Dystonia: A Clinical Approach

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Abstract- Dystonia is a common movement disorder characterised by abnormal postures of the affected body part. It has a very varied presentation and numerous causes, and this can create difficulties with diagnosis and appropriate investigation. This article aims to provide a clinical approach to patients with dystonia, focussing on how to create a differential diagnosis and to plan rational testing.

Key Words: Dystonia, Diagnosis, Investigation, Treatment, Primary

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INTRODUCTION

Dystonia is a movement disorder that is characterised by abnormal postures of the affected body part. There are a number of features of these abnormal postures that make one suspect dystonia rather than another cause. First, these postures are not usually fixed, and as muscle activity shifts in intensity, the posture also changes. The slow writhing movements that can be caused by this phenomenon are known as athetosis. Second, the postures tend to be worsened, or indeed may only appear, when the affected body part is in a particular position, or when performing a particular task (e.g. writing). Third, patients will often find that if they touch the affected body part, the abnormal posture will resolve to a certain extent -- this is a "sensory trick" or "geste antagoniste". Fourth, the postures are characterised by co-contraction of agonist and antagonist muscles. As well as abnormal postures, patients with dystonia may also develop a tremor, usually of the body part affected by dystonia. This tremor tends to be jerky, and, just like the abnormal postures, may be worsened or only appear when the limb is in a particular position or performing a particular task. Pain is not typically the predominant clinical feature in patients with dystonia, although it can occur, particularly in cervical dystonia.

HOW SHOULD ONE CLASSIFY DYSTONIA ?

Dystonia can be classified in a number of ways (Table 1), but clinically the most useful classification system is the aetiological one. This divides dystonia into six main categories: primary dystonia, dystonia plus, secondary dystonia, heredodegenerative dystonia, paroxysmal dystonia and psychogenic dystonia. These are discussed in detail below, with the exception of paroxysmal and psychogenic dystonia. Readers are directed towards other sources[1-8] for discussion of these rare forms of dystonia.

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Table 1. *Different ways of classifying dystonia*

By age at onset	By distribution	By aetiology
Young-onset dystonia (< 28 years)	Focal	Primary (dystonia only +/- tremor; no neurodegeneration).
	Segmental	Dystonia-plus syndromes
Adult-onset dystonia (> 28 years)	Multifocal	- Dopa-responsive dystonia
	Hemidystonia	- Myoclonus dystonia
	Generalised	- Rapid-onset dystonia parkinsonism
		Secondary
		Heredodegenerative
		Paroxysmal
		Psychogenic

The most useful clinical distinction to try to make when faced by a patient with dystonia is if the patient has primary dystonia or has a secondary/heredodegenerative dystonia. This fundamental distinction is of enormous benefit in guiding diagnosis, investigation and treatment.

PRIMARY DYSTONIA

In primary dystonia patients have dystonia as the only clinical feature with or without tremor. There should be no secondary cause evident, and brain imaging will be normal.

When deciding if a patient probably has primary dystonia, it is important to bear in mind that many patients with secondary and degenerative dystonia can present with dystonia as the only clinical feature, and indeed might have normal brain imaging initially. What can one do in this situation to help reach the conclusion that the patient does indeed have primary dystonia?

The key to answering this question is to think of the normal patterns of presentation of primary dystonia, and to ask oneself if the patient fits in with these. Primary dystonia has an anatomical distribution that very much depends on age at onset. Therefore, patients with young onset dystonia (<28 yrs) tend to have dystonia that starts in a limb, and then becomes generalised. This type of dystonia almost never affects the face and bulbar muscles. Patients who develop dystonia between the ages of 30 and 40 tend to develop focal dystonia of the hand (writer's cramp) or other task-specific dystonias (e.g. musician's dystonia). Patients who develop dystonia over the age of 40 (mostly in 50's and 60's) tend to develop focal dystonia of the cranio-cervical muscles e.g. cervical dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm, Meige syndrome (blepharospasm + oromandibular dystonia). Knowledge of these patterns is important in considering if the dystonia is indeed primary. For example, a 60 year old woman presenting with isolated foot dystonia, even if dystonia is her only clinical feature, would make one very suspicious that primary dystonia is not the cause, and other causes need to be considered. Apart from an unusual distribution of dystonia for age at onset, there are other "red flags" that should make one cautious about diagnosing primary dystonia, and these are listed in Table 2.

Young-onset primary dystonia is commonly caused by mutations in the DYT1 gene[9]. In such patients, a single GAG deletion in the DYT1 gene causes onset of dystonia in a limb which will then usually spread, typically over months to a year or so, to affect the rest of the body, but sparing the face and bulbar muscles[10]. A number of atypical phenotypes have also been described[11]. The gene is inherited in an autosomal dominant fashion, but

Table 2. *"Red flags" on history and examination that suggest the dystonia may not be primary*

Abnormal birth/perinatal history
Developmental delay
Seizures
Previous exposure to drugs e.g. dopamine receptor blockers
Continued progression of symptoms
Prominent bulbar involvement by dystonia
Unusual distribution of dystonia given age of onset (e.g. leg dystonia in an adult)
Unusual nature of dystonia (e.g. fixed dystonic postures)
Hemidystonia
Presence of another movement disorder (other than tremor)
Additional neurological symptoms (pyramidal signs, cerebellar signs, cognitive decline)
Other systems affected (e.g. organomegaly)

has very reduced clinical penetrance, so that only about 30% of mutation carriers will develop dystonia. In addition, this penetrance is age dependent, so that mutation carriers who pass the age of 30 without developing dystonia, almost never develop dystonia later in life[10]. Mutation carriers who do not develop dystonia have a subnormal response to experimental techniques that cause plastic changes in the brain, in comparison to an excessive response to the same technique in mutation carriers with dystonia[12]. This adds weight to the theory that susceptibility to undergo plastic change may be excessive in people with dystonia, and that this drives the development of abnormalities in the motor system. There is marked variability in the severity of DYT1 dystonia, with some patients just having mild focal dystonia, while others are severely disabled. The mutation is common in the Ashkenazi Jewish population due to a founder effect[13], but is seen in many other populations. Patients with DYT1 dystonia often respond extremely well to deep brain stimulation of the internal segment of the globus pallidus[14] (see below).

Adult onset focal dystonias (writer's cramp, task-specific dystonias, cranio-cervical dystonias) are common, and although familial forms exist[15-19], no genes are as yet available for testing. The typical pattern of presentation is progression of symptoms over 3-12 months, then a plateau after which further progression or spread of dystonia is unusual. Remissions may occur in focal dystonia, but these are rare, and patients will often relapse later[20]. Excessive practice of a particular movement is a clear precipitant to the development of dystonia in task-specific dystonia (e.g. musician's dystonia), another piece of evidence that some forms of primary dystonia might be caused by abnormalities in the control of brain plasticity processes.

In patients with young-onset dystonia (<30 yrs) which is clinically of the primary type, a minimum set of investigations would include MRI brain imaging, copper studies, DYT1 gene testing and a trial of levodopa if appropriate (see below under dopa-responsive dystonia). One should always keep in mind that some secondary/degenerative forms of dystonia can present with dystonia as the only clinical feature and have normal imaging, therefore the clinician should be alert to the development of symptoms that are at odds with the diagnosis of primary dystonia (e.g. continued progression of symptoms), and investigate as appropriate.

Patients with clinically typical adult-onset primary dystonia often do not require extensive investigation. Copper studies are appropriate in patients under 60 years of age, and consideration should be given to a trial of levodopa in younger patients (see under dopa-responsive dystonia below). Again, development of symptoms that would be unusual for primary dystonia should always prompt a re-evaluation of the patient and appropriate further investigations.

DYSTONIA-PLUS SYNDROMES

Dystonia-plus syndromes are a group of three conditions where dystonia occurs with other symptoms and signs, but there is no neurodegeneration, and they are therefore somewhat different to the secondary/degenerative disorders discussed below.

Dopa-responsive dystonia

This is an autosomal dominant condition caused in about 80% of cases by mutations in the GTP cyclohydrolase 1 gene (GTPCH1)[21,22]. The product of this gene catalyses a rate-limiting step in the production of tetrahydrobiopterin, which itself is an essential cofactor in the conversion of tyrosine to dopamine. It is also a cofactor in the synthesis of serotonin and the metabolism of phenylanaline.

Patients with DRD commonly present in childhood with limb dystonia which gradually progresses. There may be additional parkinsonism, and even mild spasticity and other pyramidal signs. Many patients will show diurnal fluctuation where symptoms are better in the morning and become worse as the day goes on[21]. There have been many other patients reported with atypical presentations e.g. writer's cramp, rest tremor and bradykinesia, with some of these patients presenting in their 20's[23]. All patients show a dramatic and sustained response to levodopa, without the development of dyskinesias and fluctuations seen in Parkinson's disease[24].

DRD is rather complex to diagnose definitively as the GTPCH1 gene is large, and a huge number of mutations have been reported. This makes gene testing difficult and it is often not readily available. As tetrahydrobiopterin is also needed for the breakdown of phenylanaline, a phenylanaline loading test, where patients are given a drink containing a certain amount of phenylanaline and their plasma levels are measured for some hours afterwards, can be helpful as a diagnostic aid, and will show reduced clearance of the phenylanaline in patients with DRD[25]. This test is not fool-proof however and false positive and false negative results do occur. In specialist centres it may be possible to measure CSF pterins (such as tetrahydrobiopterin) and this is a more reliable test, and also enables one to look for other deficits in the dopamine synthesis pathway that can rarely cause DRD (e.g. sepiapterin reductase definiciency[26], tyrosine hydroxylase deficiency[27]).

A trial of levodopa is a pragmatic diagnostic tool, as patients with DRD due to GTPCH1 mutations will all respond well. However, one must be cautious that patients with young-onset Parkinson's disease, particularly due to Parkin mutations, can present with dystonia and parkinsonism, and would also have an initial excellent response to levodopa. As one would not want to treat such patients with levodopa initially, a DAT scan can be a helpful tool. This will be abnormal in young-onset Parkinson's disease and normal in DRD. As DRD is treatable, and the clinical picture can be so variable, all patients with young-onset dystonia (< age 30) in whom no clear cause for the dystonia has been identified should have a trial of levodopa.

Myoclonus dystonia

This is an autosomal dominant syndrome characterised by the childhood onset of myoclonus and dystonia[28,29]. The myoclonus is usually the dominant clinical feature, and the dystonia may be very minimal (when dystonia is absent, such patients are often categorised as "essential myoclonus"). The myoclonus and dystonia typically mainly affect the face, neck and arms, although leg involvement also occurs. The myoclonic jerks are typically very brief – sometimes called "tic-tac" or "lightning" jerks[28,29]. Both the dystonia and myoclonus usually respond very well to alcohol.

In many patients, mutations are found in the epsilon sarcoglycan gene[30-32]. This gene is inherited in an autosomal dominant fashion, but shows maternal imprinting[33,34]. This means that children inheriting the mutation from their mothers will almost never have symptoms, while those inheriting the gene from their fathers almost always will[33,34].

Rapid-onset dystonia parkinsonism

This very rare condition causes the rapid onset of generalised dystonia with or without parkinsonism[35]. The symptoms usually plateau after the period of rapid

evolution, but do not usually recover. The symptoms often seem to be triggered by an infection or other illness. The condition is inherited in an autosomal dominant fashion, and mutations in the ATP1A3 gene have been found in some families[36].

SECONDARY DYSTONIA

Dystonia may occur secondary to brain lesions, most of which are located in the putamen[37]. Dystonia may develop some months, even years, following the lesion. The dystonia in such cases tends to be hemi-dystonia, and therefore any patient with hemidystonia, even if this is the only clinical finding, should have brain imaging.

Dystonia, in the form of an acute dystonic reaction, can occur secondary to a large variety of drugs. This typically occurs within the first 48 hours of exposure to the drug, and is characterised by dystonic spasm affecting the face and larynx, oculogyric crisis, and often extreme psychological distress. Patients should be managed as a medical emergency, as respiratory problems from bulbar dystonia can result. As well as basic supportive treatment, the offending drug should be withdrawn, and patients should be given anticholinergic medication intravenously to try to reverse the dystonia.

Dopamine receptor blocking drugs, which are a common cause of acute dystonic reactions, also cause movement disorders in a small proportion of patients chronically exposed to these drugs. These movement disorders may consist of choreiform movements, typically of the face (tardive dyskinesia), or tardive dystonia. The dystonia characteristically involves the axial muscles, so patients walk with their back and neck arched[38]. Both syndromes are very difficult to treat. If possible, the offending drug should be withdrawn immediately. If it is not possible to stop the drug, then it should be changed to an atypical dopamine receptor blocker – clozapine has the best evidence for effect[39-42], but requires blood monitoring. Other drugs that may help include anticholinergics and baclofen, and deep brain stimulation may also be an option for some severely affected patients[43-46].

Dystonia may also occur secondary to infections for example as part of Sydenham's chorea, and following Japanese B encephalitis.

HEREDO-DEGENERATIVE DYSTONIA

A huge number of degenerative neurological conditions cause dystonia as part of a wider phenotype of neurological dysfunction. Many of these conditions are rare and testing for all of them can be laborious, expensive and sometimes invaisive. In view of this a rational approach is needed for patients in whom an heredo-degenerative dystonia is suspected.

The key here is to look for "syndromic associations". These are symptoms or signs present in the patients in addition to the dystonia which help to greatly narrow down the diagnostic possibilities. For example, if your patient with a suspected degenerative dystonia also has a peripheral neuropathy, then this narrows down the diagnostic possibilities to just a few (e.g. neuroacanthocytosis, spinocerebellar ataxia, metachromatic leucodystrophy).

Table 3 give a list of conditions that cause dystonia as part of a degenerative nervous system disorder. These conditions are divided by their common syndromic associations. Table 4 lists useful diagnostic tests that can be applied after a list of differential diagnosis has been made.

TREATMENT

Treatment of dystonia very much depends on the underlying cause, and the distribution of the dystonia itself. Botulinum toxin injections are the first line treatment for dystonia affecting the face and neck[47,48]. They have less usefulness in hand dystonia, where hand weakness can occur and may cancel out any improvement in the posture. Patients with generalised dystonia are not generally suitable for botulinum toxin injections, unless they are being used to treat a particular focal problem (e.g. foot posturing that is severely impairing gait).

Medical treatment relies mainly on anticholinergics. These are drugs that have significant side effects, particularly for older patients, but younger patients may be able to build up slowly to large doses with a good effect

Table 3. *Causes of heredodegenerative dystonia classified by their syndromic associations. Adapted from[3].*

Dystonia and parkinsonism	Parkinson's disease
	Progressive supranuclear palsy
	Multiple system atrophy
	Corticobasal degeneration
	Wilson's disease
	Huntington's disease
	Spinocerebellar ataxia (esp. SCA3)
	GM1 gangliosidosis
	Neuronal brain iron accumulation syndrome
	Rapid onset dystonia-parkinsonism
	X-Linked dystonia parkinsonism
Dystonia and eye movement disorder	Niemann-pick C
	Ataxia telangectasia
	Spinocerebellar ataxia
	Wilson's disease
	Huntington's disease
	Progressive supranuclear palsy
Dystonia with prominent bulbar involvement	Neuronal brain iron accumulation syndrome
	Neuroacanthocytosis
	Wilson's disease
Dystonia with Ataxia	Spinocerebellar ataxia
	Wilson's disease
	Huntington's disease
	DRPLA
	Multiple system atrophy
	Neuroacanthocytosis
	Cervical dystonia and ataxia
	GM2 gangliosidosis
Dystonia with Peripheral Neuropathy	Metachromatic leucodystrophy
	Spinocerebellar ataxia
	Neuroacanthocytosis
	GM2 gangliosidosis
Other	Mohr-Tranebjaerg syndrome (dystonia and deafness)
	Aminoacidaemias (infantile onset neurodevelopmental syndromes)

on the dystonia. Other drugs which are used (without much empirical evidence) include clonazepam (which can be useful for dystonic tremor), tetrabenazine, baclofen and gabapentin. As mentioned above, all patients with young-onset dystonia (< age 30) who do not have a clear reason for their dystonia deserve a trial of levodopa. Occasionally, patients with dystonia which is not DRD are reported to have a limited response to

Table 4. *Investigations that may be considered in the investigation of heredo-degenerative dystonia. Testing should be guided by syndromic associations. Adapted from[3].*

Genetic tests
- Huntingtin (Huntington's disease)
- PANK2 gene (Neuronal brain iron accumulation)
- SCA 1, 2, 3, 5, 7, 17 (Spinocerebellar ataxia)
- Ferritin light chain (Neuronal brain iron accumulation)
- DRPLA gene (DRPLA)
- NPC1/2 (Niemann pick C)
- ATM (Ataxia telangectasia)
- TIMM8A (Mohr-Tranebjaerg syndrome)
Bloods
- Acanthocytes (Neuroacanthocytosis, neuronal brain iron accumulation)
- Copper, Ceruloplasmin (Wilson's, neuronal brain iron accumulation)
- Plasma amino acids (Amino acidaemias)
- White cell enzymes (GM1/2 gangliosidosis, metachromatic leucodystrophy)
- Alphafetoprotein (Ataxia telangectasia)
- Immunoglobulins (Ataxia telangectasia)
- CK (Neuroacanthocytosis)
- Lipid chromatography (HARP)
Urine tests
- Urinary organic acids (Amino acidaemias)
- 24hr urinary copper (Wilson's)
MRI brain
- Iron deposition (Neuronal brain iron accumulation)
- Caudate atrophy (Huntington's disease)
- Leucodystrophy (Metachromatic leucodystrophy)
- White matter high signal (Amino acidaemias)
Functional imaging
- Abnormal DaT scan (Parkinson's disease, corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy)
Other
- Slit-lamp examination (Wilson's)
- Liver biopsy (Wilson's)
- Nerve conduction studies (Metachromatic leucodystrophy, neuroacanthocytosis, spinocerebellar ataxia, GM2 gangliosidosis)
- Electro-retinography (Neuronal brain iron accumulation)

levodopa.

Peripheral surgical and brain lesion operations for dystonia have now been largely replaced by deep brain stimulation (DBS) of the internal segment of the globus pallidus. This can be a very successful operation for patients with primary dystonia, and has most evidence to support its use in childhood onset generalised dystonia, such as DYT1 dystonia[14]. Such patients may get an 80-

90% improvement in symptoms which seems to be sustained over time[14]. Some patients with treatment resistant focal dystonia have also had benefit from DBS[49-52] as well as patients with myoclonus dystonia[53]. Patients with secondary/degenerative dystonia tend to have less response to DBS[54], although in very selected cases such operations may be appropriate, as the small functional gains can make a significant difference to quality of life.

REFERENCES

1. Bhatia KP, Bhatt MH, Marsden CD. The causalgia-dystonia syndrome. Brain 1993;116:843-51.
2. Bhatia KP. Familial (idiopathic) paroxysmal dyskinesias: an update. Semin Neurol 2001;21:69-74.
3. Edwards MJ, Quinn NP, Bhatia KP. Parkinson's Disease and Other Movement Disorders. Oxford: Oxford University Press, 2008.
4. Espay AJ, Morgante F, Purzner J, et al. Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol 2006; 59:825-34.
5. Fahn S, Williams DT. Psychogenic dystonia. Adv Neurol 1988;50:431-55.
6. Mink JW. Paroxysmal dyskinesias. Curr Opin Pediatr 2007;19:652-6.
7. Schrag A, Trimble M, Quinn N, et al. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain 2004; 127:2360-72.
8. Schrag A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2005;18:399-404.
9. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;17:40-8.
10. Bressman SB, Sabatti C, Raymond D, et al. The DYT1 phenotype and guidelines for diagnostic testing. Neurology 2000;54:1746-52.
11. Edwards M, Wood N, Bhatia K. Unusual phenotypes in DYT1 dystonia: a report of five cases and a review of the literature. Mov Disord 2003;18:706-11.
12. Edwards MJ, Huang YZ, Mir P, et al. Abnormalities in motor cortical plasticity differentiate manifesting and non-manifesting DYT1 carriers. Mov Disord 2006;21:2181-6.
13. Bressman SB, de Leon D, Kramer PL, et al. Dystonia in Ashkenazi Jews: clinical characterization of a founder mutation. Ann Neurol 1994;36:771-7.
14. Coubes P, Cif L, El Fertit H, et al. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg 2004;101: 189-94.
15. Almasy L, Bressman SB, Raymond D, et al. Idiopathic torsion dystonia linked to chromosome 8 in two Mennonite families. Ann Neurol 1997;42:670-3.
16. Bentivoglio AR, Ialongo T, Contarino MF, et al. Phenotypic characterization of DYT13 primary torsion dystonia. Mov Disord 2004;19:200-6.
17. Leube B, Hendgen T, Kessler KR, et al. Evidence for DYT7 being a common cause of cervical dystonia (torticollis) in Central Europe. Am J Med Genet 1997;74:529-32.
18. Ozelius LJ. Update on the genetics of primary torsion dystonia loci DYT6, DYT7, and DYT13 and the dystonia-plus locus DYT12. Adv Neurol 2004;94:109-12.
19. Valente EM, Bentivoglio AR, Cassetta E, et al. Identification of a novel primary torsion dystonia locus (DYT13) on chromosome 1p36 in an Italian family with cranial-cervical or upper limb onset. Neurol Sci 2001;22: 95-6.
20. Koukouni V, Martino D, Arabia G, et al. The entity of young onset primary cervical dystonia. Mov Disord 2007; 22:843-7.
21. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol 2003;54:S32-S45.
22. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994;8:236-42.
23. Bandmann O, Marsden CD, Wood NW. Atypical presentations of dopa-responsive dystonia. Adv Neurol 1998;78: 283-90.
24. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology 1991;41:174-81.
25. Bandmann O, Goertz M, Zschocke J, et al. The phenylalanine loading test in the differential diagnosis of dystonia. Neurology 2003;60:700-2.
26. Abeling NG, Duran M, Bakker HD, et al. Sepiapterin reductase deficiency an autosomal recessive DOPA-responsive dystonia. Mol Genet Metab 2006;89:116-20.

27. Bartholome K, Ludecke B. Mutations in the tyrosine hydroxylase gene cause various forms of L-dopa-responsive dystonia. Adv Pharmacol 1998;42:48-9.
28. Quinn NP. Essential myoclonus and myoclonic dystonia. Mov Disord 1996;11:119-24.
29. Quinn NP, Rothwell JC, Thompson PD, et al. Hereditary myoclonic dystonia, hereditary torsion dystonia and hereditary essential myoclonus: an area of confusion. Adv Neurol 1988;50:391-401.
30. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. Nat Genet 2001;29:66-9.
31. Valente EM, Edwards MJ, Mir P, et al. The epsilon-sarcoglycan gene in myoclonic syndromes. Neurology 2005; 64:737-9.
32. Asmus F, Zimprich A, Tezenas Du Montecl S, et al. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. Ann Neurol 2002;52:489-92.
33. Grabowski M, Zimprich A, Lorenz-Depiereux B, et al. The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. Eur J Hum Genet 2003;11:138-44.
34. Müller B, Hedrich K, Kock N, et al. Evidence that paternal expression of the epsilon-sarcoglycan gene accounts for reduced penetrance in myoclonus-dystonia. Am J Hum Genet 2002;71:1303-11.
35. Brashear A, Dobyns WB, de Carvalho AP, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. Brain 2007;130:828-35.
36. de Carvalho Aquiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na+/K+ -ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron 2004;43:169-75.
37. Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 1994;117:859-76.
38. Kiriakakis V, Bhatia KP, Quinn NP, et al. The natural history of tardive dystonia. A long-term follow-up study of 107 cases. Brain 1998;121:2053-66.
39. Karp BI, Goldstein SR, Chen R, et al. An open trial of clozapine for dystonia. Mov Disord 1999;14:652-7.
40. Adityanjee, Estrera AB. Successful treatment of tardive dystonia with clozapine. Biol Psychiatry 1996;39:1064-5.
41. van Harten PN, Kampuis DJ, Matroos GE. Use of clozapine in tardive dystonia. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:263-74.
42. Trugman JM, Leadbetter R, Zalis ME, et al. Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. Mov Disord 1994;9:441-6.
43. Franzini A, Marras C, Ferroli P, et al. Long-term high-frequency bilateral pallidal stimulation for neuroleptic-induced tardive dystonia. Report of two cases. J Neurosurg 2005;102:721-5.
44. Cohen OS, Hassin-Baer S, Spiegelmann R. Deep brain stimulation of the internal globus pallidus for refractory tardive dystonia. Parkinsonism Relat Disord 2007;13:541-4.
45. Zhang JG, Zhang K, Wang ZC, et al. Deep brain stimulation in the treatment of secondary dystonia. Chin Med J (Engl) 2006;119:2069-74.
46. Trottenberg T, Volkmann J, Deuschl G, et al. Treatment of severe tardive dystonia with pallidal deep brain stimulation. Neurology 2005;64:344-6.
47. Jankovic J. Dystonia: medical therapy and botulinum toxin. Adv Neurol 2004;94:275-86.
48. Comella CL, Thompson PD. Treatment of cervical dystonia with botulinum toxins. Eur J Neurol 2006;13:16-20.
49. Bereznai B, Steude U, Seelos K, et al. Chronic high-frequency globus pallidus internus stimulation in different types of dystonia: a clinical, video, and MRI report of six patients presenting with segmental, cervical, and generalized dystonia. Mov Disord 2002;17:138-44.
50. Eltahawy HA, Saint-Cyr J, Poon YY, et al. Pallidal deep brain stimulation in cervical dystonia: clinical outcome in four cases. Can J Neurol Sci 2004;31:328-32.
51. Foote KD, Sanchez JC, Okun MS. Staged deep brain stimulation for refractory craniofacial dystonia with blepharospasm: case report and physiology. Neurosurgery 2005;56:E415.
52. Islekel S, Zileli M, Zileli B. Unilateral pallidal stimulation in cervical dystonia. Stereotact Funct Neurosurg 1999; 72:248-52.
53. Cif L, Valente EM, Hemm S, et al. Deep brain stimulation in myoclonus-dystonia syndrome. Mov Disord 2004; 19:724-7.
54. Cif L, El Fertit H, Vayssiere N, et al. Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. J Neurosurg Sci 2003;47:52-5.