Hereditary Juvenile-Onset Craniocervical Predominant Generalized Dystonia with Parkinsonism

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Abstract

Objective: To report a unique hereditary, juvenile onset, craniocervical predominant, generalized dystonia and parkinsonism affecting four members of one family.

Family Description: A father and three of his four daughters presented to us over the past 30 years with a similar picture of generalized dystonia, starting in the craniocervical region in the second or third decade of life. They later developed moderate parkinsonism, mainly manifesting bradykinesia, rigidity and abnormal postural reflexes. Biochemical and genetic tests excluded Wilson's disease, Huntington's disease and Oppenheim's dystonia.

Conclusion: This is a new type of familial dystonia-parkinsonism where the craniocervical dystonic symptoms are most prominent in the early stages while parkinsonism becomes the predominant problem later in life. A search for the genetic mutation in this family is underway.

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Primary generalized dystonia is a clinically and genetically heterogeneous group of movement disorders that is usually inherited in an autosomal dominant manner with reduced penetrance [1]. The gene for classic Oppenheim dystonia, DYT1, has recently been characterized as a unique deletion of a GAG triplet found in over 70% of patients with the classic clinical features [2–5]. Oppenheim's dystonia has been reported to be especially common among Ashkenazi Jews [6], with the same triplet deletion among American and Israeli Ashkenazi Jews [7]. PGD is classified by age at onset and distribution of symptoms. Most cases of childhood-onset PGD start in a limb and then spread to other limbs and the trunk, affecting the neck and cranial muscles only later in the course of the disease [8–10]. Inzelberg et al. [5] found that only 5% of familial cases of PGD presented with dystonic speech or blepharospasm.

There are several familial disorders characterized by dystonia and parkinsonism. Familial early-onset generalized dystonia and parkinsonism is classically seen in patients with dopa-responsive dystonia, known as Segawa disease, both in the autosomal dominant and the autosomal recessive forms [11–13]. Another form of dystonia-parkinsonism is known as rapidly progressive dystonia-parkinsonism and manifests between 14 and 45 years of age. The clinical course is characterized by rapid evolution of dystonic spasms, dysarthria and dysphagia over a period of several hours to weeks [14]. Dystonia-parkinsonism may also be transmitted as an X-linked recessive form known as Lubag [15–17]. This disease usually starts between age 30 and 45 years, with dystonia affecting the face, neck, trunk or limbs. This subsequently generalizes, in most cases, within 6 years. Parkinsonism, including rigidity, bradykinesia, postural instability and tremor develops in many of the cases with dystonia at onset or may be the sole manifestation of the disease in late-onset cases [3,4,10].

We describe here a unique Ashkenazi Jewish family with juvenile onset of generalized dystonia predominantly affecting the craniocervical region with parkinsonism. This family does not carry the DYT1 deletion.

Family description

Over the past 30 years, the father and three of his four daughters [Figure 1] presented to us with a similar picture of generalized dystonia. In each it started in the craniocervical region in the second or third decade of life and later developed into moderate parkinsonism, manifested mainly by bradykinesia, rigidity and abnormal postural reflexes.

The father was born after a normal pregnancy and delivery, and attained the normal developmental milestones. He was healthy until the age of 30 when he developed dysarthria and dysphagia and shortly thereafter torticollis and jaw-opening dystonia. During the course of several years he developed bradykinesia, rigidity in all four limbs, mildly abnormal postural reflexes and truncal dystonia. There was no tremor. No cerebellar or pyramidal signs were observed. A trial of treatment with levodopa did not bring any symptomatic benefit. Over the subsequent years he progressed to develop severe postural instability and impairment of fine motor movement. During preparation for thalamotomy at age 38, he developed ischemic stroke in

PGD = primary generalized dystonia

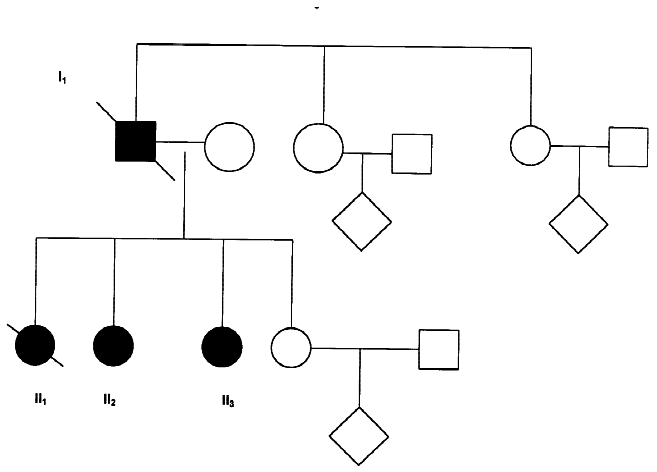

Figure 1. Family tree

the left middle cerebral artery territory with aphasia and right hemiparesis. Gradually he became wheelchair bound and was bedridden at the age of 50. He died at the age of 60 years due to aspiration pneumonia. Autopsy was not performed.

The first daughter was born after a normal pregnancy and probably a normal delivery. Her developmental milestones were normal. Her presenting symptom was dysarthria at age 6, with increased tone at the wrists with reinforcement. Blepharospasm was first reported at age 20. She subsequently developed jaw-opening dystonia and torticollis, hypophonia and later bradykinesia, rigidity in all four limbs and mildly abnormal postural reflexes. At about the same time severe kyphoscoliosis was noted with compensatory lumbar hyperlordosis. She underwent right thalamotomy at age 23 and subsequently cervical laminectomy (C1–C7), neither of which was effective. She gained no benefit from a trial of treatment with levodopa. She died of unknown cause after abdominal surgery at age 35.

The second daughter followed normal developmental milestones but was noted to have mild mental retardation. She completed 6 years of elementary school and was able to read and write. Bronchial asthma and ulcerative colitis were diagnosed and treated accordingly. She developed spastic dysphonia at age 14 and jaw-opening dystonia a few years later. She began to show parkinsonian signs, namely hypomimia, positive glabellar sign, bradykinesia, abnormal postural reflexes and rigidity in all four limbs. She gained moderate benefit from carbidopa/levodopa (25/250 mg), up to three pills a day, with improvement of her gait and amelioration of both the bradykinesia and jaw-opening dystonia. She recently also developed levodopa-induced foot dystonia, mild axial dyskinesia, and orthostatic hypotension. She is now 52 years old and lives in a closed community of disabled people because of her mild mental retardation and severe motor disability. Magnetic resonance imaging of her brain showed mild generalized atrophy with significant bilateral caudate nuclei atrophy. Wilson's disease was excluded because of normal serum ceruloplasmin, absence of Kayser-flaisher ring on slit lamp eye examination and 24 hour copper excretion in the urine. Huntington's disease and Oppenheim's dystonia were tested genetically for the known mutations on chromosome 4 and 9, which were not found.

In the third daughter, developmental milestones were normal although mild mental retardation was also noted. Her presenting symptom was torticollis in the second decade of life, and a few years later she developed bradykinesia, rigidity and subsequently mildly abnormal postural reflexes that did not respond to levodopa. She is now 49 years old and married to a mentally retarded man but has no children. Two sisters of the propositus and a fourth daughter, now aged 80, 75 and 47 years respectively, were examined and found to be healthy.

Table 1. Clinical characteristics of the four affected patients

Family	Age at symptom onset	First symptom	Other manifestation	Cognitive state	Levodopa response
I_1	30 yr	Torticollis	Bradykinesia, rigidity, abnormal postural reflexes	Normal	None
II_1	20 yr	Blepharospasm	Bradykinesia, rigidity,	Normal	None
II_2	14 yr	Hypophonia, dysarthria	Bradykinesia, rigidity, abnormal postural reflexes	Mild mental retardation	Poor
II_3	24 yr	Torticollis	Bradykinesia, rigidity	Mild mental retardation	None

Discussion

We report a new form of hereditary, juvenile-onset familial primary generalized dystonia with parkinsonism, where craniocervical dystonic symptoms are most prominent in early stages while parkinsonism becomes the main problem later in life.

Among Ashkenazi Jews, more than 90% of childhood-onset generalized dystonia that begins in the limbs is due to a mutation in the DYT1 gene, as determined by a recent survey in Israel among families with Oppenheim-type torsion dystonia [5,7]. A search for the genetic mutation in the present family is currently underway.

Familial generalized dystonia starting at an early age and presenting in the craniocervical region is rare, although familial torticollis has been reported [18]. The family described is unique in that the blepharospasm, torticollis, spastic dysphonia and jaw dystonia presented early in the course of the disease during the

second or third decades of life. Moreover, in contrast to the classical tendency of craniocervical dystonia to remain focal or segmental, in this family dystonic postures spread over several decades to other body regions to become generalized or multifocal. The clinical course in all affected family members is different from that associated with the GAG deletion in the DYT1 gene. Only recently, after the mutation for Oppenheim's dystonia was characterized, could we confirm this clinical impression by genetic testing, having failed to detect the GAG deletion in this family.

The combination of dystonia at an early age with parkinsonism in the forth or fifth decades of life is interesting from the pathogenetic point of view. A similar course is seen in dopa-responsive dystonia and in juvenile Huntington disease. Dopa-responsive dystonia is characterized by childhood-onset leg dystonia and gait disorder, with diurnal motor fluctuations and parkinsonian symptoms such as bradykinesia, loss of postural reflexes and rigidity, with dramatic response to low doses of levodopa. Even though this family was not assessed genetically for dopa-responsive dystonia, the clinical evolution and lack of response to levodopa makes this diagnosis highly unlikely. Huntington's disease was suspected especially after we observed bilateral caudate atrophy in patient II, but genetic testing excluded this possibility.

In conclusion, we report a new familial dystonia-parkinsonism syndrome in an Ashkenazi Jewish family with hereditary, juvenile-onset, craniocervical predominant dystonia that does not carry the DYT1 deletion. A search for the genetic mutation in this family is presently underway.

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Erratum

In the report "Pseudohypotension in a patient with malignant hypertension" by R. Jaffe et al., published in the June issue (*IMAJ* 2000;2:484–5), we wish to correct two important errors. The second key word should be malignant hypertension (not malignant hypotension), and the first word of the article should be Pseudohypertension (not Pseudohypotension).