Twelve-year follow-up of a large Italian family with atypical phenotypes of DYT1-dystonia

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Abstract

Background. A heterozygous mutation in the *TOR1A* gene (DYT1) accounts for an isolated dystonia typically presenting during childhood or adolescence with initial involvement of a limb, rapid spreading to other limbs and trunk, and sparing of craniocervical muscles. However, atypical phenotypes in terms of age at onset, site of presentation, and spreading have been reported.

Methods and Findings. In 2006, we described a large Italian family showing atypical phenotypes and intrafamilial clinical variability of DYT1-dystonia. Here, we report a 12-year follow-up of this family, focusing on disease onset in three previously asymptomatic DYT1 mutation carriers as well as on reassessment of the originally affected individuals.

Conclusions. The new cases confirm the intrafamilial phenotypic heterogeneity of DYT1-dystonia. Moreover, this case series highlights that symptoms in atypical phenotypes seem not to spread significantly and rarely worsen in the long term. Prolonged follow-up of DYT1-positive pedigrees may expand the clinical spectrum of DYT1-dystonia.

Introduction

DYT1-dystonia (OMIM #128100), the most common form of monogenic dystonia, is inherited in an autosomal dominant fashion with reduced penetrance (30-40%).[1] In most cases, it is due to an in-frame GAG trinucleotide deletion in the *TOR1A* gene, which maps on chromosome 9q34 and encodes an ATP-binding protein named torsin A.[1-3] The typical phenotype of DYT1 is characterized by leg or brachial dystonia beginning before age 26, progression to generalized dystonia within about five years from disease onset, and sparing of craniocervical and bulbar muscles.[1] However, atypical DYT1 features in terms of age at onset, body distribution, and spreading of symptoms have been reported.[4-7] Intrafamilial phenotypic variability has also been described, which was hypothesized to depend on the age at disease onset.[9] Therefore, long-term follow-up of DYT1-positive pedigrees may further outline typical and atypical phenotypes.

In 2006, we described a large five-generation family with DYT1-dystonia from Northern Italy.[10] Among 42 examined family members, 19 were found to carry the GAG deletion in the DYT1 gene and four were clinically affected, thus receiving a diagnosis of definite DYT1-dystonia. A fifth deceased family member (II:1) was rated as having been symptomatic through history reported by her relatives, but her genetic status was unknown.[10] In this paper, we describe a 12-year follow-up of this family, focusing on disease presentation in previously asymptomatic carriers as well as on clinical reassessment of the affected family members originally reported. In addition to confirm the wide phenotypic spectrum and intrafamilial clinical heterogeneity of DYT1-dystonia, this case series with prolonged follow-up reveals that atypical phenotypes are unlikely to progress significantly as for body distribution and only rarely worsen in terms of severity of symptoms and signs over time.

Methods

We periodically assessed the fifteen unaffected DYT1 mutation carriers and the affected family members of the family described in 2006.[10] After providing informed consent, all subjects were interviewed on their symptoms and underwent a complete neurologic examination, which was partly videotaped. Here we report on their last clinical evaluation and compare it with their first assessment. Videotapes obtained at the time of the last assessment are provided. Information on one family member deceased during the follow-up was anonymously obtained from his relatives.

Results

Over a 12-year period, only three previously asymptomatic DYT1 mutation carriers (IV:26, V:20, V:32) developed symptoms and one family member (III:29) died of lung cancer without manifesting dystonia. A simplified family tree is shown in Figure 1.

Subject IV:26 – Late clinical presentation (Video 1, Segment 1)

This is a 56-year-old, right-handed male trader. His medical history was unremarkable until age 46, when he first noticed mild postural tremor of the right arm. Over few years, the tremor spread to involve the left arm and the right leg, and the patient started complaining of fatigue of the right hand while writing and shifting gears. Examination at age 56 revealed subtle dystonic posturing of the fingers in both hands and mild dystonic tremor of the hands and right foot, which worsened with fatigue. He could write comfortably and legibly without cramps or spasms in the right arm. He was diagnosed with multifocal dystonia.

Subject V:20 – Early onset without generalization (Video 1, Segment 2)

This 21-year-old, right-handed girl is the daughter of subject IV:26. She reported having writing difficulty just before age 10 and spasms in the left hand soon later, when she learnt to write

with the left hand. She rapidly became unable to perform manual tasks that required finger dexterity. Neurologic examination at age 21 revealed slow twisting movements of the right hand and fingers when maintaining a posture and abnormal wrist flexion during writing in both arms, mainly on the right. There were no mirror movements nor alleviating maneuvers. Mild toe curling on the left was detected at rest, which was complained by the patient. Dystonia was aggravated by stress and fatigue. She was diagnosed with multifocal dystonia.

Subject V:32 – Late clinical presentation (Video 1, Segment 3)

This is a 30-year-old, right-handed woman and the youngest daughter of the proband (subject IV:43). She first noticed stiffness of the first three right fingers and mild difficulty in handling little objects with the right hand during her first pregnancy at the age of 29. Her first neurologic evaluation at age 30 revealed mild dystonic posturing of the right fingers, involuntary pronation of the right forearm and jerky postural tremor of the right hand. There were no writing difficulties. She was diagnosed with focal dystonia.

Reassessment of the affected family members originally reported

The proband (IV:43), a retired 65-year-old builder, developed cervical dystonia at age 43 after surgery for a lumbar hernia. Dystonia slowly spread to the limbs and trunk over a decade and the patient was diagnosed with generalized dystonia at age 53.[10] At the follow-up visit at age 65, he showed retrocollis with mild torticollis to the left and a tendency to shoulder abduction while walking. Subtle dystonic posturing of the upper limbs and slow twisting movements of the toes were noticed. Facial muscles were spared. Symptoms remained stable over twelve years and the patient was still independent in most daily activities (Video 2, Segment 1).

The proband's son (V:30), a 40-year-old right-handed plasterer, complained of difficulties in writing since he was 22. He originally showed right wrist extension and twisting movements of the fourth and fifth right fingers during writing.[10] At the follow-up evaluation when he was 40,

writer's cramp was still the only clinical manifestation (Video 2, Segment 2). Neither mirror dystonia nor sensory tricks were observed.

The proband's older daughter (V:31) is a 36-year-old right-handed cashier. She reported marked difficulties in writing since age 10, which rapidly progressed to involve the left hand. During her first evaluation at age 24, jerky action tremor of both arms and bilateral writer's cramp were observed.[10] At the follow-up assessment at age 36, bibrachial dystonia with rapid twisting movements and jerky action tremor of the hands was detected. The patient showed moderate difficulty in performing rapid sequential movements with her fingers. Abnormal wrist flexion and tightened handgrip appeared in both hands during writing. There were no gestes antagonistes. She was diagnosed with segmental dystonia. Over the 12-year period considered, dystonia remained confined to the arms, but the severity of symptoms considerably worsened (Video 2, Segment 3). Although independent in most daily activities, the patient reported significant psychological stress and social embarrassment.

Individual III:28 is an 81-year-old institutionalized woman who was diagnosed with generalized dystonia in her late forties.[10] She first noticed involuntary movements of her trunk and right shoulder at age 43. Over the following five years, symptoms spread to her limbs, neck, and face, causing severe twisting of the trunk, tremulous cervical dystonia, mild spasmodic dysphonia, and excessive blinking. Jerky action tremor of the hands and bilateral writer's cramp were present. Due to advanced age and poor general condition due to non-neurologic comorbidities, we did not videotape her follow-up evaluation.

Table 1 summarizes demographic and clinical features of clinically affected individuals.

Discussion

After a 12-year follow-up of the large DYT1 family reported in 2006, we described disease onset in three previously asymptomatic mutation carriers and reassessment of four subjects originally affected.[10] Overall, seven out of 19 DYT1 mutation carriers were clinically manifesting, thus indicating an estimated penetrance of nearly 37% in this pedigree, which is consistent with previous literature.[1] As for newly diagnosed patients, focal arm dystonia was the clinical presentation and age at onset ranged from childhood (V:20) to the fifth decade (IV:26). Individuals IV:26 and V:20 showed rapid, albeit mild in severity, spreading of dystonia to other limbs, whereas symptoms remained limited to the site of onset in subject V:32. Patients who were clinically affected in 2006[10] did not show significant spreading of clinical manifestations over this prolonged period and worsening of dystonia in terms of severity was observed only in one family member (V:31). Dystonic tremor was the presenting symptom in two family members (IV:26, V:32) and the predominant clinical manifestation in three (IV:26, V:31, V:32). Dystonia was never itself responsible for severe disability.

This pedigree summarizes atypical features of DYT1-dystonia previously reported, including late presentation, axial onset, craniocervical and bulbar involvement, and limited spread of symptoms.[1,4-8] Although onset after the third decade is not unusual in DYT1-dystonia,[4,6-8] this family differs from nearly all previously published pedigrees with adult-onset cases, in which at least one individual showed early-onset generalized dystonia. Cervical and trunk dystonia have rarely been described at onset and evidence of blepharospasm and larynx involvement in DYT1 is anecdotal.[1,8] Moreover, this family does not show the age-related caudal-to-rostral shift of the site of presentation reported in other DYT1-positive pedigrees.[9] More rapid and diffuse spreading of dystonia was observed in family members with higher age at onset, which is unexpected in generalized primary dystonia. Limited or no spreading of dystonic manifestations was observed in most individuals of this family as already reported in DYT1-dystonia, especially for upper-limb onset.[4]

Our case series confirm the wide clinical spectrum and intrafamilial phenotypic variability of DYT1-dystonia.[10] Furthermore, this prolonged follow-up provides evidence that in atypical DYT1 phenotypes dystonia is unlikely to spread significantly and progression of symptoms in terms of severity may only rarely occur in the long term. Further detailed long-term follow-up of DYT1-positive pedigrees may strengthen our observations and expand the phenotypic spectrum of DYT1-dystonia.

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Author Contributions

Francesca Magrinelli (Corresponding Author): study concept and design, acquisition, analysis and interpretation of data, first and final draft of manuscript, preparation of videos.

Ruggero Bacchin: acquisition, analysis and interpretation of data, first draft of manuscript.

Michele Tinazzi: study concept and design, analysis and interpretation of data, critical revision of first draft of manuscript for intellectual content, final revision of manuscript and videos.

Mattia Gambarin: study concept and design, acquisition, analysis and interpretation of data, first draft of manuscript, preparation of videos.

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Legends for Figure and Supplemental files

Figure 1. Simplified pedigree of the reported family.

Black symbols indicate clinically affected individuals. Dots within symbols denote asymptomatic carriers. Deceased members are marked with a diagonal bar. The proband is indicated by an arrow. A thin horizontal bar above symbols indicates individuals who underwent genetic testing. Family members who became clinically affected over the 12-year follow-up are marked with an asterisk. Age (y) of genetically proven DYT1 mutation carriers who were asymptomatic at the time of last assessment or death is reported.

Video 1. Clinical examination of newly diagnosed family members.

Segment 1 (Subject IV:26). Minimal posturing of the fingers and jerky postural tremor of both arms are evident. There is jerky postural tremor of the right foot. No difficulties while writing are observed.

Segment 2 (Subject V:20). Slow twisting movements of the right hand are evident when maintaining a posture. There is mild toe curling on the left at rest. Bilateral writer's cramp with abnormal wrist flexion and subtle dystonic tremor of the right hand are present.

Segment 3 (Subject V:32). Involuntary pronation of the right forearm and jerky postural tremor of the right arm when maintaining a posture are observed, especially during pinch grip. No abnormalities while writing are detected.

Video 2. Last assessment (right panel) of the affected family members originally reported compared to their first assessment in 2006 (left panel)

Segment 1 (Subject IV:43). Retrocollis with mild torticollis to the left and a tendency to shoulder abduction during walking are evident. Subtle dystonic posturing of the upper limbs is

present while walking and maintaining a posture. There are no writing difficulties. The clinical picture remained stable over the 12-year follow-up.

Segment 2 (Subject V:30). Writer's cramp on the right with no sensory tricks nor mirror movements is evident and have not significantly changed from 2006 to 2018.

Segment 3 (Subject V:31). Rapid twisting movements and jerky action tremor of the hands are shown. There are abnormal wrist flexion and tightened handgrip in both hands during writing. Although remaining confined to the arms, dystonia worsened in terms of severity over the 12-year period considered.