

# DYSTONIA - A REVIEW OF CURRENT CONCEPTS AND THEIR APPLICATION IN PAKISTAN

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Primary dystonia is believed to be the third most frequent movement disorder after essential tremor and Parkinson's disease.<sup>1</sup> Although prevalence reports have varied, dystonia is presently estimated to affect approximately 220 per million people worldwide.<sup>2</sup> The term "dystonia" was first coined by Hermann Oppenheim in his landmark work published nearly a century ago.<sup>3</sup> However, the recognition and characterization of this hyperkinetic movement disorder began even earlier, in the first half of the 19th century.<sup>4</sup>

Despite tremendous advances in the understanding of this neurologic disorder, the condition is still best described by its morphologic characteristics. The phenomenology of the various hyperkinetic movement disorders such as dystonia, choreoathetosis, myoclonus and tics, is determined by the quality and temporal aspects of the muscular contractions. The formal definition of dystonia was proposed by the Scientific Advisory Board of the Dystonia Medical Research Foundation in 1984, as "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures."<sup>5</sup> This definition was later modified to "dystonia is a neurologic disorder dominated by involuntary, sustained or spasmodic, repetitive, and patterned contractions of muscles, frequently causing twisting or other abnormal movements or postures." The term "patterned" describes repeated involvement of the same group of muscles, a key feature that helps differentiate dystonia from other hyperkinetic movements.<sup>6</sup>

## CLASSIFICATION

The clinical spectrum of dystonia is remarkably variable, and the dystonic syndromes are now considered heterogeneous disorders. Dystonias have been classified by etiology (primary or secondary), by distribution in the body (focal, segmental, multifocal or generalized) and by age of onset (Table 1).<sup>7</sup> Early-onset dystonia (presenting

before 20 years) usually has onset in a limb and a tendency to generalize; late-onset dystonia (presenting after 20 years) is generally focal (cervical dystonia, blepharospasm) or segmental.<sup>7-11</sup>

The age of onset of dystonia has prognostic implications. Generally, the earlier it presents, the more likely it is to be secondary in origin and to generalize from a focal area in the body. The pattern of distribution of dystonia in the body has therapeutic implications. A focal or segmental distribution is likely to do well with local but often expensive treatments like neurolysis with the botulinum toxins. Oral medications or rarely globus pallidus surgery may be a better choice for patients with severe generalized dystonia.

## ETIOLOGY

From the etiologic standpoint, dystonia is classified as primary (with no identifiable exogenous cause), association (for example to a degenerative disorder) or dramatic levodopa responsiveness (to suggest dopa-responsive dystonia), and secondary dystonia, which by definition has a clearly identifiable cause (exposure to dopamine modulating drugs, stroke, perinatal injury) or pathologic association (for example, to an inherited disorder like Wilson's Disease, dopa-responsive dystonia, X-linked dystonia-parkinsonism, etc).

Secondary dystonias can also be seen in many neurodegenerative diseases (Table 1). For example, 59% of patients who present with the classic phenotype of corticobasal degeneration can manifest dystonia.<sup>12</sup>

## PATHOPHYSIOLOGY AND PATHOGENESIS

The pathogenesis of dystonia is unknown. Although the neuronal circuitry of the basal ganglia appear to be altered, it is not known whether these changes are primary or

TABLE 1. Classification of Dystonia<sup>8</sup>

1. By Age at Onset	Early-onset dystonia: <26 yr Late-onset dystonia: >26 yr
2. By Distribution	Focal (single body region) Segmental (contiguous region) Multifocal (for e.g. hemidystonia) Generalized
3. By Etiology	<p>3.1 Primary or Genetic</p> <p>Autosomal dominant</p> <p>Early-onset limb dystonia (DYT1) Mixed dystonias (DYT6, DYT13) Late-onset craniocervical dystonia (DYT7)</p> <p>3.2 Secondary dystonias</p> <p>Dystonia-plus syndromes</p> <p>Dopa-responsive dystonia (DRD) Rapid-onset dystonia parkinsonism (RDP) Myoclonus-dystonia (M-D)</p> <p>Hereditodegenerative dystonias</p> <p>Autosomal dominant (e.g. Huntington disease, Spinocerebellar ataxia 3 [SCA3], Dentatorubralpallidoluysian atrophy [DRPLA]) Autosomal recessive (e.g. Wilson disease, GM1, GM2 gangliosidosis, Metachromatic leukodystrophy, homocystinuria) X-linked (e.g. Lumbag's X-linked dystonia-parkinsonism)</p> <p>Acquired causes</p> <p>Drug-induced (e.g. tardive dystonia) Basal ganglia, particularly putamenal lesions due to stroke, tumour, AVM, demyelination, etc) Trauma (Intracranial and peripheral)</p> <p>Unknown etiology</p> <p>Parkinson disease Corticobasal degeneration Multiple system atrophy Progressive supranuclear palsy</p>

secondary.<sup>8</sup> Nevertheless, the involvement of basal ganglia in the pathophysiology of dystonia is clearly established and robustly supported by several functional and physiological imaging studies.<sup>13,14</sup> Recent literature also implicates sensori-motor cortex in the generation of focal dystonia.<sup>15</sup>

Genetic factors are increasingly being recognized as critical players in the pathogenesis of dystonia. Aside from the obvious association of some forms of secondary dystonia with inherited disorders, fifteen genetic subtypes, designated DYT 1-15, have been defined in association with primary dystonias (Table 2).<sup>9,10,11</sup> Adult-onset focal dystonia (DYT7), being the most common (90% of all dystonias), has an estimated prevalence of 30 per 100,000 in the general population.<sup>16,17</sup>

The exact nature of the vulnerability imposed by genetic influences remains unclear. The currently proposed etiology for primary dystonia is a combination of genetic predisposition with an environmental insult.<sup>1</sup>

## DIAGNOSIS

A detailed history followed by a thorough general and neurological examination is key to diagnosis. History should especially focus on the age of onset of abnormal movements, their distribution and pattern of progression, specific triggers, associated symptoms, family history, and exposure to toxins and drugs. Additional work-up including brain imaging, and metabolic and genetic testing is guided by the clinical features of the disease.

Hemidystonia, dystonia present at rest and at symptom-onset, the presence of other neurological signs, a young age at onset, progressive pattern and onset in one limb are all features strongly suggestive of genetic causes. Dystonia is commonly seen in the rare genetic disorder of copper metabolism, Wilson's disease. This should be excluded in younger patients who have dystonia, as it is a treatable and potentially fatal condition if not recognized early. Dopa-responsive dystonia (DRD) is a rare form of dystonia that responds dramatically to levodopa therapy and a trial of this medication should be considered in younger patients. Appropriate laboratory tests and imaging studies

TABLE 2. **Dystonia (DYT) Genetic Loci**<sup>8,9,10</sup>

Designation	Age at Onset	Clinical Features	Inheritance and Chromosome	Gene
DYT1 (Oppenheim's)	Mean age 12.5, < 28 yr in majority	Early limb onset, usually generalizes	AD 9q34	TorsionA (Gene test available commercially)
DYT2	Early onset		AR	
DYT3 (Lumbag's)	Mean 35 yr Adult-onset	Males of Philippino ancestry, generalized dystonia with parkinsonism	XR Xq13.1	
DYT4	13-37 yr	Single Australian family Whispering dysphonia and torticollis	AD	
DYT5a DRD,(Segawa's)	Childhood onset	Dramatic response to levodopa Usually limb onset	AD 14q22.1-q22.2	GCH1 (Gene test available is research labs)
DYT5b DRD	Infant	Infantile parkinsonism	AR 11p	TH
DYT6	Mean 19 yr	Two Mennonite families with craniocervical or limb dystonia	AD 8p21-p22	
DYT7	28-70 yr	Large German family with late-onset craniocervical dystonia	AD 18p	
DYT8 Paroxysmal dyskinesias	Early childhood adolescent onset	Brief attacks of dystonia, chorea and athetosis May or may not be precipitated by movement	AD 2q33-q35	Myofibrillogenesis regulator 1
DYT9	2-15 yr	Episodic choreoathetosis, ataxia, spasticity	AD 1p	
DYT10	6-16 yr	Paroxysmal choreoathetosis, precipitated by sudden movements	AD 16p11.2-q12.1	
DYT11	Variable	Myoclonus, dystonia, alcohol responsive	AD 7q21 11q23	
DYT12	Childhood, adolescent	Rapid-onset dystonia parkinsonism	AD 19q13	ATP1A3
DYT13	5 yr to adult	Single Italian family with cervical dystonia	1p36.13-36.32	
DYT14	Childhood	Dopa responsive dystonia	AD 14q13	
DYT15	Childhood to adult	Single Canadian with alcohol-responsive myoclonic dystonia, limb dystonia	AD 18p11	

should be considered in patients clinically suspected of having a secondary form of dystonia.

### DYSTONIA IN PAKISTAN AND ASIA

There is very little information in the literature on the epidemiology and characteristics of dystonia in Asia. Jamora et al have reported DYT1 mutations in Singapore in 2006.<sup>18</sup> They screened 54 patients with primary non-familial dystonia (focal n=41; segmental n=11; multifocal

n=1) for GAG deletions in the DYT1 gene. Thirty-nine (72%) patients were of Chinese ethnicity, 7 (13%) Indian and 5 (9%) of Malay origin. Fifty-nine percent patients were male and had the onset of dystonia at the mean age of 47 years. These authors did not detect any mutations in exon 5 of the DYT1 gene in any patient, and concluded that the frequency of DYT1 mutation amongst Asians (1.0%) was comparable to the West (1.56%). A Japanese study of 159 patients screened for DYT1 (GAG deletion) found this in 0.62% patients and a Taiwanese study of 189 patients found 1.5% patients affected.<sup>19,20</sup>

TABLE 3. **Classification and Characteristics of 28 Pakistani Patients with Dystonia**<sup>22</sup>

Classification by Age at Onset	Number of Dystonia Patients
Childhood (0-12 years)	8
Adolescent (13-20 years)	8
Adult-onset (> 20 years)	12
Total	28
<b>Classification by Etiology</b>	
Primary (Idiopathic) non-familial dystonia	8
Wilson's disease with dystonia	7
Dystonia with striatal CT scan lucencies	2
Parainfectious	1
Dystonia after head or peripheral trauma	2
Drug-induced dystonia	5
Dystonic tic	1
Paroxysmal kinesigenic dystonia	1
Dopa-responsive dystonia	1
Total	28
<b>Classification by Distribution</b>	
Focal dystonia	8
Segmental dystonia	7
Hemidystonia	2
Generalized and Multifocal dystonia	11
Total	28

A community survey of primary dystonia in the city of Kolkata, India, has been recently reported by Das et al.<sup>21</sup> A population of 52, 377 was screened and 29 subjects with dystonia were diagnosed. Twenty-three of the 29 had primary dystonias and all cases had focal, mostly limb dystonia. Mean age of onset of dystonia was found to be earlier in women (43.5 years) than in men (46.6 years). The crude prevalence rate (CPR) of 43.91/100,000 in that region was noted to be higher than reported in other global studies. Naiya et al attempted to identify DYT1 mutations in 178 primary dystonia patients and 63 controls in Kolkata.<sup>22</sup> They did not detect anyone with the commonly reported 3 base-pair GAG deletion and concluded that the DYT1 gene might have a limited role in the causation of dystonia in the Indian population.

A MEDLINE search did not show reports of any genetic or clinical studies done on patients with a Pakistani ancestry. There is a case report of 2 Pakistani siblings with dystonia who were found to have a novel mutation in the PANK2 gene leading to pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease) by Saleheen et al.<sup>23</sup>

A prospective study on movement disorders was done in Pakistan from 1988 to 1990. This was part of a doctoral thesis at the Civil Hospital, Department of Neurology in Karachi.<sup>24</sup> The study aimed to delineate clinical characteristics of all cases of movement disorders

presenting to this facility during the specified period. Since this center is one of the largest public health facilities in Pakistan and draws large patient populations from the region, the results may be reflective of overall geographic trends. Seventy-two cases of movement disorders were identified in this 2-year study. These were 44 males (61.1%) and 28 (38.8%) females. Of these 72 patients, 28 (38.8%) cases were diagnosed with dystonia (Table 3). Fourteen patients had a pure dystonic syndrome, 11 had dystonia with tremor, 2 subjects had dystonia with myoclonus and one had dystonia without myoclonus. Overall, 12 of the 28 dystonia patients (42.8%) were females.

Eight patients had childhood onset-dystonia (below age 12 years), 8 had adolescent onset dystonia (age 13 to 20 years) and 12 patients had adult-onset dystonia (after 20 years of age). Eight (28.5%) patients had non-familial primary dystonia; 7 (87.5%) of these were males. This male predominance may be related to fewer females generally seeking medical attention at tertiary medical centers. Seven patients (25%) had dystonia associated with Wilson's disease and 5 (17.8%) had drug-associated dystonia. Eight (28.5%) patients had focal dystonia, 7 (25%) had segmental dystonia and 11 (39.2%) had generalized or multifocal dystonia.

## MANAGEMENT

In secondary dystonia with an identifiable cause like Wilson's disease, the treatment of the underlying disease is the mainstay of management. Symptomatic therapy can be employed in selected cases. In secondary dystonia with an identifiable but irreversible disease (e.g., stroke) and in primary dystonia, only symptomatic therapy can be employed.

There are many symptomatic therapies available. The goal is to reduce the dystonic muscle spasms, in an effort to reduce associated pain, disfigurement and disability. Generally, oral and surgical treatments are preferred for generalized dystonias, while neurolysis with botulinum toxin usually offers the best therapeutic option for focal and segmental dystonias. Patients may benefit from a combination approach using multiple treatment modalities. A comprehensive multidisciplinary management approach incorporating physical and occupational therapy, pain management, and psychiatric management generally offers the best hope for reduced disability and improved quality of life for the patient.

## DOPAMINERGIC DRUGS

About 5% of childhood dystonias may present with dopa-

responsive dystonia (DRD). These patients improve substantially with even small doses (100 mg) of a levodopa formulation, but some may require up to 1000 mg in divided doses. Because the presentation of DRD is multifaceted and maybe wrongly attributed to cerebral palsy, levodopa should be considered in all patients with childhood and young-onset dystonia. If no meaningful improvement is evident after a month of treatment, the diagnosis of DRD is unlikely.<sup>25</sup>

### **ANTIDOPAMINERGIC DRUGS**

Most clinical trials have produced mixed results with antidopaminergic drugs. Because of the potential for causing tardive dyskinesias, conventional neuroleptics should be avoided. The atypical neuroleptics may have a better safety profile but can be an expensive choice in Pakistan. Tetrabenzazine is a dopamine-depleting agent that can improve dystonia symptoms and does not cause tardive dyskinesia.<sup>16</sup> An initial dose of 25 mg can be titrated up to 100 mg in divided doses. Sedation, orthostasis and worsening of depression are common adverse effects.

### **ANTICHOLINERGICS DRUGS**

Anticholinergics like trihexyphenidyl and procyclidine can be beneficial in generalized dystonias and are likely to be more affordable for long-term therapy in Pakistan. Trihexyphenidyl can be started at 2 mg at bedtime and titrated up to higher tolerated doses of 12 to 100 mg in divided doses.<sup>25</sup> They are better tolerated by younger patients and should be avoided in the older population because of their tendency to cause significant cognitive and other adverse effects in this sub-group.

### **OTHER ORAL THERAPIES**

Many patients with dystonia often require a combination of oral and other therapies. Muscle relaxants, such as the benzodiazepines, baclofen, tizanidine, cyclobenzaprine, metaxalone, carisoprolol, methocarbamol, orphenadrine, chlorzoxazone and dantrolene could provide additional benefit. Baclofen can be particularly helpful in oromandibular dystonia and clonazepam in blepharospasm and myoclonic dystonia.<sup>25</sup> Patients with a chronic disorder like dystonia may have associated pain, depression and insomnia. These symptoms should be aggressively treated when present.

Status dystonicus or dystonic storm is a rare life-threatening condition characterized by acute worsening of the dystonic syndrome, with a potential to severely

compromise bulbar and ventilatory functions. These patients are best managed in an intensive care unit and may benefit from the Marsden cocktail (benzhexol, tetrabenzazine, pimozide) and possibly with intrathecal baclofen therapy.<sup>11</sup>

### **BOTULINUM TOXIN AND OTHER FOCAL TREATMENTS**

Intramuscular injections of the botulinum toxin serotypes A or B improve symptoms by blocking the release of acetylcholine at the neuro-muscular junction.<sup>25</sup> The effect lasts for an average of 3 months, hence the treatments have to be repeated 3-4 times annually. Resistance can develop with prolonged use of high doses and treatments should be spaced out at 3 monthly or longer intervals to prevent this. In Pakistan, the serotype A is available and although it is a very expensive therapeutic option, it can be very effective in relieving symptoms of focal dystonias like oro-mandibular-lingual, laryngeal, and cervical dystonia, and blepharospasm and writer's cramp. However, local side effects like ptosis, dysphagia and weakness can result. The treatment should therefore be administered by trained and experienced physicians, to minimize the potential for adverse effects.

Other local treatments like injections of lidocaine, phenol and alcohol, etc., have been used without proven efficacy.

### **DEEP BRAIN STIMULATION (DBS) OF THE GLOBUS PALLIDUS (GPI)**

Over the past decade, deep brain stimulation, particularly involving the globus pallidus internum (GPI), has emerged as a viable surgical option for the management of dystonia. This adjustable and largely reversible procedure has mostly replaced ablative procedures in centers where this surgery is available.

Primary generalized dystonia seems to respond the most to this surgery, better than secondary dystonia, although uncontrolled evidence also suggests that cervical, tardive and pantothenate kinase-associated neurodegeneration associated dystonia may also improve.<sup>8,25</sup>

In this surgical procedure, a microelectrode is placed in the GPI, often bilaterally. The electrode is connected with a wire to a stimulator, which is placed in the thorax. The stimulator delivers continuous electrical impulses to the GPI. After the surgery, an external magnet is used to control the parameters of the electrical impulses that are delivered to the GPI. DBS programming is thus done to improve the symptoms of dystonia. The battery needs to be replaced every few (generally 3-5) years. The drawbacks of the procedure, besides the obvious surgical risk, is the

expense and the need for an experienced surgical and neurology team for immediate and long-term postoperative management, including DBS programming. Complications like infections and malfunction of the hardware are not uncommon and the stimulation itself can cause unwanted cognitive, psychiatric and motor effects.

In Pakistan, where DBS has not yet been introduced, ablative surgery of the GPi or thalamus may be considered in select cases of primary generalized dystonia who have failed medical therapy. A good multidisciplinary management team and appropriate patient selection for movement disorder surgery is necessary to ensure a successful outcome.

### SUPPORTIVE AND PHYSICAL THERAPIES

Physical and occupational therapies can be very helpful and should be used to prevent contractures. Well-fitted neck and limb braces and splints can sometimes be used to improve posture and muscle spasms. Dystonia is usually a life-long chronic and disabling disorder. Education of patients and their families, genetic counseling and psychosocial support should all be part of a comprehensive therapeutic approach.

### SUMMARY

Dystonia is a neurological syndrome, characterized by stereotypic, abnormal muscle contractions and movements that can be disabling. It has many etiologies and is often associated with pathology affecting the circuits of the basal ganglia. A diagnostic work-up should aim at identifying treatable causes of dystonia. Symptomatic therapies like oral medications can decrease muscle spasms and associated pain, depression and insomnia. Focal dystonias usually respond well to intra-muscular botulinum toxin therapy and rarely surgeries like deep brain stimulation of the pallidum may be helpful in severe cases. These interventions need to be complemented with patient and caregiver education, and appropriate rehabilitative and psychosocial support. Although in many instances, dystonia remains a chronic lifelong disorder, a comprehensive and thoughtful management approach can often succeed in improving function and the quality of life of patients suffering from this challenging neurologic condition.

### REFERENCES

1. Defazio G. in Stacey MA, editor. *Handbook of Dystonia*. 2007:11-20.
2. Stacey MA, editor. *Handbook of Dystonia*:11-20.
3. Oppenheim H. (Dysbasia lordotica progressive, Dystonia musculorum deformans). *Neurologisches Zentralblatt, Leipzig* 1911; **30**:1090-1107.
4. Pearce JM. A note on scrivener's palsy. *J Neuro Neurol Surg Psych*. 2005; **76**:513.
5. Grundmann K. Primary torsion dystonia. *Arch Neurol* 2005; **62**: 682-685.
6. Shahed J, Jankovic J. in Stacey MA, editor. *Handbook of Dystonia*. 2007:1-10.
7. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. *Adv Neurol*. 1998; **78**:1-10.
8. Tarsey D and Simon DK. Dystonia. *N Engl J Med*. 2006; **355**: 818-29.
9. Bressman SB. Dystonia genotypes, phenotypes and classification. *Adv Neurol*. 2004; **94**:101-107.
10. Gonzalez-Alegre P. The inherited dystonias. *The Neurologist*. 2006; **12**:151-158.
11. Bhidayasiri R. Dystonia genetics and treatment update. *The Neurologist*. 2006; **12**:74-85).
12. Vanek ZV and Jankovic J. Dystonia in corticobasal degeneration. *Movement Disorders*. 2001; **16**:252-251.
13. Hallett M. Disorder of movement preparation in dystonia. *Brain* 2000; **123**:1765-1766.
14. Eidelberg D., Moeller JR, Ishkawa T, et al. The metabolic topography of idiopathic torsion dystonia. *Brain* 1995;**118**: 1473-1484.
15. Levy LM, Hallet M. Impaired brain GABA in focal dystonia. *Ann Neurol*. 2002;**51**: 93-101..
16. Nutt JG, Muentner MD, Aronson A, et al. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. *Mov Disord* 1988; **3**:188-194.
17. ESDE Collaborative Group. A prevalence study of primary dystonia in eight European countries. *J Neurol* 2000; **247**:787-792.
18. Jamora RDG, Tan EK, Liu CP, Kathirvel P, Burgunder JM, Tan LCS. DYT mutations amongst adult primary dystonia patients in Singapore with review of literature comparing East and West. *J Neurol. Sci*. 2006; **247**: 35-37.
19. Matsumoto S, Nishimura M, Kaji R, Sakamoto T, Mezaki T, Shimazu H, et al. DYT1 mutation in Japanese patients with primary torsion dystonia. *Neuroreport*. 2001; **12**:793-5.
20. Lin YW, Chang HC, Chou YH, Chen RS, Hsu WC, Wu WS, et al. DYT1 mutation in a cohort of Taiwanese primary dystonias. *Parkinsonism Relat Disord*. 2006; **12**:15-9.
21. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Chaudhuri A, Hazra A. Community survey of primary dystonia in the city of Kolkata, India. *Movement Disorders*. 2007; **22**(14) 2031-6.
22. Naiya T, Biswas A, Neogi R, Datta S, Misra AK, Das SK, Ray K, Ray J. Clinical characteristics and evaluation of DYT1 gene in Indian primary dystonia

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- patients. *Acta Neurol Scand.* 2006; 114(3): 210-5.
23. Saleheen D, Ali T, Aly Z, Kealani B, Frossard PM. Novel mutation in the PANK2 gene leads to pantothenate kinase-associated neurodegeneration in a Pakistani family. *Pediatr Neurol.* 2007; 37 (4): 296-8.
  24. Vanek ZF. Movement Disorders in Pakistan. A 2-year prospective study to identify and characterize movement disorders presenting in a large public health facility in Karachi. Doctorate in Neurology thesis. 1992; 6-50.
  25. Jankovic J. Treatment of dystonia. *Lancet Neurol.* 2006; 5: 864-72.