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Letter to the Editor

Infantile spinocerebellar ataxia type 7: Case report and a review of the literature

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Dear Sirs,

Spinocerebellar ataxia type 7 (SCA7) is an autosomal dominant neurodegenerative disorder characterized by progressive cerebellar ataxia associated with cone-rod and retinal dystrophy [1]. SCA7 is caused by a CAG repeat expansion (from 37 to 460 repeats) in the coding region of *ATXN7* gene [1–3]. Expansion of the polyQ tract in the protein ataxin-7 leads to its accumulation in neuronal nuclear inclusions, and to selective neuronal and photoreceptor degeneration.

Age at onset may be highly variable in SCA7, ranging from birth to 76 years, with a mean age at onset in the third to fourth decade of life according to the population [1,2]. A very severe, and rarely reported, infantile form may represent a diagnostic puzzle in which conventional molecular techniques may not reveal the large expansions of *ATXN7*.

We describe a 2 year-old girl that was referred to our neurogenetics clinic due to milestones delay. She held her head steady at 4 months of age, sat unaided at 6 months, and was never able to walk independently. She uttered her first words at 1 year and 2 months of age. The child was born after an uneventful twin pregnancy through cesarean delivery at 37 weeks. At birth, her weight was 2600 g, length 46 cm and head circumference 33 cm. Her Apgar score was 9 at 5 min.

She had a family history of SCA7. Her father started symptoms in the same year of her evaluation, when he was 37 year-old. She has an asymptomatic dizygotic twin sister, with normal milestones development and 3 other siblings that were asymptomatic (Fig. 1A).

Her physical examination at 2 years and 1 month of age showed wide-based unsteady gait only possible with the support of another person, axial hypotonia, postural and cervical tremor, dysarthria, upper limb dysmetria, ankle clonus, and extensor plantar responses. At 2 years and 8 months of age, she was not able to stand even with support or to sit unaided, and presented an episode of aspiration pneumonia. Her physical examination showed aggravation of the reported signs. Fundoscopy, at 2 years and 10 months, was normal. At 3 years of age, her parents reported significant dysphagia associated with weight loss and recurrent episodes of aspiration pneumonia. At this time she also showed significant language regression and was only able to say single words utterances. In the following month, she was admitted at our hospital due to severe aspiration pneumonia, requiring intensive care unit support. She started with visual loss during the admission and also presented focal seizures, well controlled with phenytoin. She was discharged after 3 months of treatment to palliative homecare. At that time, she had weight recovery with nasoenteral feeding tube nutrition; however almost all her voluntary motor and cognitive functions were lost. She was not able to follow the examiner with her eyes and barely move herself. At homecare she needed 24 h bi-level positive airway pressure non-invasive ventilation and, after another episode of aspiration pneumonia (at age 3 years and 10 months), she is now dependent on continuous oxygen supplementation. She is still gaining weight (current weight on 75th percentile) with nasoenteral feeding tube nutrition and she is waiting for the placement of gastrostomy tube.

At 3 years and 4 months of age, electroretinogram presented prolonged latencies of records bilaterally, and flash visual evoked potentials were absent. Electroencephalogram showed disorganized base rhythms with bursts of delta waves in anterior regions. Brain magnetic resonance imaging (MRI), at 1 year and 9 months of age, showed prominence of cerebellar folia and basis cisterns. When repeated, at 3 years and 4 months of age, diffuse volume reduction of the brain and progression of the brainstem and cerebellum atrophy were seen (Supplemental Fig. 1); together with mild T2 hyperintensity areas in periventricular and centrum semiovale white matter and in the topography of the transverse fibers of the pons.

Determination of *SCA7* allele sizes by conventional polymerase chain reaction (PCR) suggested a normal homozygous genotype of 10 CAG repeats (Fig. 1B). Next, triplet repeat primed PCR (TP-PCR) protocol was employed and revealed a massively expanded allele (Fig. 1C), which was further determined to be a tract of approximately 240 CAG repeats by agarose gel electrophoresis (Fig. 1D), confirming SCA7 diagnosis.

The rarely documented infantile SCA7 phenotype is associated with massive CAG repeat expansions, generally on paternal disease transmission [1,2]. In the present report the expansion was associated with 36 years of anticipation. Table 1 summarizes the clinical, genetic, and molecular findings of the infantile onset SCA7 patients reported so far. Although infantile onset was rarely reported; juvenile disease (onset before 10 years of age) seems to be more frequent in SCA7 than in other SCAs, representing 15% of the total number of SCA7 patients in some series [4].

Infantile-onset SCA7 is remarkable for its widespread disease pathology that includes organ systems outside the central nervous system (CNS) [5–7]. Cerebellar and brain stem degeneration are so rapid in infantile forms that retinal degeneration and vision loss may not be evident; differently from adult-onset disease in which visual loss may precede, accompany, or follow the onset of ataxia. Ataxia may not be obvious in early infancy, but muscle wasting, weakness, and hypotonia are common. Other manifestations include structural cardiopathy, hepatomegaly, developmental delay, motor and cognitive regression, failure to thrive, abnormal renal function, and dysphagia (Table 1).

Symptoms of infantile-onset SCA7 with no family history (due to dramatic anticipation) may be confused with acquired or other inherited diseases. The differential diagnosis may include autosomal recessive cerebellar ataxias, mitochondrial and lipid storage disorders, as well as neuronal ceroid lipofuscinosis [1]. Proper molecular techniques, as TP-PCR, should be applied whenever a large *SCA7* repeat expansion is suspected to confirm the diagnosis.

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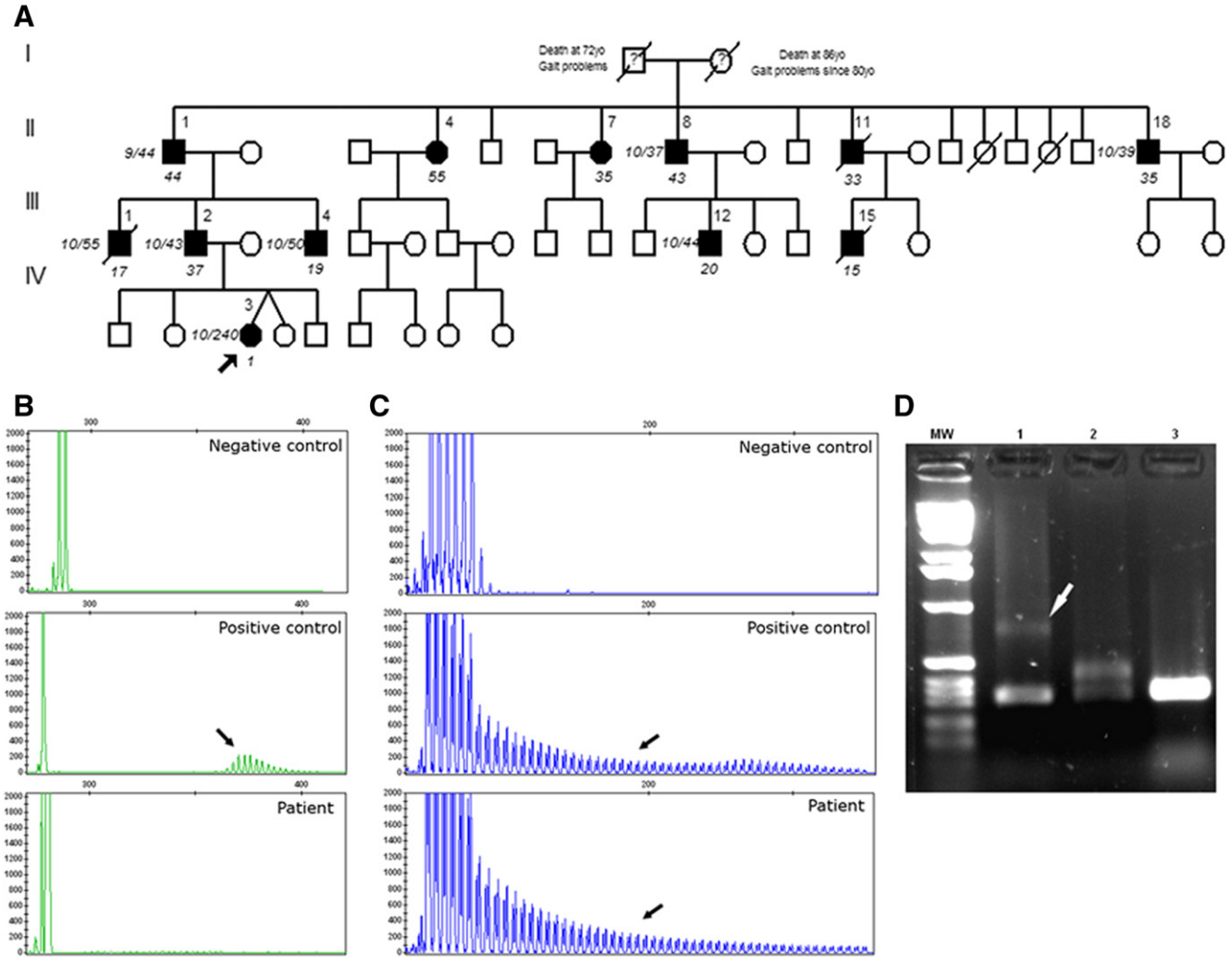

Fig. 1. Patient's family pedigree and molecular diagnosis of massive *SCA7* expansion. **A**: CAG repeats are indicated for all symptomatic members that underwent molecular diagnostic procedure. Age at onset is given in italic (years) bellow symbols. Proband is indicated with a black arrow. Squares indicate males and circle females; dark fill indicates affected individuals. Question marks indicate unknown diagnosis. **B**: Electrophoretic profile of *SCA7* allele sizes by conventional PCR (green peaks). The negative control is a normal heterozygous individual with alleles corresponding to 11 and 12 CAG repeats, while the positive control is an adult-onset SCA7 individual presenting one expanded allele with 43 repeats (black arrow). In the patient, only one peak corresponding to 10 repeats is visible. **C**: Electrophoretic profile of *SCA7* allele sizes by triple-primed PCR. In this technique, fragments of increasing length are iteratively amplified from the expanded allele, resulting in a ladder pattern of migration, identified in both a positive control and in the patient sample (black arrows). **D**: Agarose gel depicting the bands amplified by standard PCR. Lane 1: patient sample, presenting fragments of sizes correspondent to alleles with 10 and 240 CAG repeats (white arrow), respectively. Lane 2: adult-onset SCA7 positive control (10 and 43 CAG repeats); lane 3: healthy control, homozygous for the 10 CAG-repeats allele. MW: 1 kb DNA molecular weight marker.