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Phenotype variability of dystonia in monozygotic twins

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Sirs: Suggestions that dystonia may be initiated by a peripheral trauma date from the nineteenth century [1]. However, the demonstration of a direct causative link has so far been lacking. Case reports have shown that the clinical presentation of post-traumatic dystonia differs substantially from that of primary torsion dystonia [2, 3].

Family 2 of the Gemelli dystonia registry present a case of autosomal dominant transmission of a homogeneous cervical dystonia phenotype linked to a still unmapped gene [4]. We studied two twin sisters (family members III:6 and III:8; Fig. 1) who shared with all other family members the homogeneous phenotype of adult-onset craniocervical dystonia. They were identical twin sisters,

born at term by uncomplicated vaginal delivery. Neither of them received any kind of medication known to cause or to affect dystonia or were reported to have suffered any trauma. Life events of the twins were reconstructed in detail by collecting all the available information. Past medical and personal data of the twin sisters were collected from each family member by cross-referencing hospital records, interviews of relatives, and any available photographs and videos (Table 1). DNA was extracted from whole blood according to standard methods. Analysis of GT polymorphisms was carried out by PCR and acrylamide gel electrophoresis. The polymorphisms and their localization were: HD CAG (4p), D4S392 (4q), D4S1534 (4q) SCA1 CAG (6p), D9S60 (9q), DRPLA CAG (12p), D12S1328 (12q), D14S52 (14q), D16S283 (16p), D18S62 (18p), D19S215 (19p).

Monozygosity of the twin sisters was confirmed by observing identical alleles for these highly polymorphic markers. In addition, the parental alleles were reconstructed on the basis of the four sibs genotypes. For six markers all the four parental alleles were segregating, while for two markers only three different parental alleles were found. The remaining three markers were not informative. The conditioned probability of the twins being dizygotic, given the results obtained, was 1.1×10^{-4} (considering an a priori probability of dizygotic and monozygotic twins in the white population of 0.64 and 0.36, respectively).

Twin 1 (III:6) was seen at the Movement Disorders Clinic of Gemelli Hospital. She was the first-born and was breast fed; her early development was reported to have been normal. At the age of 6 years she and her twin were asked by their parents to help in farm work. As is customary among women in that rural area, twin 1 started carrying heavy bags, such as bales and pitchers, on top of her head. She had menarche at the age of 14 years. At the age of 23 she married, moved to Rome, and stopped working in agriculture. At the age of 24 she had her first uncomplicated pregnancy followed by a natural delivery. At the age of 38 a second pregnancy ended in a miscarriage. Menopause occurred at 48 years. She suffered from familial goiter and gallbladder stones. At the age of 55 the patient moved back to her village and resumed farm work; again she carried heavy weights on her head when working as a farmer. She did so for a total time of 26 years (from 6 to 23 and from 55 to 65 years of age). At the age of 65 years she reported the onset of pain and tension in the posterior muscles of the neck; a few months later, she developed retrocollis and stopped carrying weights on her head. Dystonia progressed rapidly. At the age of 66 axial dystonia (with retrocollis, irregular head tremor, and trunk involvement) was associated with severe blepharospasm, tremulous adductor laryngeal dystonia, jaw-opening movements, and dystonic posturing of the upper limbs. Typical sensory tricks

Fig. 1 The family pedigree shows the distribution of definitely affected (filled symbols) and of probably affected subjects (half-filled symbols)

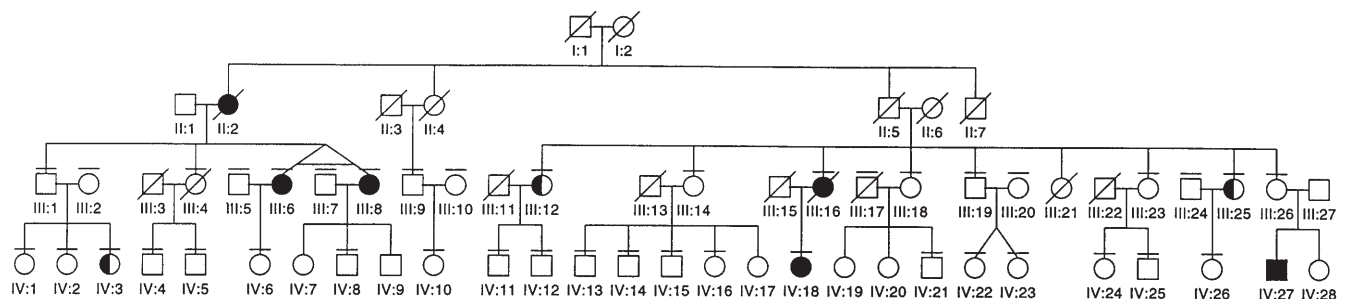


Table 1 Comparative time course of life events and of clinical features in two identical monozygotic twins affected by primary torsion dystonia

Age (years)	Twin 1		Twin 2	
	Life events	Dystonia	Life events	Dystonia
6	Starts farm work and carries weights on her head		Starts farm work without carrying weights on her head	
23	Stops carrying weights on her head			
23	Marriage			
24	First pregnancy, delivery			
27			Stops farm working. Marriage	
29			First pregnancy, delivery	
31			Second pregnancy, delivery	
38	Second pregnancy, miscarriage			
41			Third pregnancy, delivery	
49	Mild depressive syndrome			
56	Restarts farm working and carries weights on her head			
65	Stops carrying weights on her head due to dystonia	Cervical		
66		Cervical, trunk		Cranial
69		Cervical, trunk, laryngeal, upper limbs		Craniocervical
72		Severe segmental		Craniocervical

were observed. There were no pyramidal, cerebellar, or somatosensory abnormalities; intellectual function was normal. Magnetic resonance imaging of the brain was unremarkable. When last examined in 1998, at the age of 72, the clinical picture was severe and segmental, without further progression of dystonia. The patient is currently being treated with tetrabenazine, myanserine, and with botulinum toxin injections. Control of dystonia is only partially satisfactory; the patient is still incapacitated by severe axial involvement.

Twin 2 (III:8) was born few minutes after her twin sister and was fed by a wet-nurse. Early development was normal. Menarche and menopause occurred at 14 and 45 years, respectively. She had helped her parents in the fields, as her twin sister had, but unlike her sister she had refused to carry weights on her head. She married at the age of 27 and had three unremarkable pregnancies. As her twin, she was affected by familial goiter and gallbladder stones. At the age of 66 she first noted involuntary movements of the

perioral muscles. Later, dystonia slowly progressed to other facial muscles and finally to the neck. Computed tomography of the brain and laboratory tests were unremarkable. At the time of first examination, at the age of 69, she showed: blepharospasm and facial dystonia, tremulous voice, involuntary contractions of the platysma muscle, mild cervical dystonia, and mild postural tremor of the upper limbs. So far she has not required treatment with botulinum toxin; dystonia is mild, and the patient remains completely independent in daily life activities and housekeeping.

Observations of monozygotic twins with similar exposure to the environment are rare. The patients reported here had only few differences in their life events and lived in the same geographical and social environment. They had a remarkably similar phenotype that varied only in severity and progression and reproduced the prevalent family phenotype. In another reported family with adult-onset cervical dystonia, monozygotic twins presented an 8-year

difference in the age at onset, but a similar degree of progression and topographic extension and an identical phenotype [5]. Two monozygotic twins of Jewish extraction presented with generalized dystonia at the age of 16 and 23 years, respectively. They also differed in severity, response to pregnancy, and degree of diurnal fluctuations [6]. Dystonia remained confined to the lower limbs in both; their response to levodopa treatment was not tested, and a retrospective diagnosis of levodopa-responsive dystonia seems probable in our view.

Environmental factors are the most plausible variables to explain the remarkable differences in severity and progression of primary torsion dystonia in the twins reported here. What are such environmental factors? Age at marriage and the number of pregnancies varied slightly, and there were no other major differences in life events. Hormonal factors or increase in weight related to pregnancies may have affected the dystonia phenotype; however, direct load on the spinal cord, by walking while carrying weights

on the head, is the most obvious event related to the onset and progression of cervical dystonia in twin 1 and to its spread down to the trunk.

The pathogenic mechanism by which peripheral trauma may initiate dystonia in a predisposed individual has not been elucidated. Since no direct basal ganglia or brain damage occurs, a complex functional sensory-motor reorganization is thought to take place [7]. Based on current pathophysiological models, indicating that dystonia is associated with hyperactivity of the premotor areas [8], it can be hypothesized that repeated local strain may accelerate and aggravate the development of such abnormality. The observation of these monozygotic twins emphasizes the importance of repeated strain in genetically determined, otherwise typical, primary torsion dystonia. This sort of environmental cause may account for the variability of phenotype within primary torsion dystonia families.

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References

1. Gowers WR (1888) A manual of diseases of the nervous system. Churchill, London
2. Goldman S, Ahlskog JE (1993) Post-traumatic cervical dystonia. *Mayo Clin Proc* 68:443–448
3. Truong DD, Dubinsky R, Hermanowicz N, Olson WL, Silverman B, Koller WC (1991) Posttraumatic torticollis. *Arch Neurol* 48:221–223
4. Cassetta E, Del Grosso N, Bentivoglio AR, Valente E, Frontali M, Albanese A (1999) Italian family with cranial cervical dystonia: clinical and genetic study. *Mov Disord* 14:820–825
5. Uitti RJ, Maraganore DM (1993) Adult onset familial cervical dystonia: report of a family including monozygotic twins. *Mov Disord* 8:489–494
6. Eldridge R, Ince SE, Chernow B, Milstein S, Lake CR (1984) Dystonia in 61 year old identical twins: observation over 40 years. *Ann Neurol* 16:356–358
7. Byl NN, Merzenich MM, Jenkins WM (1996) A primate genesis model of focal dystonia and repetitive strain injury. I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology* 47:508–520
8. Bressman SB (1998) Dystonia. *Curr Opin Neurol* 11:363–372

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