Spinocerebellar Ataxia Type 7:
Report of a New Italian Family

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Abstract

Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disorder characterized by degeneration of the cerebellum, brainstem and retina. We herein describe a family from southern Italy whose proband was a 49-year-old man presenting with ataxia with progressive gait disturbances, clumsiness and visual impairment. A molecular analysis identified 38 cytosine-adenine-guanine (CAG) repeat expansions within the SCA7 gene. Our study confirms the marked anticipation previously observed in SCA7 and extends the small number of patients studied thus far. In this family, the disease is most likely caused by a de novo expansion of a premutated intermediate allele carried by one parent.

Key words: SCA7, ataxia, neurodegenerative disease, CAG expansion

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Introduction

Spinocerebellar ataxia type 7 (SCA7) is a rare form of autosomal dominant cerebellar ataxia (ADCA) clinically characterized by progressive ataxic syndrome and retinal degeneration. Its prevalence varies from 1% to 12% with different ethnic and geographic origins. In several studies, SCA7 represents approximately 2% of all cases of ADCA (1-5). A higher prevalence was found in Scandinavian countries, thus suggesting a founder effect (6). The disease is caused by the expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat within the SCA7 gene encoding for a polyglutamine tract in a protein of unknown function termed ataxin-7 (2, 3). Normal SCA7 alleles harbor between four and 35 CAG repeats, whereas pathological alleles carry from 36 to more than 200 repeats. De novo expansions occur on intermediate alleles carrying between 28 and 35 CAG repeats (2, 3). SCA7 mutations appear to be very rare in Italy, with only four affected families reported thus far (7, 8).

We herein describe a family from Sicily (Southern Italy) whose proband was clinically and genetically diagnosed with SCA7.

Case Report

The proband was a 49-year-old man presenting with progressive gait disturbances, clumsiness and visual impairment lasting three years. He was born at term to healthy unrelated parents after an uneventful pregnancy. His developmental milestones were normal. His family history was unremarkable for neurologic or hereditary diseases. His father died at age 86 of colorectal neoplasia, and his mother died at age 75 of cerebral ischemia. No history of neurological disturbances or visual impairments was reported. Three brothers and one sister were healthy.

The patient began to notice mild imbalance and gait incoordination at 46 years of age. One year later, he complained of impaired visual acuity. The disease exhibited a progressive course until the patient presented with unsteady walking and a tendency to fall. When he came to our clinic, a neurological examination revealed a wide-based gait, difficulty walking in a straight line, bilateral and symmetrical gait and limb ataxia, dysarthria, slight solid dysphagia, dysdiadochokinesia and mild dysmetria on finger-to-nose and heel-
The patient also exhibited neurosensorial hypoacusia, brisk deep tendon reflexes in both upper and inferior limbs and bilateral hollow feet. The International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) were used to objectively assess the severity of ataxic impairment. Both of these instruments revealed mild ataxia (scores 18/100 and 10/40, respectively). Brain magnetic resonance imaging (MRI) showed vermian and hemispheric cerebellar atrophy (Figure). Visual Evoked Potentials (VEPs) were impaired at low amplitudes. An ophthalmologic work-up revealed markedly decreased visual acuity (4/10), hypermetric saccadic eye movements and nystagmus on a lateral gaze. Fundoscopy showed optic disk pallor bilaterally and pigmentary changes in the macular and peripheral retinal regions. Decreased amplitudes and increased latencies were found on both photopic and scotopic electroretinogram (ERG). A molecular analysis searching for expansion within the SCA7 gene revealed seven CAG repeats on one allele and 38 on the other allele. Therefore, a diagnosis of SCA7 was made.

The proband’s children, a 22-year-old daughter and a 25-year-old son, both refused to undergo genetic analyses. Their psychomotor and mental development were both normal. They did not complain of any neurological disturbances and exhibited normal results on neurological examinations; however, the latter had experienced progressive visual impairment since he was 23. Therefore, a diagnosis of SCA7 was made.

### Discussion

SCA mutations exhibit a peculiar distribution in Italy compared with other European countries. A study of 225 Italian SCA families evaluating the relative prevalence of SCA subtypes revealed a very low prevalence of SCA3 and SCA6 mutations. SCA7 also appeared to be very rare (1-2%), with only two families diagnosed (7). Intriguingly, the other two Italian families previously identified exhibited different haplotypes, although these families originated from the same restricted area of central Italy (8). This argues in favor of multiple origins of the SCA7 mutation and suggests that, in Italy, these mutations originate from different pools of pathological chromosomes carrying at risk intermediate alleles that derive from unrelated ancestors (8, 9).

In the family we described, which comes from a rural area of Sicily, the disease is apparently caused by a de novo mutation. We were not able to perform a genetic analysis of our proband’s parents because they were both deceased. However, as they died at an advanced age while not exhibiting any neurological disturbances or visual failures and since our proband exhibited a low number of pathological CAG repeats (38 repeats), it is highly improbable that they were affected. Therefore, we can argue that the disease is probably caused by the expansion of a premutated intermediate allele carried by one parent. De novo expansions from large normal alleles are described in SCA7 families (8, 9). For this reason, a silent familiar history is not uncommon.

SCA7, along with dentatorubropallidoluysian atrophy, is a triplet expansion disease exhibiting the most evident anticipation between generations. Indeed, SCA7 mutations exhibit a marked meiotic instability that is greater in paternal (mean increase of +15 CAG repeats) than maternal (mean increase of +5) transmission (10), thus leading to a striking anticipation of approximately 20 years between generations (2, 3). This involves the disappearance of the mutation within af-
fected families and should lead to the rapid extinction of the disease. This has not been the case because the expansion of intermediate alleles leads to de novo mutations constituting a reservoir of the disease (8).

The proband’s son can be considered to be most likely affected since his retinal changes are strongly suggestive of cone-rod dystrophy. His visual impairment occurred at 23 years of age and this is in accordance with the mean anticipation of 20 years across generations. Moreover, since he presented with visual impairment in the absence of any neurological disturbances, we can suppose that he carries a large CAG expansion. Indeed, in patients exhibiting large CAG repeats, visual impairment is often the onset symptom commonly preceding cerebellar syndrome (10, 11). The clinical course, as well as MRI study, will clarify the condition of this young man.

As in other CAG repeat diseases, polyglutamine expansions are believed to induce alterations in the conformation of the mutated protein, conferring neurotoxic properties (11, 12). Accumulating data demonstrate that mutated ataxin-7 selectively induces neurodegeneration in specific sub-populations of neuronal cells, in particular cerebellar neurons and retina (13-16).

It is noteworthy that some distinctive characteristics of SCA7, such as cone-rod dystrophy and hearing impairment, suggest that mitochondrial dysfunction could be crucial in the pathogenesis of the disease. This has been confirmed by experimental evidence showing that polyglutamine expanded ataxin-7 activates the mitochondrial apoptotic pathway in cerebellar and inferior olivary neurons by inducing transcriptional dysregulation (14-16). Otherwise, retinal involvement may be explained by direct interaction with the cone-rod homeobox protein, a critical transcription factor required for the expression of several photoreceptor-specific genes (17).

In conclusion, we herein reported the existence of a new family with SCA7 carrying a de novo mutation due to the expansion of intermediate alleles. Our report confirms the marked anticipation (20 years/generation) previously observed in this disease (8) and contributes to extending the small number of patients studied thus far.

The authors state that they have no Conflict of Interest (COI).

References