Frequency of the DYT1 Mutation in Primary Torsion Dystonia Without Family History

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Background: Idiopathic torsion dystonia is a clinically and genetically heterogeneous movement disorder. A GAG deletion at position 946 of the DYT1 gene was the first mutation found, in early-onset dystonia, with an autosomal dominant transmission and reduced penetrance.

Objective: To evaluate the frequency of the DYT1 mutation in patients with idiopathic torsion dystonia but without a family history.

Design: Prospective cohort study.

Setting: Four botulinum toxin clinics in the Paris, France, area.

Patients: A French population of 100 patients with dystonia.

Main Outcome: Frequency of the DYT1 mutation tested by polymerase chain reaction and enzyme restriction analysis for the 946 GAG deletion, and genotype-to-phenotype correlation.

Results: Only 5 mutation carriers were identified, 4 of whom were part of a group of 10 patients with generalized dystonia. Onset was between ages 5 and 12 years as in typical early-onset dystonia. All 4 patients had cranial muscle involvement, which is atypical for DYT1 mutation carriers. One had segmental dystonia. Molecular analysis of relatives in 2 families demonstrated that the lack of family history was due to reduced penetrance.

Conclusions: For accurate diagnosis and genetic counseling, screening for the DYT1 deletion is of great interest in cases with generalized dystonia without a family history. In other cases, positive results are rare.

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TORSION DYSTONIA is a syndrome in which sustained muscle contraction causes twisting, repetitive movements, or abnormal postures. In idiopathic torsion dystonia there is no known causative environmental factor and the syndrome is not associated with another disease.1 Idiopathic torsion dystonia is clinically very heterogeneous. Age at onset is variable (from childhood to late adult life); distribution may be focal, segmental, or generalized; disease progression slow or rapid; and family history may or may not be present. Idiopathic torsion dystonia is also genetically heterogeneous, with 7 loci mapped and 2 genes identified.2 A GAG deletion at position 946 in the DYT1 gene resulting in the loss of a glutamic acid residue in the torsin A protein is the cause of most cases of early-onset generalized dystonia with family histories, especially among Ashkenazi Jews.3 However, since the disease is associated with reduced penetrance, DYT1 deletion carriers are also found in isolated cases with no family history.3,4 In addition, some patients without the typical phenotype of early-onset limb dystonia that spreads to other limbs are found to carry the DYT1 deletion as well.4 To evaluate the role of the DYT1 locus in isolated cases with idiopathic torsion dystonia, we screened 100 patients with various forms of primary dystonia without family histories for the GAG deletion in the DYT1 gene.

There were 10 patients with generalized, 21 with segmental or multifocal, and 69 with focal dystonia (Table 1). Among those with focal dystonia were 21 patients with torticollis, 19 with blepharospasm, 19 with writer’s cramp, 6 with pha-
PATIENTS AND METHODS

PATIENTS

One hundred twenty-five patients were recruited consecutively between May and September 1998 in 4 botulinum toxin clinics in the Paris, France, area: Hôpital de la Salpêtrière (n = 36), Hôpital Saint Antoine (n = 20), Hôpital Foch (n = 19), and Fondation Rothschild (n = 19) (except for 7 patients previously described\(^3\) and 24 from other hospitals). All patients were evaluated by a neurologist or a neuropediatrician using the same standardized protocol. The inclusion criteria were (1) clinical course compatible with idiopathic torsion dystonia without features suggestive of secondary dystonia and (2) absence of a family history of dystonia assessed by interview. Twenty-five patients were excluded because of positive family histories (n = 21), tardive dystonia (n = 3), or birth hypoxia (n = 1). Patients with dystonia-plus syndromes or paroxysmal dystonia were not ascertained.\(^1\) Patients were classified according to the topography of the dystonia: focal, segmental (or multifocal), or generalized.\(^1\) Ages at onset of the 3 groups were compared with the Kruskal-Wallis nonparametric test.

GENOTYPING

Blood samples were taken, with informed consent from patients, and in some cases from their relatives, for extraction of genomic DNA. Molecular screening for the GAG deletion at position 946 was performed, as previously described,\(^1\) by polymerase chain reaction amplification followed by digestion with restriction enzyme BseRI. The presence of the mutation in 1 patient was confirmed by direct sequencing.

COMMENT

Results of our study confirm that carriers of the DYT1 mutation can present as isolated cases. This has already been reported by indirect or direct genetic analyses of small series of patients of various geographical origins without family histories.\(^3\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^8\) These apparently isolated cases are mostly accounted for by incomplete penetrance of the mutation, estimated at 30% to 40%, but also by rare de novo mutations.\(^9\)\(^,\)\(^10\) Reduced penetrance, confirmed by molecular analysis of the parents, explained the absence of family histories for 2 of the carriers of the mutation in the present study.

Four of the 10 isolated cases had generalized dystonia. The proportion is similar to that in familial cases (4 of 8 families) with typical early-onset dystonia from the same population.\(^3\) However, the small number of cases with generalized dystonia in both samples precludes accurate estimation of the proportion of DYT1 carriers. The age at onset of mutation carriers (5 to 12 years old) was within the range for typical early-onset dystonia defined by Ozelius et al.\(^3\) Patients with generalized dysto-

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Table 1. General Characteristics of 100 Patients With Primary Torsion Dystonia Without Family History

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Focal (n = 69)</th>
<th>Segmental (n = 21)</th>
<th>Generalized (n = 10)</th>
<th>Total (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean ± SD, y</td>
<td>46.4 ± 14.1</td>
<td>49.0 ± 17.9</td>
<td>15.8 ± 16.5</td>
<td>43.9 ± 17.9</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>43/26</td>
<td>13/8</td>
<td>6/4</td>
<td>62/38</td>
</tr>
<tr>
<td>Disease duration, mean ± SD, y</td>
<td>6.4 ± 5.2</td>
<td>4.3 ± 2.4</td>
<td>26.0 ± 14.4</td>
<td>7.9 ± 8.7</td>
</tr>
</tbody>
</table>

Table 2. Clinical Characteristics of the 5 Patients With the DYT1 Mutation

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Ashkenazi Jew</th>
<th>Age at Onset, y</th>
<th>Disease Duration, y</th>
<th>Site at Onset</th>
<th>Distribution at Last Examination†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M*</td>
<td>No</td>
<td>9</td>
<td>45</td>
<td>Foot</td>
<td>Generalized: cranial, neck, UL, LL, trunk</td>
</tr>
<tr>
<td>2/M*</td>
<td>Yes</td>
<td>5</td>
<td>13</td>
<td>Left hand</td>
<td>Generalized: cranial, neck, UL, LL, trunk</td>
</tr>
<tr>
<td>3/F*</td>
<td>Yes</td>
<td>12</td>
<td>37</td>
<td>Right UL</td>
<td>Generalized: cranial, UL, LL</td>
</tr>
<tr>
<td>4/F</td>
<td>No</td>
<td>6</td>
<td>16</td>
<td>Left hand</td>
<td>Generalized: cranial, neck, UL, LL, trunk</td>
</tr>
<tr>
<td>5/F</td>
<td>No</td>
<td>11</td>
<td>1.5</td>
<td>Left LL</td>
<td>Segmental: left LL, trunk</td>
</tr>
</tbody>
</table>

* Patients previously described by Lebre et al.\(^5\)
† UL indicates upper limb; LL, lower limb.
nia who did not carry the mutation had a later age at onset, as previously reported. Although onset was in one limb as in typical early-onset dystonia, the phenotype of 4 of 4 mutation carriers was atypical because of cranial involvement. This has also been observed by other investigators. The dystonia of the fifth carrier was segmental, and has remained so after a disease duration of 15 months. The phenotype, in this case, is unusual because of the sudden development of permanent trunk dystonia, and the involvement of the proximal part of a lower limb. To our knowledge, this is only the second case of a DYT1 mutation with a segmental phenotype to be described. Although the phenotype of DYT1 is much broader than in typical early-onset dystonia, we, like others, did not detect the mutation in patients with focal dystonia.

Genetic counseling is difficult in isolated cases of idiopathic torsion dystonia because the phenotypes can be similar to those of familial cases and because penetrance is known to be reduced in several genetically determined dystonias. It is therefore important to be able to identify gene carriers. Our study demonstrates that the DYT1 mutation can very often be detected in isolated patients with generalized dystonia, but rarely in other types of dystonias, especially those that are focal.

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REFERENCES