Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2 in a Family With Full CAG Repeat Expansions of ATXN2

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Report of a Case

A 47-year-old woman developed gait difficulty at age 36 years, slurred speech at age 37 years, and loss of hand dexterity at age 41 years. She did not have swallowing difficulty. Neurological examination revealed clinical signs typical for SCA2 including slow saccadic eye movements, truncal titubation, and hyporeflexia (Video). She was able to walk without a walker with a wide-based gait and marked staggering (3 points on the Scale for the Assessment and Rating of Ataxia [SARA]). She was able to stand only with intermittent support (4 points on SARA). She had a slight sway while sitting (1 point on SARA). She had scanning speech and occasionally was difficult to understand (3 points on SARA). She had mild dystymria on finger chase (1 point on SARA bilaterally), moderate intention tremor on nose-finger test (2 points on SARA bilaterally), and abnormal findings on the heel-shin slide test (2 points on SARA bilaterally). She had normal fast alternating movements (0 points on SARA). Her total SARA score was 16 (Video). She also had jaw-opening dystonia, facial myokymia, and shoulder muscle fasciculations but did not have spasticity, muscle weakness, bradykinesia, rest tremor, or rigidity. Magnetic resonance imaging showed marked cerebellar atrophy. Electromyography showed fasciculations and myokymia in the mentalis muscle without denervation. Genetic testing showed an expanded CAG repeat of 40/22 in ATXN2. She had no expanded hexanucleotide repeats in C9orf72 (2/5).

She had a paternal uncle who developed difficulty walking at age 62 years (Figure). Within 9 months of his symptom onset, he had lost dexterity in his hands, worse on the left side. He did not have imbalance. His neurological examination showed muscle atrophy and fasciculation in all 4 extremities. His muscle strength using the Medical Research Council grading scale was 4+/5 in the neck flexor and right upper extremity muscles, 4−/5 in the left upper extremity muscles, and 4−/5 in both lower extremities. He also had increased tone in all limbs, hyperreflexia, and a spastic gait. Sensory examination findings were normal. He also had a mild postural tremor, but there were no other clinical signs of cerebellar dysfunction. He had normal sac-
cadic eye movements. Electromyography showed diffuse denervation and the transcranial magnetic stimulation study showed prolonged central motor conduction time, consistent with a disorder affecting the cortical and spinal motor neurons. Brain magnetic resonance imaging revealed no cerebellar atrophy. Cervical, thoracic, and lumbar spine magnetic resonance imaging did not show cord compression. Thyroid and hepatic function, parathyroid hormone, Lyme titer, rapid plasma reagin, rheumatoid factor, and serum protein electrophoresis with immunofixation were normal. He was diagnosed as having ALS. He did not have SOD1 mutation or expanded hexanucleotide repeats in C9orf72 (2/9). He had 39/22 CAG repeat expansions on ATXN2. He required percutaneous endoscopic gastrostomy tube placement 18 months after the initial symptom, and he died 5 months later.

Discussion

Intermediate CAG repeat expansion in ATXN2 is associated with an increased risk for ALS.2-10 Full expansions of CAG repeats in ATXN2 (repeat range 34-39) have been reported in 10 patients with ALS.3-7 We describe 2 members in 1 family diagnosed as having ALS and SCA2, with full CAG repeat expansions in both individuals. To our knowledge, this is the first description of coexisting ALS and SCA2 in a single family. Patients with ALS who have CAG repeat expansions in ATXN2 have a younger age at onset and early spinal motor neuron involvement,2-4,7 similar to our reported case. Interestingly, our patient with SCA2 had fasciculations but no weakness or spasticity, whereas her paternal uncle with ALS had postural tremor without other signs of cerebellar dysfunction, indicating a wide range of phenotypic variability in CAG repeat expansions in ATXN2. The patient with SCA2 has both maternal and paternal family history of ALS, but she inherited the expanded ATXN2 allele from the paternal side of the family given the history of her paternal grandmother having ataxia and paternal uncle having ALS and full CAG repeat expansions in ATXN2. The fact that the maternal great aunt had ALS seems to be coincidental.

In pathologic studies, TAR DNA binding protein 43 (TDP-43) is abnormally localized in SCA2 and ATXN2 is abnormally localized in spinal cord neurons in ALS, suggesting a relationship between these two disorders.2,11 In animal and cellular models, ATXN2 is a modifier for TDP-43 toxicity.2,12 Furthermore, TDP-43 directly interacts with ATXN2,2 and intermediate expanded CAG repeats in ATXN2 can increase the pathologic form of TDP-43 by enhancing C-terminal cleavage and phosphorylated TDP-43.13

This article provides insights into the variability of neurologic presentation of CAG repeat expansions in ATXN2, which include Parkinson disease,10 SCA2, and ALS. Members in the same family carrying a mutation in ATXN2 can have different phenotypes. Genetic testing for CAG repeat expansions in ATXN2 should be considered when encountering a patient with ataxia and a family history of ALS.

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