Syndrome of the month

The dystonias

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Dystonia is a syndrome of abnormal involuntary movements characterised by sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures.[1] Dystonia may be classified according to aetiology, as primary torsion dystonia (also known as idiopathic torsion dystonia, ITD) when dystonia is the only abnormality, or as secondary dystonia when occurring in the setting of another disease. Primary torsion dystonia (PTD) is predominantly genetic in aetiology and may now be increasingly subdivided according to genetic locus, as the understanding of the molecular genetic basis of dystonia evolves.

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Estimates of the prevalence of generalised PTD vary from 1.6 per 100 000 in the north of England[2] to 3.4 per 100 000 in Minnesota[3]; this figure may be as much as five times higher in the Ashkenazi Jewish population. Focal dystonia, affecting only one part of the body, is the commonest form of dystonia, with an estimated prevalence of 12-30 per 100 000.[2,3]

The dystonias are a clinically and genetically diverse group of disorders. Recent advances in genetics may be expected to lead to improved understanding of the pathophysiology and ultimately to the development of more effective treatment for dystonia.

Clinical features

Dystonia may involve almost any muscle group with a correspondingly wide range of clinical manifestations, encompassing equinovarus posturing of the foot with toe walking, hyperpronation of the arm, lordosis, scoliosis, and torticollis. Writer's cramp, spasmodic dysphonia, blepharospasm, and oromandibular dystonia (the latter two occurring together as Meige's syndrome) all fall within the rubric of dystonia. Dystonic spasms are often intermittent initially, appearing or intensifying with voluntary movement (which may lead to an erroneous diagnosis of hysteria), but dystonic postures may eventually become fixed. Electrophysiologically, dystonia is characterised by co-contraction of antagonist muscles and overflow of activity into extraneous muscles.

PRIMARY TORSION DYSTONIA (PTD)
PTD is clinically heterogeneous and may be classified according to age at onset, body part first affected, and distribution (table 1). Severity is largely determined by age at onset.[4] The age at onset distribution of dystonia is bimodal with peaks at 9 and 45 years. There are clear clinical differences between patients with early (<20 years) and late onset (>20 years) PTD. Early onset PTD usually begins in a limb, particularly the leg, and frequently progresses to generalised dystonia. Muscles of the head and neck are frequently spared. In contrast, late onset PTD typically begins in the neck or head, for example with torticollis, and tends to remain focal in distribution. Segmental dystonia is of intermediate severity and may arise at any age.[4,5]

Early, limb onset PTD is particularly prevalent among the Ashkenazi Jewish population where inheritance is autosomal dominant with approximately 30% penetrance.[6] In the UK, generalised, multifocal, and segmental dystonia are estimated to be dominantly inherited in 85% of cases, with approximately 40% penetrance.[7] The remaining 15% of cases are thought to be non-genetic phenocopies.

The genetic contribution to adult onset focal dystonia is not yet clear. Most cases are apparently sporadic, but careful family studies suggest the existence of one or more autosomal dominant genes with low penetrance.[5,8] A small number of large families exist in which focal dystonia is inherited as a dominant trait with relatively high penetrance.[9-11] It seems likely, however, that non-genetic causes account for a proportion of cases.

DOPA RESPONSIVE DYSTONIA (DRD)
DRD occupies a unique place among the dystonias as the condition may be very effectively treated and its molecular pathogenesis is better understood than that of any other dystonia. Patients may be clinically indistinguishable from early onset PTD,[12] typically presenting in childhood with dystonia involving the lower limb which progresses to become generalised unless treated. DRD may be distinguished from PTD, however, by the dramatic and sustained therapeutic response to low doses of L-dopa.[13] Diurnal variation of symptoms with

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Table 1 Classification of dystonia by distribution

Focal dystonia	Single body part affected, eg neck (torticollis)
Segmental dystonia	Two or more contiguous body parts affected, eg one leg and trunk (segmental crural dystonia)
Generalised dystonia	Segmental crural plus any other body part
Multifocal dystonia	Two or more non-contiguous areas affected
Hemidystonia	Ipsilateral leg and arm affected

Table 2 Selected genetic causes of secondary dystonia

Disease	Additional clinical features	Inheritance	Gene/localisation/metabolic defect
Wilson's disease	Psychiatric, hepatic, ocular manifestations. Parkinsonism, BG lucencies on CT	AR	Copper transporting ATPase gene
Huntington's disease	Dementia, chorea	AD	HD gene (CAG expansion)
Hallervorden-Spatz disease	Progressive dystonia. Parkinsonism, cognitive impairment, retinopathy and optic atrophy may occur	AR	20p12.3-p13[17]
Neuroacanthocytosis	Chorea, neuropathy, acanthocytosis	AR	9q21 (chorea-acanthocytosis)[18] Triglyceride transfer protein gene (abetalipoproteinaemia)[19]
Machado-Joseph disease	Cerebellar ataxia	AD	SCA3 gene (CAG expansion)
Niemann-Pick disease, type C	Supranuclear gaze palsy, ataxia, dementia, hepatosplenomegaly, foamy cells in marrow, sea blue histiocytes on skin biopsy	AR	NPC1 gene[20]
Ataxia telangiectasia	Telangiectasia, ataxia, oculomotor apraxia, neuropathy, malignancies	AR	ATM gene[21]
Juvenile onset neuronal ceroid lipofuscinosis	Seizures, dementia, psychiatric manifestations, retinopathy, ataxia	AR	CLN3 gene[22]
Leigh's syndrome	Vomiting, subacute brain stem syndrome, encephalopathy, lactic acidosis, BG lucencies on CT	AR X linked Maternal	Pyruvate dehydrogenase deficiency Pyruvate carboxylase deficiency Mitochondrial DNA mutations[23]
Juvenile/adult metachromatic leucodystrophy	Dementia, psychiatric disorder, siezures, white matter dystrophy	AR	Arylsulphatase A deficiency
Late onset GM_1 and GM_2 gangliosidoses	Dementia, ataxia, amyotrophy	AR	β galactosidase deficiency Hexosaminidase deficiency
Lesch-Nyhan syndrome	Mental retardation, spasticity, self-mutilation	X linked	Hypoxanthine-guanine phosphoribosyl transferase deficiency
Organic acidaemias	Acidosis, episodic ataxia and encephalopathy, neutropenia/thrombocytopenia, BG lucencies on CT	AR	Propionyl CoA carboxylase, methylmalonyl CoA mutase, glutaryl CoA dehydrogenase deficiencies
Mohr-Tranebjaerg syndrome	Deafness, cortical blindness, mental retardation	X linked	DDP gene (deafness/dystonia peptide)[24]
Leber's hereditary optic atrophy - dystonia	Subacute visual loss, BG lucencies on CT	Maternal	Mitochondrial DNA mutations

BG: basal ganglia.

improvement of dystonia after sleep is a characteristic feature of DRD. It is now recognised that the DRD phenotype may encompass a number of atypical presentations including Parkinsonism, spastic paraplegia, and a presentation mimicking athetoid cerebral palsy.[14-16] Most cases are inherited as an autosomal dominant trait with reduced penetrance and females outnumber males by approximately three to one.

SECONDARY DYSTONIAS
Dystonia may occur as a symptom of numerous diseases affecting the central nervous system, accounting for about one in three cases of dystonia. This is a highly heterogeneous group of disorders, many of which are genetic (table 2). Structural lesions of the basal ganglia, athetoid cerebral palsy, neuroleptic drug exposure, and numerous metabolic, toxic, and infective disorders may all cause dystonia.[1] In most cases the clinical presentation is not dominated by dystonia; other neurological features such as cognitive impairment, seizures, visual impairment, or pyramidal lesions are present. Occasionally, however, dystonia may be the sole clinical manifestation, although there are often clinical clues indicating another underlying disease. Hemidystonia is almost always the result of a lesion of the contralateral basal ganglia or its connections; a rapid progression of symptoms, onset with dystonia at rest, and the presence of other neurological features should alert the clinician to the presence of a secondary dystonia.

PAROXYSMAL DYSTONIAS
These are an unusual group of hyperkinetic movement disorders in which dystonia, chorea, and ballism occur together in episodic attacks.[25] Clear consciousness is preserved

throughout and patients are normal between attacks. Three forms are recognised, distinguished by the duration of attacks and precipitating factors. Paroxysmal kinesigenic choreoathetosis (PKC) is the commonest form, characterised by frequent attacks (up to 100 per day), lasting only seconds and precipitated by sudden movement or startle.[26-28] The condition responds well to treatment with anticonvulsant drugs. Inheritance appears to be autosomal dominant with reduced penetrance in about two thirds of cases. Paroxysmal dystonic choreoathetosis (PDC) causes less frequent but more prolonged attacks, lasting from 10 minutes to 24 hours, which may be precipitated by a variety of stimuli, including emotion, stress, caffeine, and alcohol.[26 29 30] PDC is usually dominantly inherited with high (80%) penetrance. A more poorly defined exercise induced form exists in which attacks are of intermediate duration. The paroxysmal dystonias are frequently misdiagnosed as epilepsy or hysteria.

Differential diagnosis and investigation
Imaging and laboratory investigations are normal in PTD. The main objective of investigation of dystonia is to identify secondary dystonias, particularly those that are amenable to treatment, such as Wilson's disease. Investigations should include copper and ceruloplasmin measurement, as well as slit lamp examination of the eyes to exclude Wilson's disease in patients below the age of 50. CT or MRI scan, lysosomal enzymes, and examination of a blood smear for acanthocytes may be indicated. A careful drug history should be taken to exclude drug induced dystonia.

Identification of patients with DRD by means of a therapeutic trial of L-dopa (250 mg three times a day for three months) is essential

Table 3   Genetic loci for the primary dystonias

Symbol	Disease	Inheritance	Gene/linkage
DYT1	PTD, usually early, limb onset with progression. Commoner in Jewish patients.	AD (30-40% penetrance)	TorsinA, 3 bp deletion
DYT2	Autosomal recessive PTD (Spanish Gypsies)	AR	—
DYT3	Philippino dystonia-Parkinsonism	X linked	Xq13.1
DYT4	PTD with laryngeal involvement (one family)	AD	—
DRD (DYT5)	L-dopa responsive dystonia	AD	GCH1
		AR	TH
DYT6	Mixed phenotype PTD (Mennonites)	AD	8p21-q22
DYT7	Late onset, focal PTD	AD	18p
PDC	Pure PDC	AD	2q35-q37
	Complicated PDC	AD	1p

PTD: primary torsion dystonia. AR: autosomal recessive. AD: autosomal dominant. GCH1: GTP cyclohydrolase 1 gene. TH: tyrosine hydroxylase gene. PDC: paroxysmal dystonic choreoathetosis.

in all cases of dystonia with onset in childhood or early adult life (<30 years).

The molecular genetic basis of dystonia

Over the last decade there have been considerable advances in understanding of the genetics of dystonia. These have been driven by the need to take a positional cloning approach to understanding pathophysiology, as anatomical and neurochemical studies in PTD are generally unrevealing. A molecular genetic classification of the dystonias is now evolving, which complements the more traditional clinical classification, and allows phenotype-genotype correlations to be made (table 3). Each of the dystonia loci is associated with a characteristic, but sometimes overlapping spectrum of phenotypic manifestations. Some loci are of considerable clinical importance (such as DYT1 and DRD), while the contribution of others has not yet been fully evaluated.

DYT1

Linkage studies in Jewish and non-Jewish families with PTD led to the identification of the DYT1 locus on chromosome 9q34.[31][32] Strong linkage disequilibrium has been shown between DYT1 and a 9q34 haplotype in both familial and sporadic Jewish cases, indicating a founder mutation estimated to have occurred among the Ashkenazim of eastern Europe about 350 years ago.[33][34] The DYT1 gene is enriched in this population as a result of genetic drift, with a gene frequency estimated to be as high as 1/2000.[34] Very recently the DYT1 gene was cloned and a unique 3 bp deletion identified in all chromosome 9q34 linked families, regardless of ethnic background and surrounding haplotype.[35] The deletion results in loss of one of a pair of glutamic acid residues in a novel protein named torsinA. TorsinA is an ATP binding protein with some similarity to the family of heat shock proteins; its function in the nervous system and role in the pathogenesis of dystonia are not yet understood. The common 3 bp deletion appears to have arisen independently in different ethnic groups and, to date, no other mutations have been identified in the gene, suggesting that only a single variation in the protein can give rise to the dystonia phenotype. However, a small proportion of patients with the typical DYT1 phenotype do not carry the deletion.[35] It is not yet clear if these patients have novel mutations in torsinA, or whether other genes underlie dystonia in such cases.

Although detailed phenotype-genotype studies are still awaited, it is already clear that the DYT1 mutation produces a relatively homogeneous clinical phenotype in Jews and non-Jews, with early limb onset and spread to at least one other limb, but rarely involving muscles above the neck.[35][36] Patients with the Jewish chromosome 9q34 haplotype (DYT1^{AJ}) have a mean age at onset of 12.5 years and 70% eventually develop generalised or multifocal dystonia. However, a small proportion of patients with DYT1^{AJ} have a less severe phenotype, with late onset (never after the age of 44) and little or no progression of symptoms after long follow up. In Europe, DYT1 mutations are estimated to account for approximately 55% of families with generalised or segmental dystonia.[37] Mutation analysis of DYT1 in these patients is now under way.

It has been suggested that DYT1 mutations may also be a common cause of late onset focal dystonia. However, there is now mounting evidence that early and late onset PTD are genetically as well as clinically distinct.[10][11][38-41] In the study of Ozelius et al,[35] no patients with focal or segmental dystonia affecting muscles of the head or neck were found to have the 3 bp deletion in torsinA.

DYT2

Autosomal recessive inheritance of PTD has been proposed in a small number of consanguineous Spanish Gypsy kindreds.[42] There is no clear evidence supporting autosomal recessive inheritance of PTD outside this population, however.[43]

DYT3

The syndrome of dystonia-Parkinsonism (Lubag) is an X linked, neurodegenerative disorder confined to the Philippines. Allelic association with markers at Xq13.1 indicates the existence of a founder mutation in this population.[44][45]

DYT4

Dystonia with prominent laryngeal involvement has been reported in a large Australian family.[41][46] A genomic search has not yet identified a locus in this family.[47]

DRD (formerly DYT5)

Assignment of the DRD locus to chromosome 14q led to the identification of heterozygous mutations within the GTP cyclohydrolase I

gene (GCH1), reducing enzyme activity to 2-20% of normal in patients with DRD.[48-50] GCH1 catalyses the initial and rate limiting step of tetrahydrobiopterin synthesis. Tetrahydrobiopterin is an essential cofactor for tyrosine hydroxylase, the rate limiting enzyme in the dopamine synthesis pathway. Partial deficiency of GCH1 is believed to result in impaired CNS dopamine synthesis and thus dystonia or Parkinsonism. Inheritance is usually autosomal dominant; complete GCH1 deficiency resulting from recessively transmitted homozygous mutations causes a severe infantile neurological syndrome characterised by hyperphenylalaninaemia, severely retarded development, abnormal muscle tone, and convulsions.[51] Autosomal recessive inheritance of DRD is rare, but has been described in a family with homozygous mutations of the gene for tyrosine hydroxylase.[52]

DYT6

A locus for a mixed dystonia phenotype has recently been mapped to a 40 cM interval, spanning the pericentromeric region of chromosome 8, in two German-American Mennonite families.[53] Although some family members have a phenotype similar to the DYT1 phenotype, the wide age at onset distribution, and overall tendency to involve limb and craniocervical muscles equally, are distinguishing features of the DYT6 phenotype. This locus may be unique to the genetically isolated Mennonite population.

DYT7

Only one locus for late onset, purely focal dystonia has been identified. A gene causing torticollis and spasmodic dysphonia in a large German family with a mean age at onset of 43 years has been assigned to a 30 cM interval on chromosome 18p.[11] Similarly affected, apparently sporadic cases of focal dystonia in northern Germany were found to share a common haplotype over a 6 cM region of 18p,[54 55] suggesting that dominant inheritance at low penetrance of a founder mutation in the DYT7 gene may be an important cause of focal PTD in the German population. The contribution of this locus to focal dystonia in other populations remains to be determined.

Exclusion of the DYT1, DYT6, and DYT7 loci in five large families with dominantly inherited dystonia[10 40 41 56] indicates the existence of one or more as yet unmapped genes for PTD (unpublished data, P Jarman).

PAROXYSMAL DYSTONIC CHOREOATHETOSIS (PDC)

To date, three large families with classical PDC have been shown to be linked to a 4 cM locus at chromosome 2q35-q37.[30 57 58] A second locus for a complicated form of PDC associated with constant spastic paraplegia has been localised to chromosome 1p in a single kindred.[59] A chloride/bicarbonate anion exchanger gene, SLC4A3, known to map to the PDC locus on chromosome 2q is a candidate gene for PDC.[30]

Genetic counselling

In the UK, the recurrence risk to offspring and sibs of patients with generalised, segmental or multifocal, familial PTD is estimated to be 21%. For single cases, the risk to children and sibs falls to 14% and 8% respectively.[7] These figures may be reduced by 50%, 75%, and 90% by the ages of 15, 30, and 50, respectively, for clinically unaffected relatives. Prenatal and predictive testing have been performed in Jewish patients using the DYT1[AJ] disease associated haplotype.[60] The identification of a common mutation in the DYT1 gene, detectable by restriction digest, will simplify genetic testing, extending it to many non-Jewish families and allowing diagnostic testing to be performed. However, the low penetrance and variable expression of the DYT1 gene mean that predictive testing cannot predict phenotype. Genetic testing for non-DYT1 dystonias will remain confined to families large enough for linkage analysis.

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