or muscles, sporadic focal dystonias are most likely to initiate in the brachial region, to include speech involvement, and to become generalized. Interestingly, generalized primary dystonia is more likely to have a genetic association, and less commonly seen as compared to primary focal dystonia [24]. Mechanisms which are involved in the case of primary dystonia have been shown in Figure **2** that mentioned susceptibility states are denoting the factors which may cause secondary insults (for example environmental insults, repetitive activity, physiological stress, and increased sensory input etc.) to trigger these pathways into a dystonic state.

Pathology of Secondary and Heredodegenerative Dystonias

Dystonia involves a broad range of degenerative and destructive disorders of the nervous system, furthermore, congruently wide range of brain structures have been associated in the pathogenesis of these symptoms. In a large series of cases, neuroimaging was used to study the basal ganglia lesions and dystonia was observed in approximately a third of the cases. However, the previously mentioned report did not involve pathological assessment. Parkinson's disease is considered as the most common and

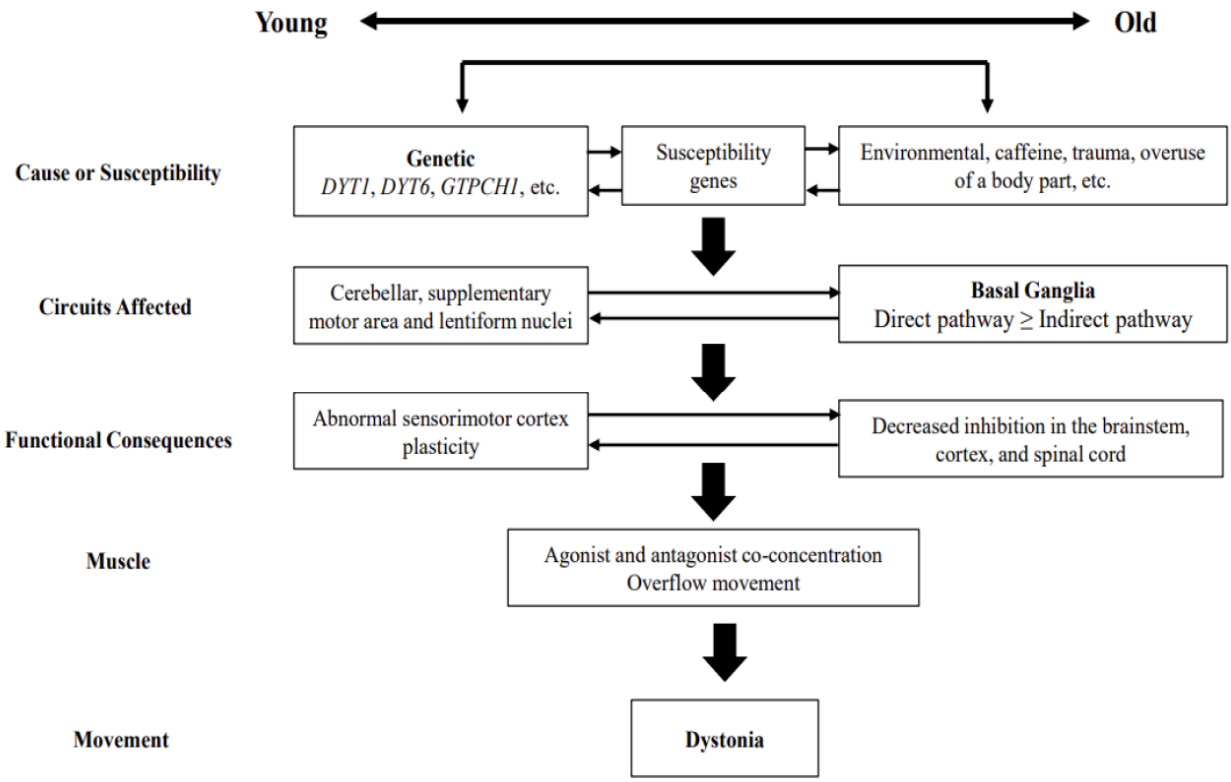

Figure 2: Mechanisms involved in the pathology of primary dystonia (Adapted from [28]).

probable cause of dystonia, in which degeneration of dopaminergic neurons is widely known [24, 29]. Nevertheless, it is now clearer that there are pathological changes in many other structures from brainstem to cerebral cortex. Dystonia has also been observed in other cases with obvious basal ganglia pathology, counting striatal degeneration associated with glutaric acidemia, pallidoluysian atrophy, basal ganglia infarction after cardiac arrest and lesions of the globus pallidus [24].

Brainstem and Cerebellar Lesions

A substantial number of articles supported the ability of brainstem and cerebellar pathology to trigger the symptoms of dystonia [24, 30]. LeDoux and Brady [31] extensively reviewed the literature on secondary cervical dystonia and reported a case series. They found that in most of the cases, there was a presence of lesions in the cerebellum or linked with brainstem afferents to the cerebellum [24, 31]. However, lesions isolated to the basal ganglia were rare in this case series. Tumors of the posterior fossa were found to trigger cervical dystonia. Additionally, following treatment of the tumor, dystonia improved in some cases. Interestingly, a number of studies found the presence of dystonia in familial forms of ataxia. Nonetheless, in the previously mentioned case, degeneration was found to be limited to the brainstem and cerebellar region [24].

DYSTONIA AND INTELLECTUAL DISABILITIES

ID is a lifelong condition and is characterized by significantly impaired cognitive and adaptive functioning [32, 33]. Comparatively higher rates of mental illnesses are experienced by the people with ID [33]. Henceforth, among the people with ID, antipsychotic drugs are the most commonly prescribed of the psychotropic drugs [36].

Movement (extrapyramidal) side effects, including acute dystonias, parkinsonism, tardive dyskinesia, and akathisia are a well-known complication of antipsychotic drugs. These previously mentioned movement side effects are thought to arise secondary to antagonism of dopamine D2 receptors in the mesocortex and striatum [34]. As compared to people without ID, people with ID are often considered to possess a greater risk of movement side effects induced by antipsychotic drugs [35].

Furthermore, Sheehan *et al*. [32] provided sufficient evidence in their study that people with ID are more vulnerable to movement side effects induced by antipsychotic drugs. Therefore, in people with ID,

assessment for movement side effects should be essential in antipsychotic drug monitoring [32].

Although there have been substantial advances in the field of dystonia genetics, in most of the cases of childhood-onset dystonia, the primary genetic causes are unknown. Researchers have found that progressive childhood dystonia can take place due to the presence of mutations in a gene called *KMT2B*. The researchers stated *KMT2B* dystonia as a dominantly inherited complex dystonia with onset in infancy or early childhood (mean age 7 years). Majority of the patients develop dystonia in the limbs along with marked cranial, cervical, and laryngeal involvement. In addition, some of the children exhibited intellectual disability, specific facial characteristics, psychiatric disorders, and other non-motor symptoms. The *KMT2B* coded protein belongs to a class of proteins that regulate transcription of other genes and that have been associated in other neurological conditions. The researchers, in addition to finding a novel genetic movement disorder, revealed a potentially essential mechanism triggering dystonia through epigenetic modification. Furthermore, it was found that oral medications do not work well to treat this specific dystonia, rather deep brain stimulation (DBS) is an effective treatment. Surprisingly, child patients profoundly responded to DBS, in some cases, the ability to walk was restored [37, 38, 39].

CLINICAL FEATURES OF DYSTONIA

Symptoms or clinical features of dystonia are appeared as a combination of dystonic movements and postures to generate a sustained postural twisting. Dystonic postures come before the occurrence of dystonic movements but in uncommon cases, dystonia can persist without any dystonic posture [46]. Generally, dystonic symptoms appear in upper limb and neck than face [47]. Sensory symptoms are also often appeared in dystonia. Pain, discomfort and abnormal sensations of muscle, phantom kinetic or postural sensation are the most commonly found sensory symptoms of dystonia. These symptoms appear a few weeks or months before dystonia [15, 48]. More specifically, pulling in the neck, neck tightness or stiffness, neck pain, head jerking, head tremor, increased limb tone, decreased arm swing are the presented symptoms of different types of dystonia [50]. Ocular symptoms such as dry eyes and irritation appear in patients who are suffering from a physiological condition characterized by recurring involuntary twitches of eyelids [48]. In accordance with another study, clinical features of dystonia could be elevated due to blood pressure, higher body temperature, rapid resting heartbeat (especially more than 100 beats per minute), production and evaporation of watery fluids from sweat gland, abnormally rapid breathing, dysfunction of autonomic nervous system and sometimes advancement of bulb dysfunction specifically medulla oblongata with difficulty of word articulating, difficulty in swallowing and failure of breathing. This movement disorder could be sustained posturing (tonic) or irregular jerking (phasic). The largest study revealed that most of the dystonia was sustained posturing which was about 69% and irregular jerking was most frequently experienced by female patients and secondary dystonia patients [50].

RISK FACTORS OF DYSTONIA

After essential tremor and Parkinson's disease, dystonia is the most common presentation of movement disorders [7]. Risk factors or determinants of dystonia are enlisted below:

1. Trauma

Trauma is the most frequently propound determinant of dystonia. Usually, trauma could be characterized as an injury to body parts affected by the dystonia and come before a month or longer of dystonia onset. Injury to the neck arising from the rapid acceleration-deceleration force from a motor vehicle accident; hand trauma where fingers are either curl into palm or extend outward without control; ocular lesion such as inflammation of cornea are the commonly reported injuries in various clinical series which lead to dystonia. Moreover, sensory features such as pain, discomfort, misrepresentation of sensory modalities have been disclosed as the imminent manifestations of dystonia [51]. Head trauma is also severe enough to associate the persistent of dystonia. An Italian case-control study established a significant relationship for precursory head trauma with sensory loss and late-onset dystonia with different localizations [52]. A case study conducted on 104 continuous patients with writer's cramp and matched controls established a meaningful association between head trauma with sensory loss and writer's cramp [53].

2. Thyroid Disorders

The development and function of the peripheral nervous system (PNS) and central nervous system (CNS) are influenced by a number of complex regulatory mechanisms. Among all of these regulatory

mechanisms, hormones act as the most dynamic regulatory factors. The role of the nervous system on the brain level as well as in peripheral organs is systemically modulated by the secretion of hormones. Normal thyroid hormone (TH), not only play an indispensable role in the proper cognitive development but also in numerous aspects of nervous system activity. TH mechanism is involved in direct interaction with idiosyncratic regulatory circuits or indirectly by the exertion of systemic effects on the metabolic pathways or circulatory system. Due to these close associations with the nervous system function, disturbance of thyroid metabolism (resulting from acquired or genetic etiologies) can lead to noticeable neurological syndromes with cognitive delay, neuromuscular manifestations, neuropsychiatric syndromes as well as movement disorders like dystonia [54, 55]. A large number of clinical studies pointed out that dystonia may have a strong association with thyroid disorders and autoimmune diseases. In Olmsted country, preexisting thyroid disorder was noticed in grown-up people with primary torsion dystonia [51]. Another study conducted by Italian movement disorder study group also showed that dystonia had a strong association with thyroid disorder [52].

3. Hypertension

Hypertension or high blood pressure has a negative effect on cerebral vasoreactivity. As a result, hypertension becomes a crucial risk factor for stroke and white matter hyperintensities (WMH). Cerebral vasoreactivity could evaluate by measuring changes in cerebral blood flow in the middle cerebral artery. Being a crucial risk factor for stroke and WMH, hypertension could also alleviate microvascular brain damage [56, 57]. Dystonia can occur as a consequence of injury or damage in basal ganglia or other parts of the brain that control movements. As brain damage could occur due to hypertension, it could also act as a risk factor for dystonia. In a case-control study, primary torsion dystonia was inversely correlated with elevated blood pressure. Due to the over-representation of elevated blood pressure in the control group with hemifacial spasm, the effects were found largely [51]. Another study conducted by Italian movement disorder study group noted hypertension as an independent factor for late age onset dystonia and significant odds ratio (OR) were observed for hypertension in blepharospasm (BSP) group. Blepharospasm group: OR = 0.3, 95% confidence interval (CI) 0.13 to 0.7, p=0.004 and non-blepharospasm group: OR 0.24, 95% CI 0.07 to 0.86, p = 0.03 [52].

4. Life Habits

An Italian case-control study conducted on primary late-onset dystonia focused on the relation between dystonia and cigarette smoking and wine drinking. Despite satisfactory study could reject a false null hypothesis, wine drinking was not established as a protective factor for primary dystonia as OR 0.78; 95% CI 0.51- 1.20. In contrast, cigarette smoking was identified as a possible risk factor for dystonia as OR 0.51; 95% CI 0.29-0.89 [52] and another survey study also revealed the association between cigarette smoking and idiopathic isolated dystonia (IID) [58]. Primary blepharospasm (BSP) is the commonest forms of late-onset dystonia. A family-based case-control study of 122 patients with primary BSP found evidence (OR = 0.23; 95% CI 0.10 to 0.8; P = 0.2) strongly supports coffee drinking as a risk factor for BSP [59]. Another multicenter case-control study also suggested coffee drinking as a protective risk factor for BSP. They found that coffee drinking was inversely interrelated with the development of primary BSP and to some extent; this interrelation may dependent on the amount of consumption [60]. Use of cocaine is also a risk factor for neuroleptic-induced acute dystonia (NIAD). A prospective study conducted on 29 patients and found that cocaine-using patients developed NIAD in a very high regard [61].

5. Occupation

Repeated motions performed in a course of normal or daily activities have been proposed as a risk factor for dystonia. Writing, typing, playing musical instruments or participating in any sports are the activities which could cause task-specific focal dystonia. Researchers have described several forms of task-specific focal dystonia. Among the writer's cramp is the most common presentation of task-specific focal dystonia [62]. This unnatural movement begins as soon as hand holds the pen or after writing a few words and symptoms stop as soon as the patient stops writing. Another form of task-specific focal dystonia is musician's cramps where the limb is affected by the involuntary movements while playing the musical instrument. This movement might lead to a severe state of being impaired and might be the reason for the loss of functionality and profession [63].

6. Use of Drugs

A number of drugs are capable of causing dystonia. Dystonia is associated with Parkinson’s disease due to

the exposure of levodopa. Depend on levodopa exposure, dystonic phenomenology could be classified as pre-treatment dystonia, early morning dystonia, peak dose dystonia and off period dystonia [64]. Anti-psychotic agents such as haloperidol, fluphenazine, and pimozide (more potent); chlorpromazine and thioridazine (less potent), quetiapine and olanzapine (atypical), risperidone (low dose) are associated with the incident of dystonia. Among them, high-potency anti-psychotic drugs are more tend to cause dystonia. The mechanism behind the different rates of dystonia which happening with various types of antipsychotic drugs could be described by the receptor blocking ratio between dopamine and acetylcholine in the basal ganglia. The higher the ratio of dopamine-acetylcholine antagonism, the higher the chance of having dystonia [44]. Anti-emetic drugs, which are used commonly, could induce dystonia. Metoclopramide, an anti-emetic drug impedes inclination of vomiting and vomiting by its antagonist activity at D2 receptors in the chemoreceptor trigger zone in the CNS. As a frequently occurring extrapyramidal symptom, acute dystonia is associated with metoclopramide. On an average, 1 in 500 patients (0.2%) who treated with a dose of 30 to 40 mg per day is suffering from dystonic reactions [65]. Patients belong to age group 12-19 are affected frequently than other age groups. Anti-depressant drugs could also induce dystonia but a number of case studies reported that selective serotonin reuptake inhibitors (SSRIs) induced more acute dystonia than other types of anti-depressant. There have been several case reports of acute dystonia in patients being treated with other drugs such as anti-convulsant drugs (carbamazepine, phenytoin), anti-vertigo agents (flunarizine and cinnarizine), anti-malarial agents (chloroquine, amodiaquine, and hydroxychloroquine) and cocaine. A number of anecdotal case reports of acute dystonia have been reported during the use of phenylpropanolamine, buspirone, ecstasy (3,4 methylenedioxymethamphetamine), diazepam and sumatriptan [44].

7. Genetics

Dystonia could be genetically inherited. Some forms of inherited dystonia appear in a dominant manner; that means only one parent who carries the defective gene is needed to pass the disorder to their child. In some cases, persons who are carrying defective gene may not develop dystonia, but having one muted gene is sufficient enough to cause a chemical imbalance which could lead to dystonia. A number of current evidences pointed out that genetics could be a significant contributor to wide varieties of dystonia. In many cases of primary dystonia, monogenic inheritance is found [66-68]. One of the most widely appeared dystonia is late-onset dystonia. This form of dystonia also has a strong genetic basis. Study based on clinical examination revealed that 23-36% close blood relatives of patients with focal dystonia have a chance of developing same and another form of dystonia. Sometimes, a combination of two or more genetic changes which is known as multigenic inheritance, each induces a low to moderate chance of developing dystonia. Together with environmental factors, multigenic inheritance may cause late-onset dystonia [13].

TREATMENT OPTIONS OF DYSTONIA

Although there is presently no cure for dystonia, multiple treatment options are available to help lessen the symptoms of muscle spasms, pain, and awkward postures. No single strategy will be appropriate for every case. The ultimate goal is to improve the quality of the patient's life and to help function with the fewest side effects possible.

1. Oral Medication

I. Anticholinergics

Anticholinergic agents have the higher rate of success in treating dystonia. In a study period of 36 weeks, daily intake of 30 mg anticholinergic agent has been shown clinically significant development in 71% of patients [23]. Among the anticholinergic agents; trihexyphenidyl, diphenhydramine, benztropine, and ethopropazine are used for their effectiveness to treat dystonia. Among them, trihexyphenidyl (muscarinic acetylcholine receptor antagonist) is the most effective and best studied anticholinergic agent [40, 69]. The effective doses of trihexyphenidyl could be 6-80 mg per day [40, 70] and maximum dose could be 120 mg per day and starting dose could be 2 mg per day [71]. More specifically, average daily doses of 41 mg per day for children and 24 mg per day for an adult have been found to be effective as the tolerance ability of adults is likely less than children. Patients may experience memory loss, restlessness, sleeplessness and frightening or unpleasant dream as central side effects and dry mouth, urinary retention, blurred vision, constipation as peripheral side effects. In the case of children, chorea, or exacerbation of a pre-existing tic disorder are observed as side effects [23].

II. GABA Receptor Agonists

A gamma-aminobutyric acid (GABA) receptor agonist is a type of GABAergic agent, which modifies the effects of GABA in the body or brain. For early or late onset dystonia, a number of GABA receptor agonists have been proven effective including:

i. Baclofen

Baclofen is mainly used to treat muscle disorder known as spasticity but it showed efficient success rate for treating different forms of dystonia. Oral baclofen, a GABA-B receptor has been proven quite effective in treating dystonia of the cranium and face. Sedating characteristics of oral baclofen also works in dystonia of larger muscles such as the neck, limbs [69]. A number of clinical improvements also found the effectiveness of baclofen in 30% of 31 children who were suffering from primary idiopathic dystonia and 42.43% of 33 children who were suffering from DYT1 dystonia [23]. The minimum dose is 25 mg per day and the maximum is 120 mg per day [70-72]. Baclofen is a second line agent and its side effects could be feeling of being sleepy, feeling of sickness with an inclination to vomit, extreme tiredness, whirling sensation in the head [71]. Seizures can take place as a consequence of doses withdrawal and in case of some patients, this second line agent is given continuously into spinal canals via an implanted radio-controlled pump for better efficacy [72].

ii. Benzodiazepines

A number of benzodiazepines (GABA-A receptor) are used to treat dystonia including diazepam, clonazepam, and lorazepam. Among them, most commonly used benzodiazepines are clonazepam and diazepam for their direct anti-dystonic characteristics [71, 72]. Different types of benzodiazepines are proven effective in 16% of various forms of dystonia. Some retrospective studies have found that up to 23% of patients with focal and generalized dystonia reported good clinical response. Particularly, it is also proven effective in cervical dystonia with previous head tremors and blepharospasm [23]. Uncontrolled dose continuation may induce anxiety inhibition and mental relaxation as well as negative interaction with alcohol which needs to be voided by controlled prescriptions. Withdrawal may cause physical dependency as well as seizures. Side effects could be confusion, dejection, impaired coordination and quick adverse effects include memory impairment, disinterestedness, feeling of being sleepy and lethargic and reduced reaction times leading to driving restrictions [23, 72].

III. Dopaminergics

There are an adequate amount of dopaminergic agents which are used to treat dystonia including levodopa, ropinirole, pramipexole, tetrabenazine [23].

i. Dopamine Receptor Agonists

Levodopa gives mild anti-dystonic effect. Dopamine transmission with levodopa has been proven effective in dose-responsive dystonia. Dose-responsive dystonia is a type of dystonia which is occurred due to mutations in the GCH1 gene encoding the enzyme GTP-cyclohydrolase. Many patients response to low doses, while others require high doses [73].

ii. Dopamine Receptor Antagonist and Dopamine Depletion

Dopamine blocking agents or antipsychotic agents are proven effective in dystonia treatment specifically clozapine. These D2 receptor blocking agents should not be applied for idiopathic dystonia unless uncontrolled situation takes place as they have the ability to produce tardive dystonia. Due to moderate anti-dystonic potency clonazepam is the safest atypical dopamine receptor antagonist which does not cause tardive dystonia [72].

Dopamine-depleting agents can reduce dopamine levels within the central nervous system by blocking the reuptake of dopamine into the presynaptic nerve terminals. Tetrabenazine (TBZ) and reserpine are the best-explained dopamine depletion. TBZ, a type of dopaminergic agent caused depletion of pre-synaptic stores of catecholamines by inhibiting the vesicular monoamine transporter 2 (VMAT2). Retrospective data represents TBZ as a safe and effective medicine to treat dystonic effects specifically for the treatment of tardive dystonia [69]. Side effects could be feeling of being sleepy, parkinsonism, inability to sleep, dejection or lonesome, feeling of nervousness, unease, worry and feeling of inner restlessness, inability to stay still, alleviated blood pressure, feeling of sickness with an inclination of vomiting and constipation [23, 72].

IV. Other Agents

Some other agents like oral and intravenous lithium, carbamazepine, lidocaine, alcohol etc. have been used to treat dystonia. But, recently no effective evidence proved their routine use to treat dystonia.

2. Botulinum Toxin

Botulinum toxin (BoNT) is a type of toxin which is originated from the bacterium *Clostridium botulinum*

and found in seven different forms (toxin A-G). To exert therapeutic benefits, botulinum toxins create a blockage to stop the release of acetylcholine into neuromuscular junction. After administration of this toxin into dystonic muscle, the muscle becomes weak but exerts improvement in dystonic symptoms. For focal and segmented dystonia, it becomes an effective treatment choice including lingual dystonia, cervical, blepharospasm and spasmodic dystonia [23]. Proper selection of muscles and accurate injection with correct dose are the principal factors for successive treatment with BoNT. Evidence-based recommendations have been established by the American Academy of Neurology (AAN) regarding the application of BoNT to treat dystonic effects. BoTN is a good treatment option for blepharospasm or cervical dystonia and for adductor laryngeal dystonia and focal upper extremity, BoTN can also be considered as an effective treatment option. For treating focal lower extremity dystonia, BoTN may also prove an effective treatment option [69].

3. Surgical Treatments

The Surgical procedure is a substitute choice for patients those are suffering from severe dystonia and not reacting positively to other treatments. A number of neurosurgical methods have been established to treat dystonia.

I. Peripheral Surgery

In the era of the nineteenth century, myectomy (muscle resection) and myotomy (muscle dissection) were applied to treat dystonia. Based on availability of electric stimulation, denervation techniques were developed for dystonic muscle. For the treatment of blepharospasm, denervation and myectomy may be accomplished alone or in combination. Results are not satisfactory because of uncontrolled therapeutic effects and inadequate therapeutic effects or pathetic adverse effects. Denervation surgical technique may cause long-lasting pain syndrome as a severe problem. Recently, both the denervation and myectomy techniques are closed down [72].

II. Brain Surgery

Dated back to 1940, ablative procedures such as thalamotomy, pallidotomy were used to treat movement disorder. In spite of being effective for surgical procedures, they have been replaced by deep brain stimulation (DBS). DBS is quite convenient over the ablative techniques. It is quite adjustable and reversible because of its non-destructive nature. Moreover, it could be performed safely without creating any risk of permanent speech, swallowing or cognitive deficits which have been reported in ablative techniques [23]. This frequently used surgical procedure has a tremendous success rate to treat primary DYT1 dystonia. DBS of the pallidum represents a significant therapeutic progress, especially for the moderate to severe, disable patients as they have failed medical management [74, 75]. Pallidal deep brain stimulation (GPi-DBS) is also beneficial to treat cervical dystonia than extracerebral surgery. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), a scale which is used to document the status (severity and treatment success rate) of cervical dystonic patients. Retrospective studies reported developments in TWSTRS subscales (severity, disability, and pain) ranged from 55 to 63%, 59 to 69% and 50 to 58%. Another two prospective studies reported more than 60% improvements for most of the subscales. Pallidal neuromodulation seems to be effective in treating less frequently documented dystonia compared to primary dystonia as well as rare type's dystonia including myoclonus dystonia or secondary dystonic form to heterogeneity disease like Wilson's disease, Meige syndrome [76].

III. Intrathecal Baclofen

Intrathecal baclofen (ITB) was introduced in 1991 to treat dystonia. In a theoretical manner, it could elevate the central side effects linked with oral baclofen administration. In some reports, ITB has been proved an effective treatment option for primary and secondary dystonia but available data is not consistent. Etiological divergence may be speculated in dystonia due to this contrariety along with few sub-classes acted well than others. Recently, it is used to treat most of the dystonic patients combined with infection, spasticity of the lower limb, catheter and pump dysfunction and cerebrospinal fluid (CSF) leak [23].

4. Physical and Occupational Therapy

Physical and occupational therapies could be the aid to mobilize the joints which become frozen, create a restriction on abnormal muscle contraction, built proper exercise programs as well as provide the related device according to the need of patients. With the proper knowledge of this disorder, therapists could expand the use of sensory tricks to improve dystonic syndromes. Examples could be various types of writing devices for those who are suffering from writing cramp.

In the case of hand dystonia, constraint-induced movement therapy is quite helpful [23]. Sensory-motor retuning, also known as constraint-induced movement therapy is beneficial in hand dystonia. To select subtypes of dystonia, orthotic devices (devices that stable body part(s) and or assist with function) are quite helpful. On the other hand, semi-rigid cervical orthoses or cervical collar could help to improve the head position in those with anterocollis (AC) [69].

CONCLUSION

Many diseases and conditions may cause dystonia. There are many underlying causes of dystonia and mechanisms, nevertheless, all the causes are not known. More research is needed to find out the contributions of all these causes to dystonia. As a non-frequent and non-fatal disorder, symptoms sometimes remain less recognized which can lead to treatment delay. There are many risk factors for dystonia. Among them, some are non-modifiable or genetically acquired but there are some risk factors which could be modified by bringing changes in lifestyle. Treatment options of dystonia have developed in a dramatic manner in the recent years. List of treatment options are quite developed, as there is a specific treatment option for specific subtypes of dystonia which target the root cause(s).

COMPETING INTERESTS

The authors proclaim that they have no competing interests.

ABBREVIATIONS

AADC = Aromatic L-amino acid decarboxylase

AAN = American Academy of Neurology

AC = Anterocollis

BSP = Blepharospasm

CAG = Cytosine-adenine-guanine

CI = Confidence interval

CNS = Central nervous system

DBS = Deep brain stimulation

EFNS = European Federation of Neurological Societies

GA = Glutaric academia

GABA = Gamma-aminobutyric acid

GAMT = Guanidinoacetate methyltransferase

GTP = Guanosine triphosphate

IID = Idiopathic isolated dystonia

ITB = Intrathecal baclofen

MELAS = Mitochondrial encephalopathy with lactic acidosis and stroke

MERRF = Mitochondrial encephalopathy with ragged red fibers

MLD = Metachromatic leukodystrophy

NIAD = Neuroleptic induced acute dystonia

OR = Odds ratio

POD = Paroxysmal dyskinesia

PNS = Peripheral nervous system

PolyQ = Polyglutamine

SSRIs = Selective serotonin reuptake inhibitors

TH = Thyroid hormone

TWSTRS = Toronto Western spasmodic torticollis rating scale

VMAT2 = Vesicular monoamine transporter 2

WMH = White matter hyperintensities

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