Prevalence of Dentatorubral-Pallidoluysian Atrophy in a Large Series of White Patients With Cerebellar Ataxia

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Background: Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare neurodegenerative disorder mainly diagnosed in Japan. Its prevalence is low in other countries. Three phenotypes are described: choreoathetoid movements, cerebellar ataxia, and progressive myoclonic epilepsy.

Objective: To evaluate the frequency of DRPLA in European patients with sporadic or autosomal dominant cerebellar ataxia.

Methods: We analyzed a series of 809 index patients with either autosomal dominant cerebellar ataxia (416 families) or progressive cerebellar ataxia without a family history of the disease (393 cases) for the DRPLA mutation.

Results: We identified a CAG repeat expansion in the DRPLA gene in one family and in one patient without a family history. The familial case illustrates the phenomenon of anticipation and the previously established correlation between the phenotype and size of the expansion. A censored-history family or expansion of large normal CAG repeats during paternal transmission could be implicated in the patient without a family history.

Conclusions: This study enables us to estimate the frequency of the disease as 0.25% in both families with autosomal dominant cerebellar ataxia and sporadic cases of ataxia in our series, confirming the very low frequency of DRPLA in Europe. In both familial and sporadic cases, molecular testing for DRPLA could be restricted to patients with ataxia with one of the following features: chorea, dementia, or myoclonic epilepsy.

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Pedigree of the family with dentatorubral-pallidoluysian atrophy (patients 1 and 2). Age at examination is indicated. Age at onset and CAG repeat sizes are given for affected patients. Circles indicate females; squares, males; black symbols, affected patients.

without a family history of the disease (393 cases). In this series, we included the patients who were previously described by Dubourg et al. All patients were screened for spinocerebellar ataxia (SCA) types 1, 2, 3, 6, and 7 and DRPLA mutations as described. Furthermore, 139 of 196 familial cases in which the previous mutations were excluded were screened for SCA types 10, 12, and 17 (TATA box-binding protein gene). Allele lengths in the DRPLA gene were determined by standard procedures, with 49 CAG repeats as the threshold for pathologic expansions.

A predominant sign was associated with cerebellar ataxia in one third of the patients from families without SCA types 1, 2, 3, 6, and 7 mutations: dementia (15.0%), mental retardation (4.5%), dystonia (3.6%), parkinsonian features (4.3%), epilepsy (2.5%), chorea (1.3%), and myoclonus (1.3%). Sporadic and familial cases were mostly of French origin (82.0%). Other families originated from Portugal (4.0%), Germany (3.0%), Spain (2.5%), Italy (2.5%), Belgium (2.0%), Austria (2.0%), Sweden (1.0%), and Poland (1.0%).

RESULTS

A CAG-repeat expansion in the DRPLA gene was identified in a single Italian family with ADCA (patients 1 and 2) (Figure) and in a patient with cerebellar ataxia but without a family history (patient 3). All of the other patients carried alleles ranging from 5 to 28 repeats.

PATIENT 1

A 17-year-old girl presented with a delay in language acquisition at age 4 years and drug-resistant epilepsy with myoclonus at age 8 years. At 17 years of age, severe cognitive impairment, cerebellar ataxia, akinesia, pyramidal signs with severe motor deficit, and spasticity were observed on examination. Brain magnetic resonance imaging showed severe cortical and cerebellar atrophy. Molecular analysis of the DRPLA gene showed a 67-CAG repeat expansion. Her father, a 45-year-old obligate carrier, and her paternal grandparents, both older than 70 years, were asymptomatic, suggesting incomplete penetrance. Unfortunately, none of the 3 was available for molecular analysis.

PATIENT 2

A paternal aunt of patient 1 (Figure) had had cervical dystonia at age 23 years and started developing progressive cognitive deterioration at age 30 years. She had generalized seizures at 30 and 36 years of age. When examined at age 37 years, she had cerebellar ataxia, severe diffuse chorea, cervical dystonia, brisk reflexes, and bilateral Babinski signs. Eye movements were saccadic. Brain magnetic resonance imaging showed cerebellar, cortical, and subcortical atrophy. Molecular analysis of the DRPLA gene showed a 62-CAG repeat expansion.

PATIENT 3

An Italian patient presented with a mild static cerebellar syndrome at age 37 years, which was associated with spastic paraparesis, mild cognitive impairment, and chorea at age 41 years. He began to have seizures at age 42 years of age. Magnetic resonance imaging showed cerebellar atrophy, predominantly of vermis. Molecular analysis showed a 61-CAG repeat expansion within the DRPLA gene. He died at age 45 years in a car accident. He had no family history, but both of his parents had died at age 30 years.

COMMENT

We identified 3 Italian patients with DRPLA in a cohort of 416 European families and 393 patients without family histories. The prevalence of DRPLA is extremely low outside Japan, and only a few families have been described in China and the United States, of which were African American. Only 16 European families have been described, including 1 case without a family history. Seven came from Great Britain, 2 each from Italy, Portugal and Spain, and 1 each from the Maltese Islands, Denmark, and France. Our cohort of 809 European index cases is the largest ever investigated, to our knowledge. The present report enables us to estimate the frequency of the disease at 0.25% in both families with ADCA (95% confidence interval, 0.0001-0.0171) and sporadic cases of ataxia (95% confidence interval, 0.0001-0.0141). The absence of DRPLA cases in the large series of families of French origin establishes its maximal relative frequency at 1.21% for a 95% confidence interval. The frequency of DRPLA was previously estimated at 1% in a cohort of 116 Italian families with ADCA, 1% in 157 Spanish families, and 2% in a cohort of 202 Portuguese families with cerebellar ataxia. No cases were identified in the other 2 populations studies: 177 white patients and 121 Spanish patients. The frequency of large normal alleles, which probably constitute a reservoir for expanded alleles, is higher in Japanese than in white populations, accounting for the higher prevalence of DRPLA in this part of the world. The familial cases confirm the previously established correlation between the phenotype and size of the expansion. Patient 1 presented with myoclonic epilepsy (onset at age 4 years) and patient 2 with an ataxic and choreoathetoid form (onset at age 23 years). The phenotype was similar to that of Japanese patients, except for the presence of cervical dystonia at onset in patient 2. Dystonia is an unusual mode of onset in Japanese patients but has been reported as the first symptom in a few patients from European and North American families. This family also illustrates the phenomenon of anticipation, with onset at age 4 years in the daughter of a still-unaffected but obligate carrier father aged 45 years.
The isolated case confirms that patients without known family histories should also be screened for DRPLA if they have the characteristic phenotype. Apparently sporadic DRPLA cases represent 19% of Japanese families with DRPLA. As in Huntington disease and SCA7, they may be due to expansions of large normal CAG repeats during paternal transmission. They may also be explained by a censored family history, since both parents died at age 30 years and might have been as yet asymptomatic carriers.

This study confirms the very low frequency of DRPLA in Europe. As the phenotype of DRPLA is well defined, testing could be limited to patients with ataxia who have chorea, dementia, or myoclonic epilepsy. These criteria would have identified the patients with DRPLA in these series through screening of only about 20% of familial cases without the common mutations of SCA types 1, 2, 3, 6, and 7.

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