

Paediatric *movement* disorders

Progress in understanding

Emilio Fernández-Alvarez
Alexis Arzimanoglou
Eduardo Tolosa

Paediatric Movement disorders is a relatively new and exciting field of Child Neurology. The present book represents the outcome of an international symposium, organized as a forum for exchange between both adult and child neurologists. The contributions of highly qualified experts represent the "state of the art" of this rapidly expanding field. A source of thought for progress in further understanding, it will prove to be a useful tool to both clinicians and scientists.



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Emilio Fernández-Alvarez ; Alexis Arzimanoglou ; Eduardo Tolosa

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Early onset primary torsion dystonia

Alfonso Fasano, Antonio E. Elia, Alberto Albanese

Istituto Nazionale Neurologico Carla Besta, Università Cattolica del Sacro Cuore, Milano, Italy

Dystonia is one of the several movement disorders that may arise in childhood. Primary torsion dystonia (PTD) is a syndrome of sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures [1-3], which is not secondary to any known cause. Non-secondary forms of dystonia encompass primary torsion dystonia (PTD), in which dystonia is the one and only symptom of the observed condition (e.g. DYT1 dystonia), dystonia plus syndromes, in which dystonia is a prominent sign, yet associated with another movement disorder (e.g., myoclonus-dystonia), and dystonia associated with hereditary degenerative conditions (such as pantothenate kinase-associated neurodegeneration or Wilson's disease) (Table I). All the non-secondary forms of dystonia can be observed in children and are considered to be of genetic origin. Advances in scientific knowledge have allowed to directly assess only a restricted number of dystonia types by genetic testing (Table II).

Table I. Classifications of dystonia.

By age at onset

- Early onset (≤ 21 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk.
- Late onset (> 21 years): usually starts in the neck (including the vocal folds), the cranial muscles or one arm. Tends to remain localised with restricted progression to adjacent muscles.

By distribution

- Focal: single body region (e.g., writer's cramp, blepharospasm).
- Segmental: contiguous body regions (e.g., cranial and cervical, cervical and upper limb).
- Multifocal: non-contiguous body regions (e.g., upper and lower limb, cranial and upper limb).
- Generalised: both legs and at least one other body region (usually one or both arms).

By cause

- Primary (or idiopathic): dystonia is the only clinical sign and there is no identifiable exogenous cause or other inherited or degenerative disease. Example: DYT1 dystonia.
- Dystonia plus: dystonia is a prominent sign, but is associated with another movement disorder. There is no evidence of neurodegeneration. Example: Myoclonus-dystonia (DYT11).
- Heredo-degenerative: dystonia is a prominent sign, among other neurological features, of a hereditary degenerative disorders. Example: Wilson's disease.
- Secondary: dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals. Examples: dystonia due to a brain tumour, off-period dystonia in Parkinson's disease.

Table II. Genetic forms of childhood dystonia that can be diagnosed by direct testing.

Gene name (locus) ¹	Gene location	Disease	Trans-mission ²
Primary torsion dystonia			
TOR1A (DYT1)	9q34	Early limb-onset or Oppenheim's dystonia	AD
Dystonia plus syndromes			
GTP-CH I (DYT5)	14q22	Dopa-responsive dystonia (DRD) or Segawa syndrome	AD
SGCE (DYT11)	7q21.q31	Myoclonus-dystonia	AD
TH	11p15.5	Dopa-responsive dystonia (DRD)	AR
Heredodegenerative syndromes			
PRKN (PANK2)	20p13	Pantothenate kinase associated neurodegeneration (PKAN) or Hallervorden-Spatz disease	AR
PARK2	6q25	Autosomal recessive early-onset parkinsonism	AR
ATP7B	13q14.3-q21.1	Wilson's disease	AR
IT-15	4p16	Huntington's disease	AD
FTL	19q13.3	Neuroferritinopathy	AD
Nuclear or mitochondrial DNA mutations	mDNA	Leigh's disease	M
DDP	Xq22	Mohr-Tranebjaerg syndrome	XR
NPC1	18q11-q12	Niemann-Pick disease, type C1	AR
PLP1	Xq22	Pelizaeus-Merzbacher disease	XR
HEXA	15q23-q24	Tay-Sachs disease	AR
ATX3	14q24.3-q31	Machado-Joseph disease	AD
Mitochondrial DNA mutations	mDNA	Leber's disease	M
GCDH	19p13.2	Glutaricacidemia	AR
ARSA	22q13.31-qter	Metachromatic leukodystrophy	AR
DJ1 (PARK7)	1p36	Autosomal recessive early-onset parkinsonism	AR
TBP (SCA17)	6q27	Spinocerebellar ataxia 17	AD
HE1 (NPC2)	14q24.3	Niemann-Pick disease, type c2	AR
MECP2	Xq28	Rett syndrome	XD
HPRT	Xq26-q27.2	Lesch-Nyhan syndrome	XR
FUCA1	1p34	Fucosidosis	AR
ATM	11q22.3	Ataxia-telangiectasia	AR
CLN3	16p12.1	Ceroid-lipofuscinosis	AR

¹ Abbreviations: ARSA, arylsulfatase A; ATM, ataxia-telangiectasia mutated gene; ATP7B, ATPase, Cu⁺⁺-transporting beta polypeptide; ATX3, ataxin-3; CLN3, CLN3 gene; DDS, dystonia-deafness syndrome gene; DJ1, oncogene DJ1; FTL, ferritin light chain; FUCA1, alpha-L-fucosidase 1; GCDH, glutaryl-CoA dehydrogenase; GTP-CH I, guanosine triphosphate cyclohydrolase I; HE1, epididymal secretory protein; HEXA, Hexosaminidase A alpha polypeptide; HPRT, hypoxanthine guanine phosphoribosyl-transferase 1; IT-15, important transcript 15 (huntingtin); MECP2, methyl-CpG-binding protein 2; NPC1, Niemann-Pick type C gene; PANK2, pantothenate kinase; PLP1, proteolipid protein 1; PRKN, parkin; SGCE, ε-sarcoglycan; TBP, TATA box-binding protein; TH, tyrosine hydroxylase; TOR1A, torsinA gene.

² Abbreviations: AD, autosomal dominant; AR, autosomal recessive; M, mitochondrial; XR, X-linked.

The diagnosis is based on clinical and laboratory work-out. The clinical features of dystonia [3] must be distinguished from those of hypertonias (such as spasticity or rigidity) and from other movement disorders (*e.g.* tremor) that can be observed in childhood [4] (*Table III*). Making a diagnosis of dystonia is not always straightforward, particularly among non-specialised neurologists or paediatricians, because the clinical spectrum is surprisingly broad, ranging from task-specific, to focal, segmental and generalised forms. *Figure 1* provides a flow chart to serve as a guide for the diagnosis.

Table III. Hypertonias observed in childhood have distinct features.

	Spasticity	Dystonia	Rigidity
Pathophysiology	Increased short-latency stretch reflexes resulting from injury to the corticofugal projection originating from areas 4 and 6 ("upper motor neuron syndrome")	Simultaneous co-contraction of agonist and antagonist muscles and proximal "overflow" of muscle activation due to basal ganglia dysfunction	Enhanced long-latency stretch reflexes resulting from basal ganglia dysfunction
Clinical features	Velocity-dependent increase of resistance to externally imposed movement (varies with the direction of joint movement)	Sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures. Dystonic postures and movements occur in variable combinations and are activated by voluntary motor tasks	Constantly increased resistance to passive motion with "plastic" quality
Postural restructuring	Flexion, adduction and intrarotation in the upper limbs; extension, abduction and extrarotation in the lower limbs	Torsion involves the main axis of the body part affected	Flexion of the body part affected
Motor performance	Muscle weakness (paralysis), loss of dexterity in distal movements	Muscle strength is unchanged, motor skilfulness is impaired	Muscle strength is unchanged, motor speed may be reduced (bradykinesia), repetitive movements may induce rapid fatiguing (akinesia)
Deep tendon reflexes	Increased	Unchanged	Unchanged
Specific clinical signs	Clasp-knife phenomenon, Babinski sign	<i>Gestes antagonistes</i> , sensory tricks, mirroring, overflow	Cog-wheeling

The occurrence of dystonia in isolation (with or without dystonic tremor) points to PTD, whereas, when dystonia is combined to other forms of hypertonia or to other dyskinesias, the diagnosis is usually that of a dystonia plus syndrome or of dystonia associated with a neurodegenerative disease.

Aetiology is one of the three descriptors used to illustrate dystonia, the other two being age at disease onset and the topography of body regions affected (*Table I*). Age at onset is the single most important feature in determining outcome [5-7]; the earlier the age at onset the more likely symptoms will be severe, with dystonia spreading to multiple regions. Only a minority of PTD cases encountered in clinical practice are linked to known loci or genes; notwithstanding that, PTD is considered to be genetically determined in most cases, with a number of still unmapped genes remaining

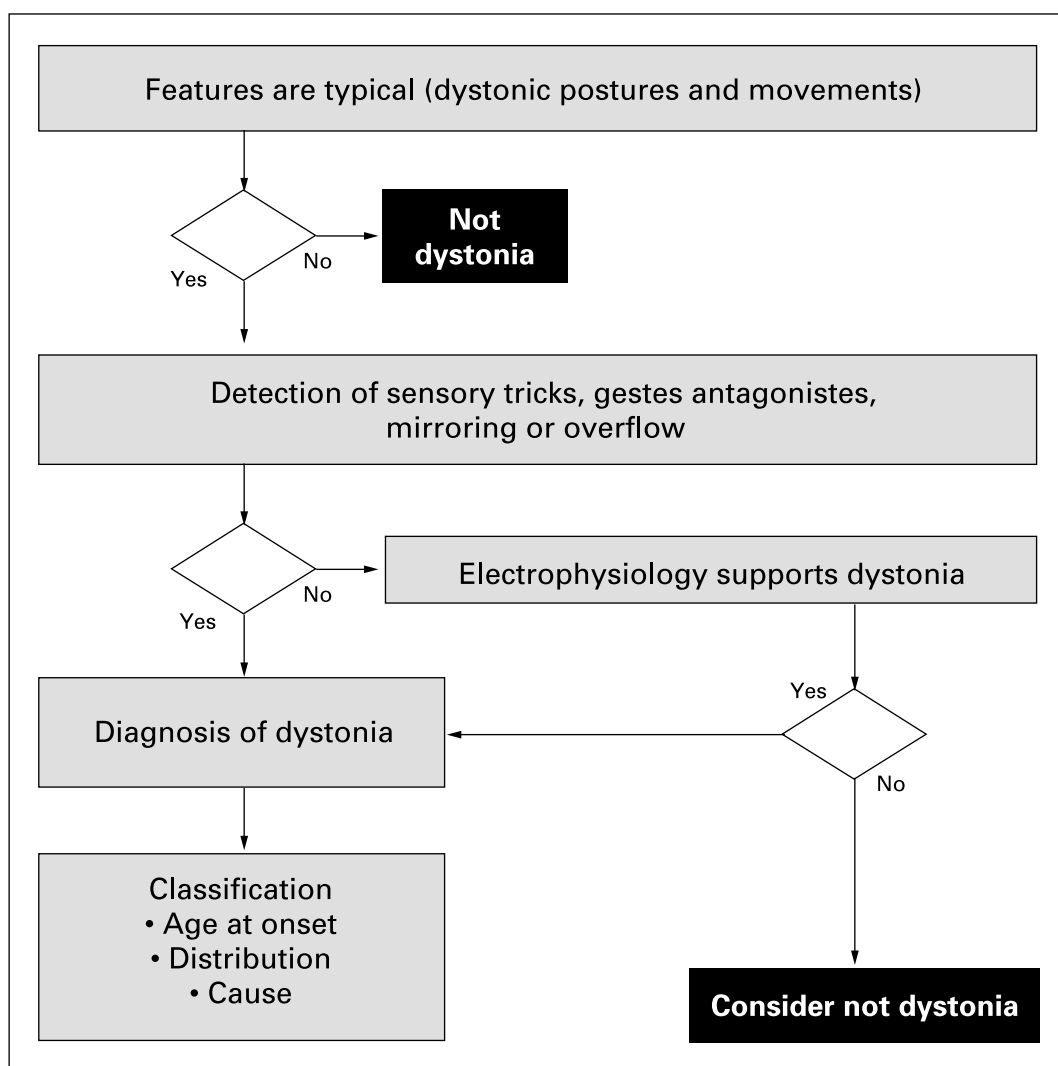


Figure 1. Flow chart for the clinical diagnosis of dystonia. Observation of characteristic clinical features [3] leads to the clinical diagnosis and to classification of dystonia, as reported in Table I.

to be identified. The diagnosis of PTD requires ruling out of a non-primary form of dystonia, which may be an engaging task. The forms of non-primary dystonias that most commonly require a differential diagnosis will be briefly dealt with hereafter.

■ Non-primary early onset dystonia

Non-primary dystonias encompass a host of disorders in which dystonia is a prominent sign, yet associated with another movement disorder (dystonia-plus syndromes), or it is a prominent symptom of a hereditary degenerative disorder or, finally, it is secondary

to exogenous factors (e.g. perinatal injury, neuroleptic medications, brain tumour, infections, etc.). Non-primary dystonias commonly start in paediatric age and require expert differential diagnostic work-out [8]. The most relevant forms of non-primary dystonias are the dystonia-plus syndromes.

Dopa-responsive dystonia (DRD) is characterized by childhood-onset dystonia, parkinsonism and sustained response to low doses of levodopa. The average age at onset is around 6 years. This syndrome has two main causes, namely: guanosine triphosphate cyclohydrolase I deficiency (DYT5: Segawa syndrome) [9], or tyrosine hydroxylase deficiency [10]. A new locus recently mapped to 14q13 (DYT14) [11] has been associated to a DRD phenotype; however, the direct observation, by one of us, of video tapes showing some of the affected family members has not allowed to detect obvious DRD features.

The most common form of the disorder has long been called Segawa syndrome; it is transmitted by autosomal dominant trait with incomplete penetrance (about 30%) and a prevalence estimated around 0.5-1.0 per million [12]. The initial symptoms commonly consist of gait difficulties, due to action dystonia in a lower limb; the disease, however, can also start with upper limb or neck dystonia [13]. In addition to dystonia, increased tendon jerks and parkinsonian features (such as rigidity and rapidly induced fatiguing in repetitive motor tasks) are also common findings in the affected limb. By 10-15 years after onset, dystonia gradually spreads to all the limbs to become generalized. The resulting picture shows asymmetric involvement of the four limbs, with more severe features in the legs [13]. One of the most important features of DRD is the occurrence of diurnal fluctuations, with patients being less affected in the morning and more in the evening [14]. All DRD patients show complete and sustained response to low doses of levodopa (50-300 mg/day), however motor benefit can occur also within a few months after the beginning of treatment. This is the main reason why a short 3-month levodopa trial is justified to rule out DRD in patients with unclassified dystonia.

Myoclonus dystonia (MD) is a syndrome with onset in childhood; dystonia usually occurs in the first or second decade (average age being 5.4 years). Myoclonic jerks commonly affect the axial muscles [15]. MD has been associated with three different genetic defects: a deficiency of ϵ -sarcoglycan (DYT11) [16], a mutation in the D2 dopamine receptor [17] and a still unknown defect mapped to a new locus (DYT15) [18]. The most common form is ϵ -sarcoglycan deficiency, that is transmitted by autosomal dominant trait with incomplete penetrance and variable expressivity [15]. The initial symptoms usually consist of myoclonic jerks and dystonia mostly affecting the trunk and the upper limbs, with a prevalent proximal involvement. Jerky movements are very brief and are precipitated by voluntary action or by psychological stress, but they can also occur at rest. Progression is very slow and leg involvement is rare, although a dystonic gait disturbance can occasionally be observed in young patients [15]. A very typical feature of MD is the relief of both myoclonus and dystonia following the ingestion of alcohol; this clinical sign is not seen in all patients [19].

■ Early onset PTD

The first observation of severe progression in patients with onset in childhood was made by Herz [20], who clearly recognized the rapid progression of the disease when it begins in childhood and classified dystonia into the three categories of early onset (shortly after birth), juvenile onset (between 5 and 15 years) and late onset (after 15 years). These observations were confirmed by Cooper [21], who differentiated dystonia patients into three age groups: childhood onset (between 4 and 6 years), adolescent onset (between 8 and 13 years) and adult forms; he also considered this classification to be of strict prognostic value. Marsden and colleagues [6] analyzed the natural history of 72 patients affected by PTD and identified age at onset as one of the most important feature in determining outcome. They first observed that the frequency of age at onset presented a bimodal distribution and suggested that “one is dealing not with a single disease, but with two populations, one with onset in childhood, the other with onset in middle life”. Nevertheless, they also noted an overlap between the two age groups and considered that the division into the two sets is based on a “gradual difference rather than on a clear distinction”. A consensus meeting attended by the members of an *ad hoc* committee [1], who convened in 1984, identified three age groups: childhood onset (0-12), adolescent onset (13-20) and adult onset (> 20 years). Based on this, early onset (encompassing cases with onset in childhood and adolescence) was distinguished from adult onset by the threshold age of 21.

Later retrospective series have confirmed that the curve representing the frequency distribution of age at onset for PTD is bimodal, with a nadir separating two clusters of patients (Table IV). These observations, however, have yielded inconsistent results on the most appropriate threshold age to distinguish the two clusters.

In a large series of 560 North American PTD patients followed at the Columbia University in New York, the frequency distribution of age at onset showed that dystonia cases clustered in two clearly distinct unimodal sets, a younger cluster with generalized dystonia and an older cluster with focal dystonia. In addition, the frequency distribution of segmental cases partially overlapped the two clusters of early- and adult-onset, giving rise to a bimodal plot with a nadir set at about 25 years [22] (Figure 2). In a subsequent analysis of a series of 178 Ashkenazi Jews, the nadir separating the early and adult onset clusters was set at 27 years [23]. The authors observed that patients with onset before the age of 21 were more likely to have a generalized form than those with older age at onset.

In 1994 a similar bimodal frequency distribution of age at onset was observed in a series of 160 Ashkenazi Jewish patients, 90 of whom were carriers of a DYT1 mutation [24]. The majority of DYT1 positive patients in this series presented an earlier age at onset than DYT1 negative patients and were almost completely included into the early onset cluster. These observations led to conclude that DYT1 dystonia arises with particularly high frequency in the early onset group of patients, especially among North American Jews. Following up on this observation, the same group proposed that the threshold age of 26 years could serve as a ceiling in referring PTD patients

Table IV. Retrospective series reporting the frequency distribution of age at disease onset in dystonia.

Recruiting centres	Patients	Age at onset (years)	Onset < 21 (% cases)	Age at onset (distribution)	Modes	Nadir	Reference
National Hospital (London)	72	1-59	66	Bimodal	0-10 and 41-50	21-30	(6)
St. Barnabas Hospital (New York)	226	NA	82	Bimodal	9 and 16-20	15	(82)
Columbia University (New York)	560	NA	27	Bimodal (for segmental dystonia)	6-10 for generalized dystonia and 50-60 for focal and segmental	~ 25	(22)
Columbia University (New York)	178	NA	NA	Bimodal	9 and 55	27	(23)
Institute of Psychiatry, King's College Hospital, National Hospital, Hospital for sick children (London)	107	2-70	65	Bimodal	5-10 and 45-50	30-35	(83)
Columbia University (New York)	160	4-74	58	Bimodal	0-10 and 31-40	21-30	(24)
Gemelli Hospital (Rome)	460	1-83	9.6	Bimodal	9 and 57	21	(64)

NA, not available.

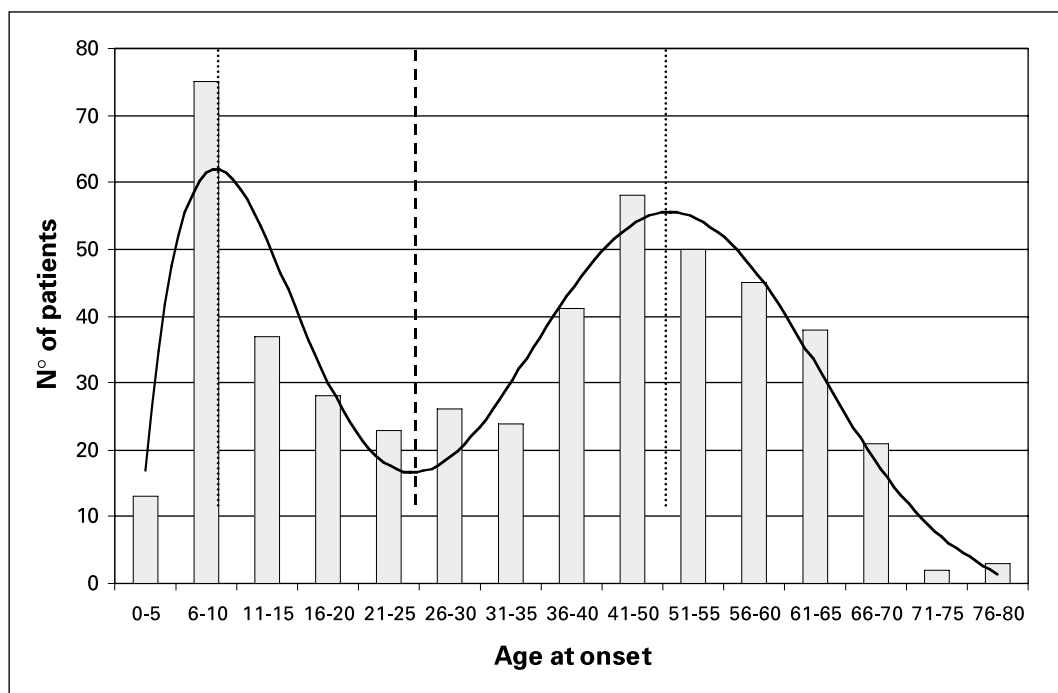


Figure 2. Frequency distribution of age at onset in 560 PTD cases seen at the Columbia University in New York. The bimodal distribution has a nadir at about 25 years (dashed line) and consists of two well-distinct clusters of patients with early and late disease onset. Dotted lines indicate modes at 6-10 years and 50-60 years, respectively (modified from [22]).

for DYT1 genetic testing [25]. More recently, 26 years of age has also been considered the most appropriate threshold to distinguish early- from adult-onset PTD [26] (Figure 3).

The afore-mentioned reports are useful criteria for defining a terminology used for classification of dystonia by age at onset; but they cannot be used to predict the outcome in individual cases. Indeed, the observation of a bimodal distribution of age at onset for PTD does not necessarily imply that the two age groups have a different disease progression or clinical prognosis. It is clear from the observations reported that, generally speaking, the earlier the age at disease onset the higher the likelihood of generalization. Nevertheless, these observations do not demonstrate that the retrospectively measured nadir of onset age distribution corresponds to a threshold predicting generalization. The issue of DYT1 testing further overlaps with this, because series of North American patients, which include a high proportion of Ashkenazi Jewish patients, do not necessarily apply to the European practice [27]. Ashkenazim or Sephardim are differently represented in North American and European patient series.

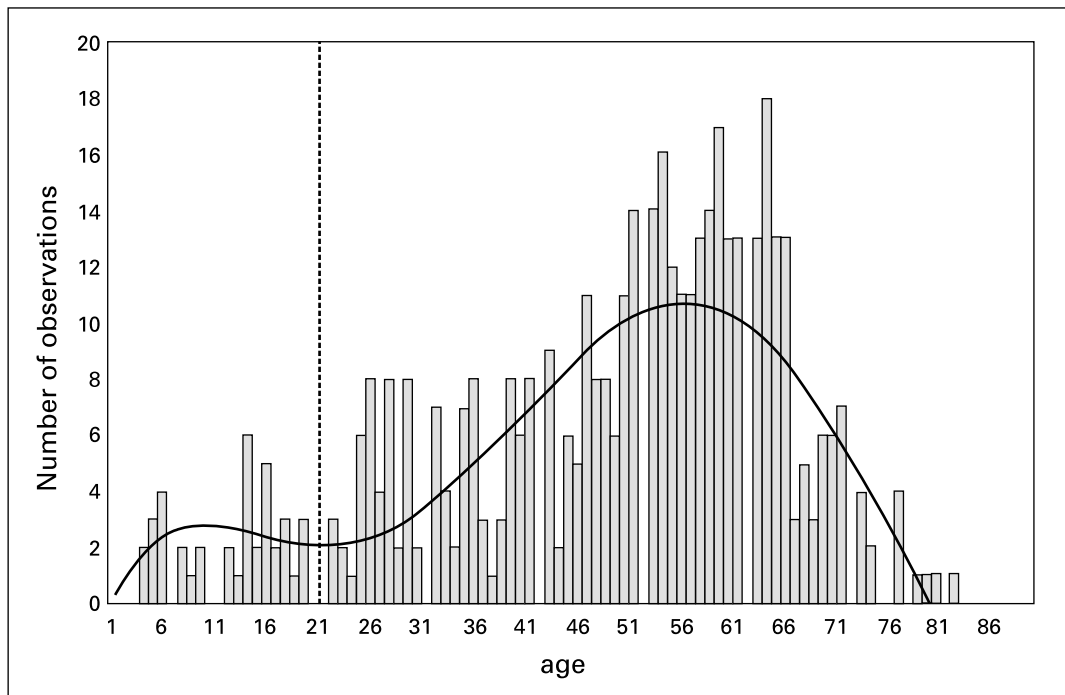


Figure 3. Frequency distribution of age at onset in 460 PTD cases seen at the Gemelli Hospital in Rome. This is a movement disorders clinic with a prevalence of adult referrals. The occurrence of a bimodal distribution is observed, with a nadir at 21 years (dashed line) that identifies two well-distinct clusters of patients with early and late disease onset.

■ DYT 1 dystonia

Typical and less typical phenotypes

The most known form of PTD is DYT1 dystonia, also called Oppenheim dystonia after the name of the German neurologist who first described generalized early-onset PTD as “dystonia musculorum deformans” [28]. The typical phenotype is characterized by early onset of dystonia, starting in one limb and rapidly progressing towards generalization. Selective or pronounced cranial-cervical involvement is considered unusual. The first symptom, especially in childhood, commonly is inversion of one foot, observed during walking. Later, the severity of dystonia increases; foot involvement occurs with less voluntary activity and later it is also observed at rest. When onset is in adolescence or in young adulthood the arms are often affected at first. DYT1 patients commonly develop generalized dystonia that can reach marked severity, and rarely have episodes of sudden worsening [29], which has been called dystonic storm (*see chapter by Nardocci et al.*). This classical phenotypic expression is particularly common in Ashkenazi Jewish patients. Indeed, it has been observed that the relatives of early-onset Ashkenazi probands have a very homogeneous phenotype, consisting of early limb involvement, onset before 40, and uncommon involvement of the cranial muscles [30]. Similar clinical features have been described in another

North American series encompassing one non-Jewish and 12 Jewish families, whose phenotypes were characterized by early onset (on average at 14.4 ± 3 and 13.2 ± 1 years of age) in a limb [31]. In a series of 178 North American Ashkenazi Jewish patients it was found that age at onset of DYT1 dystonia carriers was 12.5 years (significantly earlier than that of non-carriers) [24]. In 94% of the DYT1 carriers, symptoms started in a limb, but only rarely in the neck and the larynx, whereas neck, larynx, or other cranial muscles were the site of onset in 79% of non-carriers. It was also reckoned that most cases of dystonia with early limb onset in Ashkenazi Jewish families carried the DYT1 gene. Thus, phenotypic expression of DYT1 dystonia in the Ashkenazim population seems to be constant, with preferential onset on the dominant side [32]. The clinical features of non-Jewish North American patients affected by DYT1 dystonia are more variable [33]: early onset in a limb is common, but the clinical expression in the affected relatives is milder and a significant proportion (10-15%) of affected family members have late onset (> 44 years). The clinical features of non-Jewish European patients are even less predictable, with variable phenotypic expression within a same family and a high prevalence of patients with cervical, laryngeal and cranial involvement [34].

After the identification of the DYT1 gene it has emerged that the phenotype associated with DYT1 mutations is broader than previously thought. So far, more than two hundred DYT1-positive patients have been reported (Table V) and unusual or uncommon phenotypes have emerged. The atypical DYT1 positive phenotypes can be summarized as follows.

Generalized dystonia with cranial-cervical involvement

Early-onset dystonia usually starts in a limb, and takes a variable time to spread to the cranial, cervical or bulbar districts. This phenotype has been reported in several series and appears to be more frequent in Europe than in North America, reaching a frequency of 80% of DYT1 patients in a French series [35].

Myoclonus-dystonia like phenotype

Generalized DYT1 dystonia may be associated with rapid movements resembling myoclonic jerks; they are mostly proximal in the limbs and the trunk. This DYT1 variant appears to be more severe than DYT11 myoclonus-dystonia; jerks are not (or only partially) responsive to alcohol [36].

Focal dystonia with slow progression

Although DYT1 dystonia normally progresses to a generalized form during the first 5-10 years after onset, there are occasional reports of focal or segmental dystonia as the only clinical expression. Upper limb dystonia (writer's cramp) is the most frequent focal presentation in such cases. It has been observed that progression may occasionally occur several years after onset (even 50 [37] or 55 years [38]).

Table V. Clinical features of DYT1 patients.

Patients, n/total screened	Mean age at onset, yr (range)	Site of onset, n	Progression, n	Cranial involvement, n	Additional features	Reference
5/7	14.9 (9-38)	Arm: 5	Focal: 4 Unknown: 1	No	Writer's cramp	(84)
22/150	9.9 (2-21)	Arm: 3 Leg: 19	Generalised: 19 Segmental: 2 Focal: 1	Yes: 4		(34)
4/57	9.8 (5-17)	Arm: 2 Leg: 2	Generalised: 3 Multifocal: 1	No		(67)
10/51	9 (5-20)	Arm: 9 Leg: 1	Generalised: 7 Segmental: 2 Focal: 1 (10)	Yes: 4	Two patients with dysarthria, one with nystagmus	(50)
3/49	12.7 (9-17)	Arm: 1 Leg: 2	Generalised: 2 Focal: 1	Yes: 1		(85)
24/39	NA	NA	Generalised: 22 Focal: 2	NA	One patient with stuttering only and one with isolated hand tremor	(49)
68/550 (40 clinical affected)	NA	NA	Generalised: 26 Segmental: 1 Focal: 2	Yes: 1	19 patients with "unclassified movement disorder" A patient with tremor of the lips and jaw started at the age of 70	(51)
1/3	13 (NA)	Shoulder/ trunk	Segmental: 1	Yes	Axial dystonia	(39)
5/100	8.6 (6-12)	Arm: 3 Leg: 2	Generalised: 4 Segmental: 1	Yes: 4		(35)
97/267	14 (4-44)	Larynx: 1 Neck: 3 Arm: 47 Leg: 46	Generalised: 55 Multifocal: 10 Segmental: 12 Focal: 20	Yes: 9		(25)
10	11.1 (0.3-18)	Arm: 8 Leg: 2	Generalised: 5 Segmental: 1 Focal: 4	Yes: 2	One case with very early onset (4 months)	(86)
3/50	13.3 (10-17)	Arm: 2 Leg: 1	Generalised: 2 Segmental: 1	Yes: 2	A case of spontaneous remission after several months	(66)
6/178	14 (9-35)	Arm: 4 Leg: 2	Generalised: 3 Focal: 3	NA		(87)
6/45	21 (7-64)	Arm: 4 Leg: 2	Generalised: 3 Multifocal: 2	Yes: 2	All members of one family A case of dystonic storm with fatal outcome	(29)

5/30	8 (8-11)	Arm: 3 Leg: 2	Generalised: 4 Segmental: 1	Yes: 3		(27)
1	9	Leg	Generalised	No	Late progression and prominent tremor	(37)
3/107	NA	NA	Generalized: 3	No		(65)
5	27 (5-50)	Neck: 1 Arm: 2 Leg: 2	Generalised: 3 Multifocal: 1 Focal: 1	No	3 cases with dysarthria (one of them with severe dysphagia) 4 cases with late onset or progression (one triggered by injury and one by haloperidolo)	(38)
6/256	14.5 (7-41)	Arm: 3 Leg: 3	Generalised: 2 Multifocal: 2 Segmental: 2	Yes: 2		(88)
5/131	13 (3-31)	Neck: 1 Arm: 2 Leg: 2	Generalised: 4 Multifocal: 1	Yes: 1	Neck involvement in 2 cases Voice tremor in one case One case with bulbar muscles involvement and mild tetraparesis	(89)

NA, not available.

Late onset dystonia

Onset of dystonia may occur at a later age than 21 in some DYT1 patients. The oldest reported onset of dystonia was at 64 years [29]. Upper limb dystonia is the most frequent site of onset in these cases and the progression may be very slow, remaining limited to a focal form.

Non-limb onset

This is a very rare presentation of DYT1 dystonia: cervical onset has been reported in three cases, laryngeal onset has been described in one [25] and trunk onset also in one [39].

Despite the observed variable phenotypic expression of DYT1 dystonia, the majority of DYT1 patients shared similar phenotypic characteristics, namely limb onset in childhood, exclusion of the cranial district and progression of dystonia. The real incidence of atypical DYT1 presentations has not been established yet. Furthermore, it is unclear how broad it is phenotype heterogeneity associated with the DYT1 gene. The mere finding of a mutation in this gene is not sufficient to assess a diagnosis of DYT1 dystonia even in patients with a movement disorder [40]. Since the penetrance of DYT1 gene mutations does not exceed 40%, it is more likely for a DYT1 mutation carrier to be asymptomatic than symptomatic. Thus, it cannot be excluded that a patient with atypical features and a status of DYT1 carrier may express a coincident, yet undiscovered, gene defect.

Clinical genetics

It was originally proposed that early-onset primary dystonia is inherited as autosomal recessive trait in Jews and as autosomal dominant trait in non-Jews [41]. Later, studies from Israel [42] and from the United States [30, 43], as well as the re-analysis of Eldridge's original data [44], showed that in Jews the disorder is not autosomal recessive, but rather autosomal dominant with reduced penetrance (around 30%). The first primary dystonia locus, named DYT1, was later mapped to the region 9q32-34 in a large North-American non-Jewish family of French Canadian ancestry [45]. Linkage of dystonia with markers in the same region was also found in 12 Ashkenazi families [31]. This suggested that the mutation causing the Ashkenazi Jewish disease was in the same gene as that causing dystonia in the non-Jewish kindred. It became later apparent that the Ashkenazi families shared a common haplotype. The area containing the DYT1 gene was delineated to a 6-cM region with a strong linkage disequilibrium suggesting a single mutation event or founder mutation [46].

It was later calculated that the mutation was introduced into the Ashkenazi population about 350 years ago and probably originated in Lithuania or Byelorussia [47]. It was also reckoned that the high prevalence of the disease in Ashkenazim (estimated to be about 1:3,000 to 1:9,000 with a gene frequency of about 1:2,000 to 1:6,000) was due to the tremendous growth of that population in the 18th century from a small reproducing founder population. A founder mutation and genetic drift, rather than a heterozygote advantage, is probably responsible for the high frequency of DYT1 dystonia in Ashkenazi Jews. Subsequently, the haplotype of 174 Ashkenazi Jewish individuals affected by PTD was calculated [24]. In this group, there were 90 carriers of the DYT1 haplotype and 70 non-carriers, showing relevant phenotypic differences. Discriminant analysis of limb onset, leg involvement, and age at onset distinguished haplotype carriers from non-carriers with 90% accuracy. In 23 of the 70 non-carriers, the disease was familial and included brachial, cervical, laryngeal, and facial dystonia. Later studies confirmed that DYT1 is a common cause of early onset PTD also in non-Jews from Europe; furthermore, the observed association between idiopathic torsion dystonia and the highly polymorphic loci argininosuccinate synthetase (ASS) and Abelson oncogene (ABL) was also found in some British Jewish families [48]. Evidence for linkage to the DYT1 locus was found in 5 of 7 non-Jewish families of Northern European or French-Canadian descent, with an estimated penetrance in non-Jews of 0.40 to 0.75, higher than that observed in Ashkenazi Jews [33]. None of these families carried the Ashkenazi Jewish haplotype.

In addition to Ashkenazim, the GAG deletion has also been found in non-Jewish individuals and in families of diverse ethnic background [34, 39, 49-51]. One proposed explanation for the genetic and clinical differences observed among these populations is that the disorder in Jews is genetically homogenous, whereas non-Jews show greater genetic heterogeneity of DYT1 dystonia. This means that in Jews the presence of a single founder mutation and a genetic drift are the most plausible reasons for the higher frequency of early onset dystonia [43]; thus most cases would be due to the same mutation event and clinical homogeneity would be expected. Non-Jews are a

heterogeneous population with a lower disease prevalence; the disorder is likely to result from mutation/selection balance so that multiple mutations, including new mutations [52], are expected.

Molecular genetics

The DYT1 gene is named TOR1A [53]. The mutation causing the disease has been identified as a deletion of one of a pair of GAG triplets from the carboxy terminal in torsin A, a previously unknown protein. Mutations causing this deletion are uncommon, but some have been encountered and the unique DYT1 haplotype found in North American and Russian Ashkenazi Jews has been observed in Europe as well [54]. With the notable exception of an 18 bp deletion found in families with PTD and myoclonus, that also harboured a mutation in ϵ -sarcoglycan [55-57], the original GAG deletion is the only disease mutation identified in TOR1A.

TorsinA is a heat-shock and ATP-binding protein and a member of the AAA+ family of proteins, that is believed to serve as a chaperon in the processing and repairing of damaged proteins. Six TorsinA proteins are thought to join together to form a ring, with each of these six proteins bound to its neighbour by ATP. This structure is believed to repair other proteins that have been damaged. If repairing is unsuccessful, the damaged proteins can aggregate or die by apoptosis. An impairment of torsinA could explain why stress is capable to cause the onset or the worsening of dystonia. TorsinA mRNA has been mapped in normal human brain; it has an intense expression in dopamine neurons of the substantia nigra pars compacta, in the locus coeruleus, in the cerebellar dentate nucleus, in Purkinje cells, in several thalamic nuclei, and in the pedunculo pontine nucleus, but it is also found in most cortical areas, in the basal ganglia and in other mid-brain nuclei [58, 59]. The normal protein is widely distributed in many species and is located in the endoplasmic reticulum [60, 61]. The immunohistochemical localization of torsinA in a brain from a patient with DYT1 dystonia failed to reveal differences from control brains [62]. Finally, an intriguing, albeit unexpected, finding is the presence of torsinA in Lewy bodies [63].

Guidelines for genetic testing

The availability of direct testing for the DYT1 mutation raises the issue of developing diagnostic guidelines for searching the GAG deletion in the appropriately selected patients. Based on the experience collected in North America, on Ashkenazi Jewish and non Jewish patients, an algorithm for selecting PTD patients for DYT1 testing has been proposed [25]. This algorithm suggests to perform testing in conjunction with genetic counselling in all PTD patients with onset before 26 years; this single criterion yielded a 100% detection of clinically ascertained carriers, with a specificity of 43% for non-Jewish patients and of 63% for Ashkenazi Jewish subjects. In addition, it is suggested to test patients with onset after 26 years if there is an affected relative with early onset PTD. A notable difference in the likelihood to identify DYT1 positive patients has been observed in the Jewish and non-Jewish populations. These guidelines on DYT1 testing, which are based on a North American population, cannot be directly applied to European patients. In Europe, the number of early-onset DYT1-negative cases of generalised dystonia is higher than in North America, possibly

because of a lower representation of Ashkenazi Jews [27, 34, 64]. A revision of these recommendations has been proposed for the European population, where onset < 26 years as a single criterion does not appear to be an adequate factor to select non-Jewish individuals for DYT1 testing. It has been proposed that onset in a limb, in combination with onset < 26 years, is a better predictor of DYT1 carrier status [38].

As already mentioned, the penetrance of the DYT1 gene is not higher than 40%, meaning that the majority of those who carry a DYT1 gene mutation are not symptomatic. Therefore, it must be remembered that the identification of a DYT1 mutation is not sufficient to assert that the observed movement disorder is caused by the DYT1 gene. In keeping with this, a case of psychogenic movement disorder misdiagnosed as DYT1 dystonia, based on positive genetic testing, has been recently observed in the carrier of a DYT1 mutation [40]. A consistent clinical picture of dystonia must be observed in all cases undergoing genetic testing (*Figure 1*). Due to its simplicity, genetic testing for the DYT1 mutation could be performed in every PTD patient. A negative test would rule out DYT1 dystonia, while a positive test would allow to confirm DYT1 PTD in the presence of a consistent clinical picture and a typical DYT1 phenotype.

■ Non DYT1 early onset dystonia

DYT1 PTD is 3-5 times more common in Ashkenazi Jews compared to other ethnic groups [47], but is not the commonest cause of early onset generalized dystonia in the non-Jewish population. The frequency of the GAG deletion in non-Jewish European patients has been estimated to be 2.8% in Danish patients [65], 6% in Serbian patients [66] and 7% in German patients [67]. Furthermore, in a large series of European PTD patients only 14% of patients were carriers of the DYT1 GAG deletion; such higher prevalence could be due to the high representation of familial cases in this series (66%) [34].

The DYT1 is the only mapped PTD gene. Available evidence shows that a large group of early-onset PTD cases are not associated with mutations of this gene. Some other loci have been linked to PTD in selected families; but the majority of early or late onset PTD cases remain genetically unmapped.

Genetically classified early-onset PTD

Four forms of non-DYT1 dystonia have been observed to occur with early onset (*Table VI*). They have been named DYT2, DYT4, DYT6 and DYT13. These forms of dystonia have been described in individual families and are considered to be rare; they possibly reflect the occurrence of private mutations in yet unmapped genes.

DYT2

Autosomal recessive PTD has been described in three reports. The first observation [68] described three affected sibs whose parents were unaffected second-degree relatives. Another report described three consanguineous families of Spanish gypsies with early limb onset (average age at onset: 15 years) presenting generalized or segmental dystonia [69]. Cranial-cervical involvement was prominent. The supposed gene has

Table VI. Clinical features of DYT2, DYT4, DYT6, and DYT13 patients (AD: autosomal dominant; AR: autosomal recessive; NA: not available).

Locus (patients, n)	Mean age at onset, yr (range)	Site of onset, n	Progression, n	Cranial involvement, n	Additional features	Reference
DYT2 (3 affected)	4.7 (1-8)	Leg: 2 Trunk: 1	Generalised: 3	Yes: 3	Constant involvement of tongue and larynx AR inheritance	(70)
DYT4 (10 examined of 22 familial member affected)	NA (13-37)	Larynx: 7 Neck: 2 Leg: 1	Generalised: 8 Segmental: 1 Focal: 1	NA	Larynx involvement in 9 patients 2 relatives affected by Wilson's disease AD inheritance	(71)
DYT6 (15 affected)	18 (5-38)	Cranial: 1 Tongue: 2 Larynx: 1 Neck: 3 Arm: 7 Leg: 1	Generalised: 4 Segmental: 9 Focal: 2	Yes: 8	Frequent involvement of larynx (in 7 cases) and tongue (in 3 cases) AD inheritance	(72)
DYT13 (11 affected)	16.6 (5-43)	Cranial: 2 Neck: 6 Arm: 3	Generalised: 2 Segmental: 7 Focal: 2	Yes: 9	Possible anticipation between the first and the second generation AD inheritance	(75)

been named DYT2, but linkage to a gene locus has not been demonstrated. Recently, a DYT2-like phenotype has been observed in a Sephardic Jewish family originating from Iran with 3 sibs affected by PTD [70]. The parents were first cousins, which suggest autosomal recessive inheritance. Age at onset was in childhood, with clinical features of dystonia becoming evident at 5, 7, and 8 years. Two patients first developed in-turning of the foot with gait abnormalities; all had cervical involvement, facial grimacing, blepharospasm, and dystonic posturing and jerking of the four limbs. Two patients had dysphagia.

DYT4

A large Australian pedigree of PTD patients distributed along five generations had autosomal dominant transmission. Cranial dystonia was a prominent sign and impaired speech was common; few cases were affected by a generalized form. Age at onset varied from 13 to 37 years; the evident sign was speech dystonia in all patients but three, two of whom had cervical dystonia and later developed dysphonia. Wilson's disease was diagnosed in a brother and his sister belonging to a sibship of 11 subjects, three of whom had PTD. Linkage analysis using marker flanking the ATP7B gene yielded negative results, excluding the possibility that the disorder was due to an allele at the Wilson's disease locus on chromosome 13 [71].

DYT6

This locus was identified in two Mennonite families [72]. The disease is transmitted as autosomal dominant trait with an estimated penetrance of 30%. The locus was mapped to 8p21-q22 and haplotypes across the candidate region were identical in the affected members of the 2 families, suggesting a founder effect and a common underlying mutation. Among 220 family members overall, a total of 15 definitely affected individuals were identified. The DYT6 phenotype has been described as “mixed type”: early or young adult onset and prevalent segmental (cranial-cervical) distribution of features. The presentation at onset involves limb, cervical, and cranial muscles equally. Four patients developed a generalized dystonia. The authors reported that some affected individuals had a phenotype overlapping the classical early onset DYT1 PTD. Notwithstanding that, at variance with patients affected by DYT1 PTD, those with generalized DYT6 PTD had an older age at onset (range: 5-38; average: 18.9 ± 11.9 years); in addition, most of them presented with cranial or cervical involvement either at onset or later during the course of the disease. Furthermore, many patients were deeply disabled by the involvement of muscles in the cranial-cervical region [72].

DYT13

This locus was mapped in a family with a phenotype described as “mixed type”, consisting in prominent cervical-upper limb-cranial involvement. Onset was in infancy or adolescence in most cases [73]. Linkage with already known loci was excluded and a genome-wide search allowed mapping the DYT13 locus to chromosome 1p36 [74]. This family was followed up for several years and the affected individuals belonged to 3 consecutive generations. Anticipation of the age at onset and of the severity of symptoms was observed from the first to the second generation. Two of 11 definitely affected individuals had generalized dystonia, with upper limb or cervical onset at 5 and 20 years, respectively. The first patient with generalized PTD was a woman, who presented a dystonic postural tremor of the upper limbs at the age of 5; dystonic movements progressively spread to the all body by the age of 26. At the age of 61 she had generalized dystonia of the larynx, the limbs, and the trunk; dystonic action tremor was prominent. Notwithstanding this widespread involvement, disability was mild. The second generalized patient was a man who reported onset at the age of 20, with mild cervical dystonia. The symptoms did not progress over the following 30 years, but started a mild progression in his fifties, with dystonic posturing of the right hand and involuntary jerks of both hands and the head. He was examined for the last time at the age of 56, and the clinical picture was that of a generalized dystonia, involving the neck, and the four limbs. Notwithstanding that, he could still work in a farm and was actually engaged in a full-time physical job. Two members of this family had early-onset cervical dystonia (at 5 and 15 years), that after several years progressed to a mild segmental form with cranial involvement. One patient exhibited cranial dystonia at 5 years of age; this progressed mostly in severity, but remained segmental with upper limb involvement [75].

Genetically unclassified early onset PTD

It is not uncommon to observe PTD cases with early onset, which clinically resemble DYT1 dystonia, but turn out to be negative to DYT1 testing [64]. Most of such cases are sporadic. The Gemelli registry for movement disorders recorded 460 PTD cases of Caucasian origin. Forty-four of them (9.6%) had onset before age 21, there were 24 women and 20 men (male to female ratio of 0.83). All cases had focal dystonia at onset: in 22 patients (50%) PTD started in a limb (lower limb in 7 cases and upper limb in 15), in 12 subjects (27%) PTD made its appearance with cervical dystonia, in 5 (11%) with laryngeal involvement, in 4 (9%) with cranial dystonia and in one case (3%) the onset symptom was oro-mandibular dystonia. Progression of dystonia occurred in 34 cases (77%): after mean disease duration of 25.7 ± 15.4 years, 17 patients showed segmental dystonia and 17 generalized dystonia. Six of 10 focal cases had upper limb dystonia whereas other focal cases showed cranial or cervical dystonia (two in both cases). The screening for GAG deletion in TorA gene was performed in 25 early onset cases: 7 patients (28%) carried the DYT1 mutation; all of them exhibited limb dystonia (lower limb in 5 cases and upper in two) and after a variable time (mean 3.1 ± 2.5 years) all reached generalization of symptoms; a positive family history for dystonia was found in 5 cases (71%). Eighteen early-onset patients (72%) did not carry the DYT1 mutation: 9 of them (50%) presented with cervical onset, 8 (44%) with limb involvement (upper limb in six cases, lower limb in two) and in one case (6%) dystonia started involving the larynx. In all but two patients dystonia progressed to a second involved site: after several years of disease duration (mean 28.7 ± 19.9 years) two cases remained focal (both with cervical dystonia), 7 patients (38%) showed segmental dystonia and 9 (50%) cases had generalized dystonia (after a mean interval of 7.4 ± 19.9 years); a positive family history for dystonia was found in 12 cases (67%). The comparison of DYT1-positive with DYT1-negative early-onset cases showed that, in carriers, progression to a generalized form was faster. Furthermore, the cranial and cervical muscles were involved in different proportion among DYT1+ and DYT1- patient: in the first group only one patient had cranial involvement (oro-mandibular dystonia) at the last visit, one patient had laryngeal dystonia and four had cervical dystonia. By contrast, 17 out of 18 non-carriers had cervical dystonia, 7 had cranial involvement and 6 had laryngeal dystonia. There was a comparable incidence of positive family history in DYT1 carriers and non-carriers. Analysis of disease progression showed that the number of new involved sites per year (starting at disease onset) increased with a time-dependent trend in DYT1 carriers and in non-carriers. In addition, DYT1 patients had a higher number of involved sites and reached generalization in a time interval significantly shorter than non-carriers (*Figure 4*).

Several families with dystonia unlinked to known loci have also been described (*Table VII*). The clinical features of these patients are heterogeneous and difficult to summarize into consistent phenotypes, although some remarkable differences with DYT1 dystonia can be drawn. As a rule, DYT1-negative families often show involvement of the cranial muscles and rarely have onset of dystonia in a limb. In addition, DYT1-negative cases have less tendency to generalize than DYT1-positive dystonia and frequently remain focal or segmental forms.

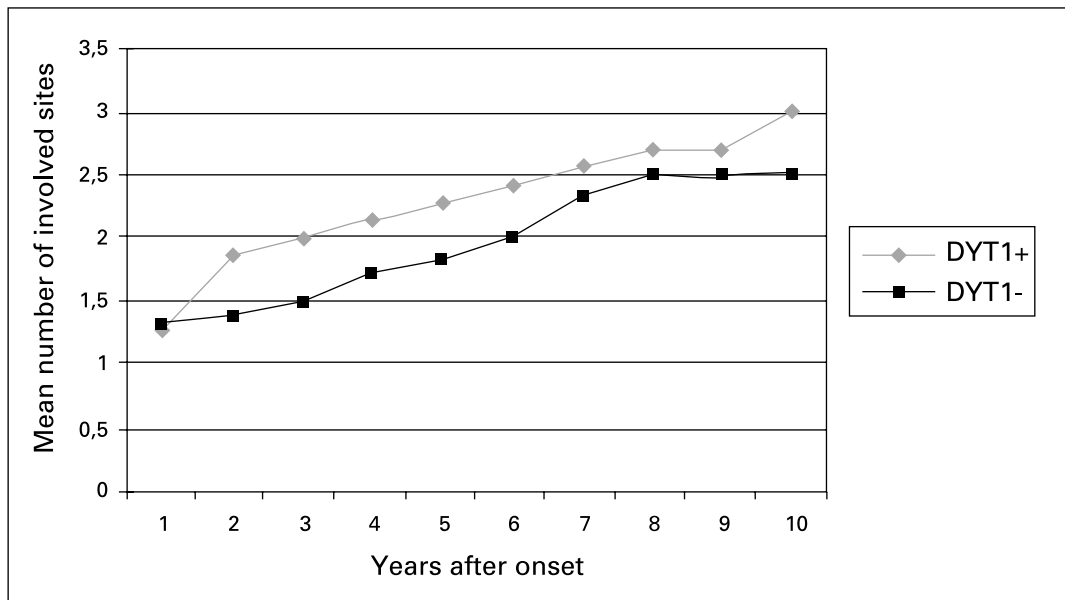


Figure 4. Mean number of involved body sites within 10 years from onset of dystonia in early onset PTD patients, of whom 18 were DYT1-negative and 7 were DYT1 carriers, followed at the Gemelli Hospital in Rome. Both groups show a progression after onset, but patients affected by DYT1 dystonia have a higher number of involved sites and reach generalization earlier than DYT1-negative PTD patients. Abbreviations: DYT1+, DYT1-positive; DYT1-, DYT1-negative.

Table VII. Clinical features of unclassified early onset PTD cases (AD: autosomal dominant; NA: not available).

Patients, n	Mean age at onset, yr (range)	Site of onset, n	Progression, n	Cranial involvement, n	Additional features	Reference
1	7	Leg: 1	Generalization	Yes: 1	Tongue involvement Family with AD inheritance	(76)
2	12,5 (12-13)	Neck: 1 Arm: 1	Generalization: 2	NA	Both familial cases The only two cases generalised among 15 early onset cases	(90)
4	18.3 (17-20)	Eye: 2 Larynx: 1 Arm: 1	Generalised: 1 Multifocal: 2 Focal: 1	Yes: 2	Laryngeal involvement in 2 patients Family with AD inheritance	(77)
4	12.3 (8-17)	NA	Generalised: 1 Segmental: 2 Focal: 1	NA	Cervical involvement in one case with onset at 8	(85)
2	6 (3-9)	Arm: 1 Leg: 1	Segmental: 1 Focal: 1	Yes: 1	One case with anarthria	(51)

7	13.6 (4-21)	Face: 1 Neck: 2 Arm: 3 Leg: 1	Generalised: 3 Multifocal: 1 Segmental: 3	Yes: 1	3 with familial history (none of the generalized cases) One generalised case with cervical involvement	(67)
2	17 (15-19)	Eye: 1 Neck: 1	Segmental: 1 Focal: 1	Yes: 1	Members of 9 familial cases with AD inheritance	(78)
6	< 18	Arm: 6	Segmental: 3 Focal: 3	No	All writer's cramp Two familial cases	(81)
2	2 both	Cervical: 2	Focal: 2	No	Identical twins (inheritance probably AD) Alcohol-responder Brief tics	(91)
35	15.4	NA	Generalised: 11 Segmental: 16 Focal: 8	NA		(66)
25	7.7 (1.5-15)	Cranial: 1 Neck: 1 Arm: 12 Trunk: 2 Leg: 9	Generalised: 22 Segmental: 3	Yes: NA	Oromandibular or laryngeal dystonia in 16 patients	(27)
2	19 and 21	Blepharospasm: 1 Neck: 1	Focal: 2	Yes: 1	Family with AD inheritance	(92)
7	15.9	Eye: 2 Neck: 5	Focal: 7	Yes: 2	All familial cases among 33 members affected belonged to 15 families	(80)
2	< 14 and < 18	Eye: 2	Focal: 2	Yes: 2	Members of 2 different families with blepharospasm AD inherited	(79)
2	5.5 (2-9)	Leg: 1 Arm: 1	Generalised: 1 Segmental: 1	No	Myoclonus Dystonia-like phenotype Familial occurrence AD	(93)

A non-Jewish North-American family unlinked to DYT1 gene had seven members affected by cervical dystonia, and five of them also by dysarthria or dysphonia [76]. Onset was with cervical dystonia in five case; one patient had early onset with leg involvement and progression towards generalization. A Swedish family had autosomal dominant transmission and variable phenotypic expression, including involvement of the face and the larynx [77]. Onset in four of the ten patients occurred before the age of 21 (*Figure 5*).

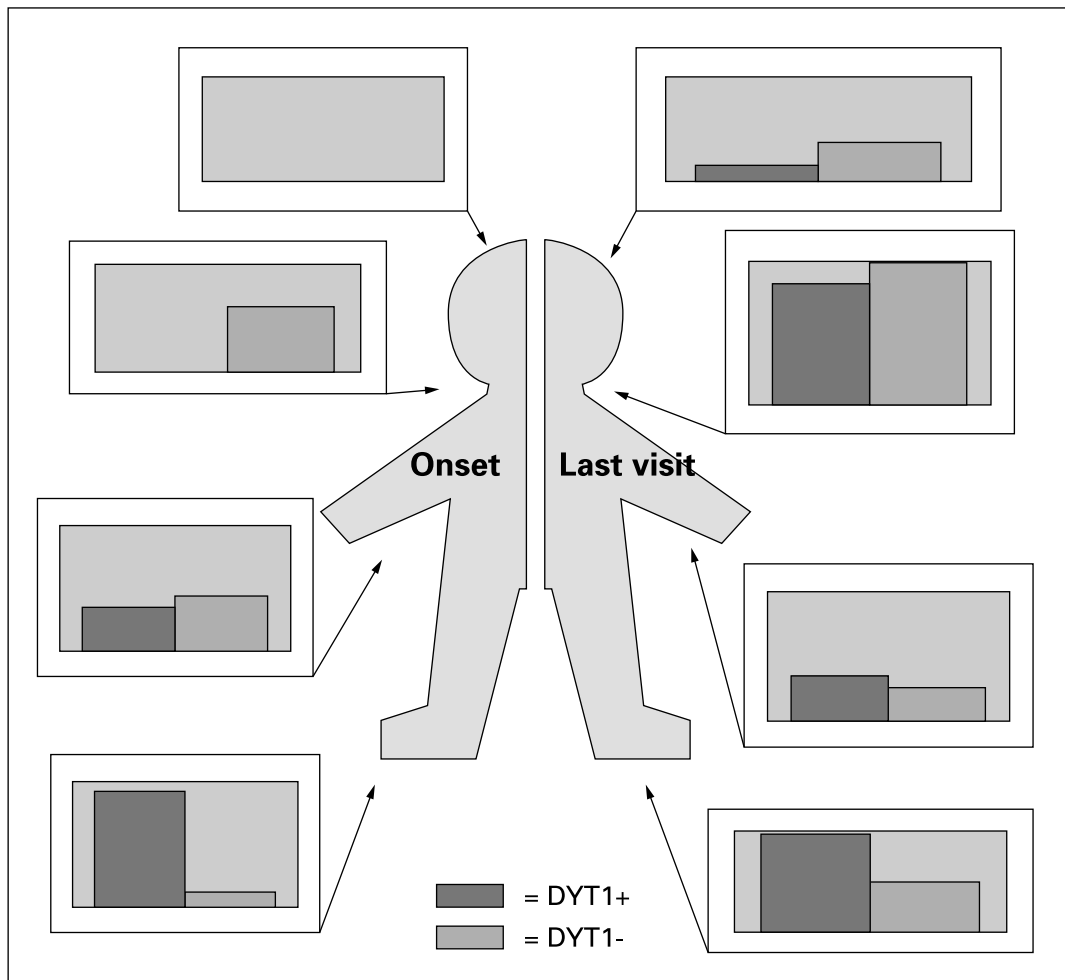


Figure 5. Body district affected at disease onset and at the last available visit in 25 early-onset PTD patients (18 DYT1-negative and 7 DYT1-positive, with a mean disease duration of 25.7 ± 15.4 years) seen at Gemelli Hospital in Rome. Histograms represent the percentage of patients who show involvement of cranial, cervical, upper limb or lower limb district at onset (left half of figure) or at the last visit (right half of figure). No DYT1-positive patient had cranial or cervical involvement at onset; at last visit all DYT1-negative patients had cervical or laryngeal dystonia whereas all DYT1-positive patients showed an involvement of lower limbs.

Young patients with DYT1-negative PTD with a severe involvement of the bulbar district leading to severe dysphagia or to anarthria have been described [51]. This is a rare observation in PTD patients, because bulbar involvement is commonly reported in secondary or hereditodegenerative forms of dystonia. By contrast, cases with mild dystonia and focal forms without progression for long time have also been reported. A family from Yorkshire was characterized by cervical dystonia at onset with progression to the arms (78). Two of the 9 patients (5 definite and 4 probable cases) had early onset, one of them with blepharospasm. Blepharospasm is very rarely

observed in young PTD patients, because it is a focal dystonia of middle age. Two families with blepharospasm in which two members had onset in childhood were recently reported [79]. Patients with blepharospasm at disease onset have been described also in another series from Germany [80]. Writer's cramp, a form of focal dystonia sometimes linked to DYT1 mutation, has been described in 6 DYT1-negative early-onset patients two of whom had a familial form [81]. In a series of 30 Italian patients (22 males and 8 females) affected by early-onset sporadic PTD, only 5 of them (23%) carried the DYT1 GAG mutation [27]. Their age at disease onset was on average 8 (range: 8-11). All carriers had onset in a limb (a leg in 2, one arm in 3). Four DYT1 carriers presented a generalised form; two of them had also oromandibular involvement. Twenty-five subjects (17 males and 7 females, M/F ratio: 2.4:1) were non carriers; their age at onset was 7.7 years (range: 1.5-15). Twenty-two of the DYT1-negative patients had generalized dystonia, 16 of whom with oromandibular or laryngeal involvement. Among the non-DYT1 carriers, onset was in a limb in 21 cases (the upper limb in 12, a lower limb in 9), in the trunk in 2 patients, in cranial muscles in one case, and in the neck in another one.

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