



Phenotypic Variability of DYT1-PTD: Does the Clinical Spectrum Include Psychogenic Dystonia?

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Abstract: Primary torsion dystonia (PTD) is a clinically and genetically heterogeneous group of movement disorders, usually inherited in an autosomal dominant manner with reduced (30–40%) penetrance. The DYT1 gene on chromosome 9q34 is responsible for most cases of early limb-onset PTD. DYT1-PTD clinical spectrum is broad, as the disease may present with several degrees of body involvement and severity. We identified an Italian family with 4 members definitely affected by PTD, genetically diagnosed as carriers of the GAG mutation at DYT1 gene. Phenotype was homogeneous when considering the presentation at onset (limb involvement and early onset), the disease progression was variable; in the subjects of the last generation, the disease progressed to a severe, generalized

PTD; in the remaining 2 subjects, dystonia presented with writer's cramp or upper body segmental dystonia of mild severity. One family member, carrier of the GAG mutation on DYT1 gene and mother of the most severely affected individual, presented with a clinically established psychogenic movement disorder resembling dystonia initially diagnosed as a severe generalized PTD. Psychogenic movement disorders are among the most controversial and challenging diseases to diagnose, in particular when the affected individual belongs to a family with an inherited movement disorder. © 2002 Movement Disorder Society

Key words: primary torsion dystonia; dystonia; psychogenic movement disorder; DYT1

Primary torsion dystonia (PTD) is a clinically and genetically heterogeneous movement disorder characterized by sustained involuntary muscle contractions, causing twisting movements and abnormal postures, not due to exogenous factors or to other underlying neurological conditions.¹ PTD can present as a sporadic or a familial disease. When familial, PTD is transmitted as an autosomal dominant trait with reduced penetrance of 30 to

40%.^{2,3} The clinical spectrum of PTD is variable in distribution (from focal to generalized dystonia) and in age of onset (from early to adult onset). Early limb-onset dystonia represents the most severe form of PTD, with high tendency to generalize within a few years and is a common clinical presentation of DYT1-linked PTD, that is due to a 3-bp deletion resulting in abnormal function of the ATP-binding protein torsin A.^{4,5} Recently, a second mutation (an 18-bp deletion, Phe323_Tyr328del) in the *TOR1A* gene was found in a patient with early-onset dystonia and myoclonic features.⁶ We observed a family with DYT1-linked PTD presenting with a typical early-onset phenotype, which included a woman carrier of the DYT1 gene mutation who had the clinical features of a psychogenic movement disorder resembling dystonia.

A videotape accompanies this article.

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Received 26 October 2001; Revised 11 February 2002; Accepted 20 February 2002

Published online 25 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mds.10236

SUBJECTS AND METHODS

The family is a non-Jewish kindred originating from Sardinia, with several members reportedly affected by PTD. The proband (arrow in Fig. 1) was referred to the movement disorder clinic of the Gemelli hospital; she was admitted as an inpatient and received neurological, psychiatric, and extensive general evaluations; she had a magnetic resonance imaging scan of the brain, and routine blood analysis. The patient consented to donate blood for genetic analysis and to be videotaped.

The family pedigree was drawn, and all the available family members were asked to be studied and to sign a written informed consent. They were interviewed to collect personal and family history, to ascertain possible causes of secondary movement disorders, and received a complete neurological examination, including specific tasks aimed to disclose dystonia.⁷ Videotape recordings of the on-site assessment were reviewed to confirm the diagnosis.

The diagnosis of primary torsion dystonia was made according to the published criteria,⁷ when dystonic movements and postures were evident to all the assessors.⁷ The diagnosis of psychogenic dystonia was made according to established criteria.⁸ The psychiatric diagnosis was assigned according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) nomenclature.⁹

Venous blood samples for DNA analysis were taken from all available subjects. DNA was extracted from peripheral blood leucocytes using standard techniques. Detection of the GAG deletion in the DYT1 gene was performed in all members of the family as described.¹⁰

RESULTS

Clinical and Genetic Study

The family originated from and lived in southern Sardinia (Family 36 of the Gemelli registry); it included 31 living individuals, 6 of whom accepted to be part of the study and were examined and blood sampled. The family pedigree is shown in Figure 1. The clinical data of five affected family members are summarized in Table 1. The ancestors of Subject III:9, from both the maternal and the paternal side, originated from white Caucasian parents; the family was not aware of any Jewish ancestor in previous generations. Four subjects (3 women and 1 man) received a clinical diagnosis of definite PTD. The mean age of the patients affected by PTD at the time of the study was 35 ± 19 years (range, 21–62 years); the mean age at onset was 12 ± 6 years (range, 7–20 years), the mean disease duration was 23 ± 21 years (range, 2–52 years).

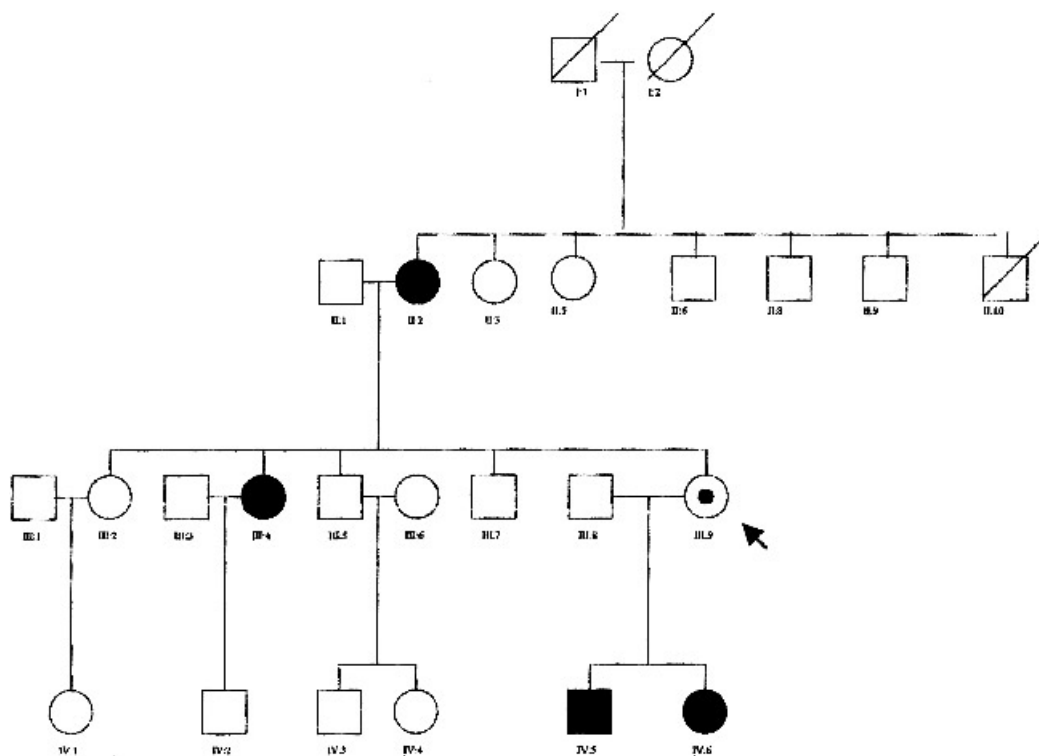


FIG. 1. Family pedigree. Black symbols denote individuals with primary torsion dystonia (PTD), deceased members are marked with a diagonal bar. The black dot denotes the individual with psychogenic dystonia.

TABLE 1. *Clinical presentation of symptoms*

Subject no.	Age (yr)/sex	Presentation	Onset (yr)	Presentation at onset	Clinical diagnosis	GAG deletion in DYT1 gene
II:2	62 F	Neck, trunk, dystonia in the right upper limb	10	Posturing of right hand; writing problems	Segmental dystonia	+
III:9	41 F	Wheelchair bound; relapsing posturing of both lower limbs and false weakness (complete remission periods)	38	Fluctuating abnormal posture of the left leg	Psychogenic dystonia	+
III:4	33 F	Writer's cramp	10	Writing problems	Focal dystonia	+
IV:5	21 M	Severe generalized dystonia	7	Posturing of the right foot when walking	Generalized dystonia	+
IV:6	22 F	Right arm and leg dystonia	20	Writer's cramp	Hemidystonia	+

The pedigree indicates an autosomal dominant transmission; affected individuals are distributed over three generations; in all of them, dystonia presented at onset with the hallmarks of DYT1-PTD phenotype: early age at onset (before 20 years) and involvement of a limb. No anticipation of age at onset was observed but dystonia progressed rapidly in the two affected individuals of the last generation, whereas in two subjects belonging to the previous generations, dystonia did not progress beyond a segmental distribution. One subject (III:9) received the diagnosis of clinically definite psychogenic dystonia: her clinical features are reported here in some detail.

The clinical condition of this woman was strictly dependent on the disease progression in her family. In her mother (II:2), dystonia presented with writer's cramp at age 10 years. The clinical picture slowly evolved toward a segmental presentation; the severity of the disease was moderate, and this woman was independent in everyday life activities.

The proband's sister (III:4) presented with a writer's cramp at age 10 years; dystonia did not progress in the following 20 years. When examined for the last time, at the age of 33, she still had writer's cramp, without any involvement of other body areas.

The proband's daughter (IV:6) was in good health until age 20 years, when she developed a mild writer's cramp, with a clinical picture similar to the presentation of her grandmother and her aunt; after 2 years, dystonia progressed to involve the right foot.

In the proband's son (IV:5), dystonia started in the right foot at age 7 years (a dystonic posture was evident when walking and running; see Fig. 2). After several months, the right upper limb was also involved (Fig. 3) and, in a short time, this boy was unable to write but was still independent in most daily activities. Within approximately 5 years, dystonia progressively worsened to become generalized and the boy became completely disabled. During the following years (from age 14 to 19), dystonia progressed, and the patient became unable to sit

on a chair (Fig. 4), to feed himself, or to speak. Quite recently, he has also developed troubles when swallowing. He is currently bed-ridden and completely dependent for all daily activities. Drug treatments have not helped him.

Molecular genetic analysis revealed the presence of the GAG deletion in the DYT1 gene in all the family members affected by PTD (Subjects II:2; III:4; IV:5; and IV:6) and in the proband (III:9).

At the time of the first evaluation, the proband (III:9) was 41 years old; she was married and had two sibs. She was referred to the movement disorder clinic with a diagnosis of severe generalized familial PTD. Her personal history was uneventful until disease onset. No data are available on her psychological condition before the onset of the movement disorder, and there was no evidence of psychiatric disturbances.



FIG. 2. Subject IV:5 at age 7 years. The picture illustrates the presentation at onset, i.e., task-induced dystonia of the right foot. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com/movementdisorders]



FIG. 3. Subject IV:5 during writing. A writer's cramp became evident a few months after the onset; neck, right shoulder, and elbow are maintained in an abnormal position during writing. At the time of this picture, the patient was not able to do his homework anymore.

This woman was obviously informed that dystonia is an inherited disease and that undoubtedly she carried the gene; her relatives reported that, before onset of her movement disorder, she could not understand why dystonia had skipped her but had severely affected her son. Therefore, she had an intense sense of guilt. When she was 38 her son was 17 and had been wheelchair-bound for a short time (her daughter had not yet developed dystonia); that was the age when she presented abruptly with a movement disorder, consisting of bizarre abnormal posturing of her left lower limb that involved the leg and foot. The patient and her relatives described this movement as "inconstant and spontaneously remitting." A gross, irregular tremor of the trunk and lower limbs was also reported; the symptoms were so severe that this patient was unable to walk unaided. This clinical picture is shown by the videotape. She spent several months a year in a wheel chair (as her son did) with remarkable intervals, lasting days or weeks, of spontaneous recovery from dystonia and return to normal life. There was no temporal relationship of relapses in the mother and the disease course in her son. On the occasion of her daughter's wedding, the patient recovered for approximately 2 months and was able to organize the ceremony before falling ill again soon after the marriage.

The relationship between this woman and her son was pathological: she was overprotective and symbiotic with her son, who used to spend all his time with his mother. The mother had abandoned the marital bed, and shared the bedroom with her son.



FIG. 4. Subject IV:5 at age 19 years. Dystonia had progressed to the classic presentation of generalized Oppenheim dystonia. The same clinical picture was observed at the time of the study, 2 years later.

As the patient reported that the involuntary movements worsened during her period, complete gynaecological and endocrinological assessments were performed but no evidence of disease emerged. Psychogenic physical signs, such as false weakness, were present. A psychological and psychiatric workup allowed the following diagnosis to be made, based on DSM criteria: Axis I, primary psychiatric diagnosis of conversion disorder; Axis II, no personality or developmental disorders; Axis III, coexisting physical disorders, none; Axis IV, severe psychosocial stressors, severely invalidating disease of her son; sense of guilt (she—unaffected—had transmitted a disfiguring disease to her son); Axis V, global assessment of current functioning, 45% of residual function, severely impaired.

The movement disorder improved with low doses of clozapine but the treatment was withdrawn after a few days because the patient poorly tolerated side effects of the drug (dizziness and sleepiness). A diagnosis of clinically definite psychogenic dystonia⁸ was made based on the occurrence of the symptoms listed in Table 2. Molecular genetic analysis revealed the DYT1 mutation.

DISCUSSION

All the patients in this family, including Subject III:9 received a diagnosis of PTD by local physicians, which was confirmed by genetic analysis. Later, when the family was referred to our movement disorder clinic, the clinical features of Subject III:9 led us to revise the diagnosis of PTD in this case, while confirming it for the remaining four affected subjects. In Subject III:9, the features of the movement disorder were mainly dystonic; however, the clinical presentation did not include the typical features required for a clinical diagnosis of dys-

TABLE 2. *Clinical features suggesting psychogenic dystonia in Subject III:9*

Clues suggesting psychogenic dystonia (Fahn and Williams, 1988)	Observed
Inconsistent or incongruous dystonia (adult onset dystonia; first symptom: foot dystonic posture)	+
False weakness	+
Sudden weakness	+
Onset with at rest dystonia	+
Spontaneous pain	+
Tenderness to light touch	+
False sensory changes, including blindness	—
Multiple somatizations	—
Bizarre tremor or other movement disorders (gait)	+
Startle-induced elaborate movements	—
Excessive slowness of voluntary movements	—

tonic movements (twisting nature, constant and predictable directional quality). Furthermore, the psychogenic nature was strongly supported by several features (see Table 2), including leg onset, which is very uncommon among adults, and frequent in subjects with psychogenic dystonia, as reported by Lang.¹¹ Two more points in favour of psychogenic origin were pain as prominent feature of leg dystonia, and the extremely rapid progression.

The variability of DYT1-PTD among members of the same family is not a surprise, as it has been described for a long time.^{12,13} In the four subjects affected by PTD, the phenotype at onset was not variable, as dystonia presented in all cases with one limb affected at early age. In this family only the progression differed, as symptoms progressed rapidly in the two subjects belonging to the last generation, whereas in previous generations symptoms did not progress (see Table 1). Albeit from its earliest descriptions, idiopathic torsion dystonia was mistaken for a manifestation of a psychiatric disturbance,¹⁴ during the past two decades, it has been clarified that psychogenic dystonia is an uncommon condition, accounting for less than 5% of the diagnoses among subjects described in the largest series of dystonic patients.^{8,15} In 1988, Fahn and Williams⁸ set a list of criteria aimed to orient the clinical diagnosis of psychogenic dystonia with different degrees of certainty.

Williams and colleagues in 1995 extended the same criteria to the entire category of movement disorders.¹⁶ The term psychogenic is intended to distinguish these syndromes from organic diseases; the clinical presentation may resemble closely a specific movement disorder, or, sometimes, more than one symptom may coexist in addition to bizarre and complex motor sequences and posture and gait disturbances.¹⁶ According to the above-mentioned criteria, in Subject III:9, we postulated a diagnosis of clinically definite psychogenic dystonia (see

Table 2) even though this woman carried the TOR1A mutation at the DYT1 gene.

The occurrence of psychogenic dystonia in subjects with a positive family history of dystonia has been observed⁸ but psychogenic dystonia had never been diagnosed in a subject who is a carrier of a dystonia gene. DYT1-PTD is inherited as an autosomal dominant trait with low (30–40%) penetrance; therefore, the occurrence of asymptomatic gene carriers is observed in almost all large families. The peculiar feature of being the unaffected mother of a severely affected child is the main reason for the development of a psychogenic movement disorder in Subject III:9.

The finding of a psychogenic movement disorder does not indicate an unequivocal psychiatric diagnosis. Different conditions may be present to support this clinical picture such as somatoform disorder, factitious disorder, and malingering. In this case, a psychiatric diagnosis of conversion disorder was made, possibly linked to an intolerable suffering, caused by the awareness that she had transmitted the gene causing an extremely disabling movement disorder to her son.

In conclusion, in this case, the clinical presentation was the hallmark of the diagnosis, which may be controversial or difficult to accept for the patient or for the local physicians but is fully compatible with the condition of carrier of a low penetrance dystonia gene. This finding raises an important point when considering that, in our clinical–genetic studies, the ultimate diagnosis is based on genetic testing. The present observation highlights that genetic evidence must be congruent with the clinical expression of the postulated gene and, in this particular case, with the clinical features of dystonia. Cases like this remind one that the results of lab testing must always be interpreted within the clinical context.

Acknowledgments: Mr. Ernesto Armati provided technical assistance in preparing the videotape. This study was supported by Telethon (C.38 to A.R.B. E.1165 to A.A.).

Legend to the Videotape

Subject III:9 is sitting. When raising the left leg the foot is inverted with plantar flexion; adduction and internal rotation of the left leg are evident. After a while, the leg drops because of painful cramps; when she is asked to stand up, involuntary movements and pain stop. She stands up easily but shortly thereafter a gross tremor of her left leg appears. When trying to walk without support, she cannot move her left leg; gait (difficult, irregular) is possible only with support and after two or three steps, a painful contraction takes over and she loses balance. When sitting, the left leg undergoes a

painful cramp, which resolves as soon as she is distracted. In the outstretched arms, an irregular oscillation of both arms appears with false weakness of the left arm. An abnormal and painful posture of her left foot appears when she attempts to perform the heel-to-toe foot tap test. During the pull test the patient is about to fall but recovers unaided; during the test, no abnormal posture or movements of the legs are appreciable.

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