Two in One

Report of a Patient With Spinocerebellar Ataxia Types 2 and 10

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Objective: To report a rare case of the coexistence of 2 spinocerebellar ataxia (SCA) mutations in a single patient.

Design: Case report.

Setting: University hospital, Movement Disorders Center.

Patient: A 54-year-old man of Mexican, American Indian, and French descent with an 11-year history of gait and limb ataxia.

Main Outcome Measures: Findings of clinical examination, magnetic resonance imaging, and video electroencephalographic monitoring.

Results: Neurologic history revealed a gradually progressive gait and limb ataxia along with muscle cramps and sensory symptoms in his distal extremities; examination revealed executive dysfunction, dysarthria, ataxia, and sensory neuropathy. Episodes of loss of awareness were reported, but electroencephalograms were negative. Brain imaging demonstrated severe cerebellar and brainstem atrophy. Genetic evaluation of the case revealed mutations in both the SCA2 and SCA10 genes.

Conclusion: Our patient has a unique combination of genetic mutations for 2 different SCAs, types 2 and 10, which to our knowledge, has not been previously reported. His clinical phenotype is largely consistent with SCA2, but his possible seizures and Mexican heritage suggest influences of SCA10.
ture and gait, 17 of 34; kinetic functions, 17 of 52; speech, 4 of 8; and oculomotor function, 1 of 6. At a more recent follow-up examination at age 54 years, his total International Cooperative Ataxia Rating Scale score had increased to 49 of 100, with the following subscores: posture and gait, 17 of 34; kinetic functions, 26 of 52; speech, 4 of 8; and oculomotor function, 2 of 6.

His history was significant for ataxia in multiple family members including his sister, mother, and maternal grandmother (Figure 1). His maternal ancestry was of Mexican, American Indian (Yaqui tribe), and French descent. His sister reported a 20-year history of slowly progressive gait and limb ataxia (onset age, 34 years), along with dysarthria and mild cognitive impairment. His mother developed gait and limb ataxia at about age 60 years and required a wheelchair after about 10 years of disease. Both affected family members reported muscle spasms, dysphagia, and urinary incontinence; neither has had documented seizures, although his sister has been treated with carbamazepine for episodes of bilateral leg stiffness. The patient’s paternal ancestry was also of Mexican and French descent; however, there is no known history of ataxia or neurologic disease in his father or paternal relatives. All of these relatives lived far from the patient and were unavailable for direct examination.

The patient’s brain magnetic resonance imaging demonstrated severe cerebellar (hemispheric and vermal) and brainstem atrophy (Figure 2). Routine and prolonged video electroencephalogram recordings were performed but did not capture seizure activity, though activation procedures were not performed. His genetic evaluation revealed expanded repeats for SCA2 (abnormal allele CAG repeats, 38 [normal CAG repeat range, 15-31]) and SCA10 (abnormal allele ATTCT repeats, 962 [normal ATTCT repeat range, 10-29]). His sister and mother are known to have SCA2 mutations but have not been available for additional gene testing for SCA10, despite our efforts.

Both SCA2 and SCA10 are dominantly inherited SCAs but result from different genetic mutations. The SCA2 mutation is due to an expanded CAG trinucleotide repeat in the gene coding for the cytoplasmic protein ataxin-2 on chromosome 12q24. Affected SCA2 individuals have 32 or more CAG repeats, with 37 to 39 repeats representing the most frequent pathologic expansion. Normal alleles range from 15 to 31 CAG repeats (most commonly 22 repeats) and may have CAA interruptions. Anticipation may occur, particularly with paternal transmission; those affected individuals generally have longer CAG repeat lengths and earlier symptom onset age. Mean age at onset is typically in the fourth decade. SCA2 has been reported in various ethnicities including Cuban, Indian, Italian, Mexican, South African, and Spanish. Besides ataxia, SCA2 features may include slowed saccades (which may progress to ophthalmoparesis), brisk deep tendon reflexes (which may progress to areflexia), peripheral neuropathy, dementia, myoclonus, dystonia, chorea, and levodopa-responsive parkinsonism. Milder phenotypes with less prominent ataxia, neuropathy, dystonia, and myoclonus but greater parkinsonian features have been associated with shorter CAG repeat expansions.

SCA10 maps to chromosome 22q13 and is caused by an unstable pentanucleotide repeat expansion ATTCT in intron 9 of the SCA10 gene, ataxin-10. Affected SCA10 individuals have 800 to 4500 ATTCT repeats; normal alleles range from 10 to 29 repeats. Penetration is usually complete, although reduced penetrance has been reported in individuals with 360 to 370 repeats.
Greater instability of repeat expansion occurs with paternal transmission; in SCA10, however, unstable repeat lengths may lead to either intergenerational expansion or contraction.\textsuperscript{17,18} Anticipation has been observed with contraction of ATTCCT repeats,\textsuperscript{17} thereby suggesting a more complex genotype-phenotype relationship between repeat length and onset age. Symptoms typically begin around ages 10 to 40 years. Besides ataxia, epilepsy (generalized or complex partial seizures), mild cognitive impairment, and abnormal eye movements (eg, ocular dysmetria, fragmented pursuit, and gaze-evoked nystagmus) may occur.\textsuperscript{15,16-20} SCA10 has been described predominantly in Mexican and Brazilian kindreds\textsuperscript{15,19,20} but also in Argentine and Venezuelan families.\textsuperscript{21,22} Common American Indian ancestry has been hypothesized to play a role in the origins of SCA10 in Mexican and South American families.\textsuperscript{23} Interestingly, our patient has both Mexican and American Indian heritage. The SCA10 phenotype, however, differs in Mexican and South American populations.\textsuperscript{15,19,21,22} Epilepsy is notable in Mexican kindreds, and some patients have hematologic or hepatic dysfunction. Brazilian patients, however, do not have seizures and lack prominent extracerebellar involvement (ie, neuropathy, cognitive dysfunction, or systemic disease); epilepsy was found in only 3.75\% of the Brazilian SCA10 cases, in contrast to up to 60\% of SCA10 patients from other geographic regions.\textsuperscript{24} Dystonia and parkinsonism were reported in the Argentinean family, and peripheral neuropathy has been noted primarily in Mexican patients.\textsuperscript{24}

Our patient has a combination of genetic mutations for 2 different SCAs, types 2 and 10, a combination that, to our knowledge, has not been previously reported. His phenotype includes features common to both SCAs, namely cerebellar ataxia, dysarthria, sensory polyneuropathy, and mild cognitive dysfunction, but also elements specifically associated with the 2 distinct SCA syndromes. His muscle spasms, cramps, and hyporeflexia are more typical for SCA2, whereas his Mexican heritage and possible seizures are more frequently associated with SCA10. While his repeat expansions for both SCAs fall within the pathological ranges, the expansions are mild, a feature that may explain some aspects of his presentation. Whereas prominent slow saccades, highly characteristic of SCA2, were not evident in our patient, prior studies demonstrate that saccadic velocity deficits correlate with repeat length.\textsuperscript{8,25} As such, his mildly slowed saccades may reflect the smaller SCA2 repeat expansions (ie, 38 alleles). Alternatively, his SCA10 mutation may have influenced the phenotypic expression of the saccadic deficits. Overall, our patient exhibits a unique clinical phenotype not explained by either SCA2 or SCA10 alone.

By using distinct clinical features (eg, cerebellar syndromes with or without parkinsonism, retinopathy, or dementia), the clinician may consider testing for specific SCAs, although in many cases, there is phenotypic overlap. In our case, we tested for both SCA types because of his overlapping clinical features and ancestral background. Our patient, along with the few other combined SCA case reports,\textsuperscript{14} demonstrates that patients who harbor shared SCA phenotypes could actually carry 2 different SCA mutations. With the growing availability of commercial genetic testing panels, it is important to raise the clinician’s awareness of this possibility and not to stop the evaluation with 1 positive test result in cases of atypical presentation.

This patient and his family also may provide unique opportunities to study the interactions of 2 genetic mutations and their effect on clinical expression of disease. Though the clinical and genetic effects of combined SCA mutations are unknown, it has been postulated that SCA8 may modify the effect of polyglutamine transcripts in SCA6 patients.\textsuperscript{1} Whether SCA10 similarly modifies SCA2, or vice versa, remains to be seen. Furthermore, finding 2 genetic mutations in a patient may have important implications regarding counseling on genetic risk, genetic testing, and disease prognosis.

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