late in the course of the disease, in contrast to the early-onset typically seen in PKAN. A further differentiating feature, at least in our patient, was the absence of the classic "eye of the tiger" sign that is strongly associated with PKAN.[6] Therefore, although PKAN might be a differential diagnosis in cases of neuroferritinopathy, the age of symptom onset, the time course of the development of bulbar symptoms, and the MRI appearance might all be useful distinguishing features.

Our patient presented in his twenties with generalized limb-onset dystonia, a normal MRI scan, and no cognitive impairment. At this initial stage, the clinical picture was quite similar, apart from age at onset, to idiopathic primary generalized dystonia such as is seen in dystonia associated with the DYT1 mutation. Although it is relatively easy to exclude DYT1 dystonia by genetic testing, the differentiation of neuroferritinopathy patients presenting at this early stage from idiopathic DYT1-negative primary generalized dystonia is important. Not only do the two conditions have very different prognoses, but, with the increasing use of deep brain stimulation for primary generalized dystonia (and with the poorer response of those with secondary dystonia to this procedure), there are therapeutic implications of making a correct diagnosis. There are ongoing studies of imaging techniques that can detect very small amounts of iron deposition not visible on standard MRI.[4] Such techniques might be useful in the early stages of the condition to differentiate patients with neuroferritinopathy from patients with primary generalized dystonia.

In conclusion, neuroferritinopathy should be considered in the differential diagnosis of patients with generalized dystonia even if they have a normal standard brain MRI scan and no bulbar involvement. Such patients can present as de novo cases without a clear family history. A normal serum ferritin level is not sufficient to exclude the condition.

Legend to the Video

The patient is seated in a wheelchair. Dystonic posture is evident in the left foot. With arms outstretched, there is dystonic posturing of both hands, particularly the right. A lateral shift of the neck to the left is apparent. Bulbar involvement by dystonia is evident, and his speech is indistinct. There is no evidence of finger–nose ataxia. When using a communication aid, dystonic posturing of both hands is clearly seen.

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Autosomal Recessive Primary Generalized Dystonia in Two Siblings From a Consanguineous Family

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Abstract: We describe the clinical features of a brother and sister with non–dopa-responsive, childhood-onset, generalized dystonia. The children were born to consanguineous parents, had no family history of neurologic disease, no evidence of structural or metabolic causes of dystonia, and negative testing for the GAG946 deletion mutation in the *DYT1* gene. This report supports the existence of a generalized type of dystonia with autosomal recessive inheritance (DYT2). © 2004 Movement Disorder Society

Key words: movement disorders; dystonia; autosomal recessive; dyt2; neurogenetics

Currently, at least 13 types of primary dystonia can be distinguished on a genetic basis.[1,2] Of these types, 10 forms are autosomal dominant (AD), 1 is X-linked recessive (Dystonia 3), and 2 types are inherited in an autosomal recessive (AR) manner (tyrosine hydroxylase deficiency and Dystonia 2). Tyrosine hydroxylase deficiency has been reported in rare cases of dopa-responsive dystonia, although the deficiency of this enzyme primarily presents as infantile parkinsonism.[3,4] The existence of a distinct type of autosomal recessive (AR) primary dystonia (Dystonia 2 or DYT2) is still controversial and has been questioned by some authors.[5]

The pattern of inheritance of the most common type of primary dystonia, idiopathic torsion dystonia (ITD), was the subject of debate for many years, with some authors in favor of AR transmission[6] and others supporting AD inheritance with reduced penetrance.[7] It is now clear that ITD is dominantly inherited with penetrance of 30 to 40%. Incomplete penetrance has also been described in other types of primary dystonia.

This article includes Supplementary Video, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat.

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Only a few dystonia pedigrees suggestive of recessive inheritance have been reported in the literature.[8–13] However, no mutation analysis or homozygosity mapping was performed in these families. Hence, the occurrence of AR primary dystonia remains uncertain.

We studied 2 siblings of a consanguineous marriage who presented with a rapidly progressive form of generalized dystonia. These cases provide additional indirect evidence in support of the existence of primary generalized dystonia with AR inheritance.

Patients and Methods

We performed serial neurological examinations in a brother and sister born to consanguineous parents of Arab descent. The patients presented at ages 4 and 6 years, respectively, with unilateral leg dystonia that generalized over the next few months. Both patients were carefully evaluated every 2 to 4 months from the time of symptom onset. The female patient has been followed for more than 6 years and her brother for more than 5 years.

Patient Descriptions

Case 1

A 6-year-old, right-handed girl presented for evaluation of difficulty walking for the past few weeks. She had initially developed posturing of the right foot during ambulation. Prenatal history, birth, past medical history, and developmental history were unremarkable. The mother and father were 23 and 28 years old, respectively, and were first cousins (their parents were brother and sister). They were of Caldean Babylonian descent from Northern Iraq, and there was no history of Jewish ancestry. The patient had two younger brothers who, at the time of her initial evaluation, were both asymptomatic. The proband's parents had normal physical and neurological examinations. A three-generation pedigree inclusive of more than 30 individuals (with 5 maternal and 10 paternal uncles and aunts) indicated no evidence of neurologic disease in other family members, although these individuals could not be examined by the authors. The child's neurological examination showed right leg dystonia elicited by walking. The remainder of her neurological examination, the physical examination, and a neuro-ophthalmologic evaluation were normal. A magnetic resonance imaging (MRI) scan of the brain and spine, liver function tests, ceruloplasmin levels, 24-hour urine copper, and plasma amino acids were normal. Genetic testing showed absence of the GAG946 deletion mutation of the *DYT1* gene. The patient did not respond to treatment with levodopa/carbidopa (10 mg/kg). Over the course of the following few months, her dystonia progressed rapidly to result in asymmetric involvement of all four extremities and the trunk. This dystonia prevented crawling and ambulation without the use of a walker. Treatment with trihexyphenidyl (30 mg/day), clonazepam (3.75 mg/day), and oral baclofen (100 mg/day) resulted in variable and incomplete responses. Three months after the last increase of trihexyphenidyl dose, the child's gait significantly improved, although she continued to have dystonia. Her gait partially worsened over time, but the improvement persisted even after discontinuation of all medications. By age 12 years, she had dystonia involving all four extremities and the trunk, worsened by movement and with sparing of the face and neck and absence of dysarthria. The patient has had fluctuations in symptom severity but no subsequent evidence of progressive worsening.

Case 2

A 4-year-old, right-handed boy (the oldest brother of Patient 1) presented for evaluation of progressive difficulty walking for 10 days. He had developed stiffening of the right leg during ambulation, which was followed by involvement of the left lower extremity within approximately 1 week. Prenatal, birth, and past medical history and development were unremarkable. The neurological examination showed lower extremities dystonia elicited by walking and more severe on the right side. Mild upper extremity dystonia was elicited by movement and was also more prominent on the right side. The remainder of the examination was normal. An MRI of the brain and spine, liver function tests, and plasma amino acids were normal. The patient did not respond to treatment with levodopa/carbidopa (10 mg/kg). Over the course of the following 3 months, his dystonia progressed with asymmetric involvement of all four extremities, markedly more severe in the legs, preventing independent ambulation. There was partial improvement of his gait with oral baclofen (80 mg/day). He had fluctuations in symptom severity after the initial period of rapid progression, but no evidence of continued progressive worsening. On neurological examination at age 9 years, he demonstrated generalized dystonia clearly exacerbated by movement and more severe on the right side. Assay of white blood cell lysosomal enzyme panel (Jefferson Medical College, Philadelphia) and urine organic acids (Baylor College of Medicine, Houston) were normal.

Discussion

The patients were diagnosed with a generalized form of dystonia with the following characteristics: (1) dystonia beginning in one leg and progressing over days to months to involve both legs, the trunk, and to a lesser degree the arms, resulting in loss of independent ambulation; (2) fluctuations in severity, both spontaneously and in response to treatment, but no evidence of progressive worsening after the initial rapid phase of generalization; (3) uncomplicated prenatal and birth history and normal developmental milestones; (4) no additional abnormalities on examination; (5) absence of structural central nervous system abnormalities or biochemical derangements, and negative genetic testing for the GAG946 deletion mutation in the *DYT1* gene; (6) no response to levodopa/carbidopa administration, arguing against the diagnosis of dopa-responsive dystonia; (7) consanguinity with the parents being first cousins, suggesting AR inheritance; (8) variable and incomplete response with trihexyphenidyl and high-dose oral baclofen. Interestingly, both siblings developed symptoms at almost the same age. This finding suggests a developmental influence on the first manifestations of a genetic predisposition for dystonia. It is tempting to speculate that the neurologic substrate must be sufficiently mature to exhibit this symptom.

The clinical features of these patients fall in the proposed category of Dystonia 2 (DYT2 or AR generalized dystonia) and are similar to various forms of primary generalized dystonia with childhood onset. The best-characterized disorder in this group is ITD, and this diagnosis was formally excluded by testing for the GAG946 *DYT1* deletion. Several forms of dystonia including ITD are transmitted as AD traits with incom-

plete penetrance.[1,2] Furthermore, cases of this disorder once thought to be inherited in an AR manner were later shown to be dominantly inherited. This finding has led to uncertainty regarding the existence of a form of primary dystonia with AR inheritance.[5] Although the possibility of incomplete penetrance of an AD trait cannot be excluded in our pedigree, the consanguinity of the parents, occurrence of disease in both sexes, and absence of neurologic disease in three generations comprising more than 30 individuals strongly suggest AR inheritance. There are only a few dystonia pedigrees described in the literature, mainly of consanguineous Spanish Gypsies, clearly suggestive of AR inheritance.[9,10] The clinical features of affected individuals in some of these families are similar to manifestations seen in our patients; however, there are also important differences. In two of three consanguineous families, a total of 5 affected individuals were reported with leg onset dystonia rapidly progressing to involve the trunk and upper extremities. On the other hand, these cases had later age at onset and involvement of the face and speech, two characteristics not present in our patients. A third consanguineous pedigree had features of myoclonic-dystonia. Khan and colleagues recently reported a kindred with DYT2-like dystonia. Three affected siblings born to first cousins of Iranian Sephardic Jewish ancestry had limb onset dystonia in childhood slowly generalizing to mild limb and marked craniocervical involvement.[13] AR inheritance has also been suggested in a few other isolated pedigrees, although in only one of these families there was consanguinity with the parents being second cousins.[8,11,12] The interpretation of these cases remains open to questions. In 1934, Santangelo described 3 non-Jewish Italian siblings (a brother and 2 sisters) born to second cousins.[8] The children developed generalized dystonia at age 9 years, which was associated with cognitive deficits and impairment of oculomotor function. The oldest affected patient manifested ongoing slow neurologic deterioration more than 10 years after onset of the disease. Liver function and copper metabolism were not tested. In a more recent report, Lisker and coworkers described 3 Mexican children of mixed Spanish and indigenous ancestry (2 sisters and a brother) who developed generalized dystonia with cranial involvement and dysarthria at age 7 years.[11] There was no consanguinity and liver function, and copper metabolism were normal. Generalized dystonia with cranial involvement and dysarthria was also described in a brother and a sister of mixed ancestry born in an isolated community in the northwestern Cape.[12] Age at onset was 10 years in both children. An older brother had unilateral dystonia and a history of meningitis and seizures at 5 months. Copper metabolism was normal in all 3 patients. There was no consanguinity in the parents, and the father was not examined by the authors. To our knowledge, none of the above patients were tested for *DYT1* mutations.

Of interest, recessively inherited dystonia has also been described in spontaneous mutations in rodents,[14] arguing for the possibility of dystonia with this pattern of inheritance in humans. Childhood-onset primary dystonia is frequently found in apparently sporadic cases. Only a percentage of these is caused by the GAG deletion in *DYT1*.[15,16] The remaining cases may due to other unknown genetic factors with unknown pattern of inheritance. It is possible that a fraction of these cases may be due to inheritance of rare recessive traits.

In summary, this report suggests the existence of a rare generalized type of primary dystonia with AR inheritance. Although there is only a very limited literature on this topic, identification of additional families will permit genetic studies to identify the locus for this disorder.

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Legends to the Video

Segment 1. Case 1 at age 10 years. The girl shows asymmetric limb and truncal dystonia with sparing of the face. At the time of the video, the patient was on oral baclofen (80 mg/day).

Segment 2. Case 2 at age 7 years. The patient displays generalized asymmetric dystonia with sparing of the face. At the time of this video, the patient was on oral baclofen (80 mg/day).

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