The differential diagnosis of cerebellar ataxia is very broad, with both genetic and nongenetic causes. Non-genetic causes of ataxia include vascular disease, tumors and paraneoplastic syndrome, alcoholism, and vitamin E deficiencies. Genetic causes of ataxia include autosomal-dominant, autosomal-recessive, X-linked, or mitochondrial DNA mutations. Genetic testing for ataxia is expensive, and about half of the patients with a family history of ataxia still do not have identifiable mutations in genes that are known to be associated with ataxia. In addition, many new ataxia genetic mutations are not yet available for testing in commercial laboratories.

Growing evidence suggests an association between repeat expansion disorders and both cerebellar ataxia and motor neuron diseases. Pathological CAG repeat expansions of ataxin-1 (ATXN1) usually present as cerebellar ataxia, spino-cerebellar ataxia type 1 (SCA1); however, the large CAG repeat expansion of ATXN1 can present as amyotrophic lateral sclerosis (ALS)-like disorders. Full CAG repeat expansions (>34) in ATXN2 cause SCA2, whereas an intermediate CAG repeat expansion (between 27 and 33) in ATXN2 is a risk factor for ALS. Another repeat expansion, the GGGGCC hexanucleotide repeat in C9orf72, has been discovered as the major genetic cause of ALS and frontotemporal dementia (FTD), accounting for 23% to 46% of familial ALS, 7% to 24% of familial FTD, approximately 4% to 7% of sporadic ALS, and 3% to 6% of sporadic FTD. Interestingly, cerebellar ataxia has been reported in 2 cases with pathological hexanucleotide repeat expansions in C9orf72, both with a family history of ALS. One case had ataxia onset at the age of 20 years with hyperreflexia but no lower motor neuron sign. The other case was diagnosed as having olivopontocerebellar atrophy with the disease onset at age 53 years. However, few detailed clinical characteristics in these 2 cases were described. Here, we present a family with pathological hexanucleotide repeat expansions in C9orf72 with the diagnosis of ALS and ataxia, and we describe the detailed clinical history, neurological examination, video, and imaging studies. This case history highlights the importance of considering genetic testing for hexanucleotide repeat expansions in C9orf72 in ataxia patients with a family history of ALS or dementia.

Report of a Case

When first seen at our medical center, the patient was a 65-year-old woman with a 2-year history of progressive gait ataxia, frequent falling, poor handwriting, cognitive symptoms, urinary incontinence, Raynaud phenomenon in her toes, orthostatic hypotension, and constipation. She did not take any medications. On examination, her sitting blood pressure was 100/80 mm Hg and her standing blood pressure was 90/60 mm Hg. She scored 25 out of 30 on the Montreal Cognitive Assessment, losing 2 points in the visuospatial domain (copying...
the cube and drawing the clock), 1 for language (fluency), 1 for abstraction, and 1 for delayed recall. Her muscle strength was 5/5 throughout without fasciculations. Her reflexes were normal except for absent ankle jerks. Her facial expression was hypomorphic and she had 1+ bradykinesia in bilateral hand opening and closing and finger taps in the Unified Parkinson Disease Rating Scale. She did not have any rigidity, rest tremor, or spasticity. She had normal sensory examination findings. She had prominent scanning speech, dysmetria in bilateral finger-nose-finger test, finger chase, and heel-shin slides. She had impaired fast alternating movements. Her gait was wide based and unsteady. She was unable to perform tandem gait or stance, and she could not stand on 1 foot. Thirty-five months later, she fell frequently, even with a walker. She could only walk with maximal assistance. She also had short stride length and loss of heel strikes in addition to ataxia (Video). Her brain magnetic resonance imaging showed pontine and cerebellar atrophy with the hot cross bun sign in the T2-weighted images (Figure 1). Autonomic nervous system test results revealed mild neurogenic orthostatic hypotension. Urodynamic study confirmed the diagnosis of neurogenic bladder. Her initial nerve conduction study and electromyography findings showed normal motor and sensory nerve conduction and no evidence of fasciculation or denervation, and repeat electromyography 4 years after ataxia symptom onset showed similar findings. More extensive neuropsychological evaluation also performed 4 years after ataxia onset revealed impairment in semantic processing and socioemotional functioning, consistent with frontotemporal lobe dysfunction, but was too mild to meet the diagnostic criteria of FTD. Additionally, she displayed some emotional lability. She was diagnosed as having possible multiple system atrophy (MSA) based on clinical presentation of ataxia, parkinsonism, autonomic dysfunction, and fast progression.

Written informed consent was obtained from the patient. The patient's family history is shown in Figure 2. Her father developed muscle weakness at the age of 47 years and was diagnosed as having ALS. He died 2 years later. Her brother also developed muscle weakness and atrophy in his right leg at the age of 62 years. He developed difficulty in drinking and right arm weakness 2 months later, when he came to Columbia University for an evaluation. On examination, he had weak tongue strength and tongue atrophy with dysarthria. He had 5/5 arm strength, 3/5 strength in the right hip flexor, 5−/5 strength in the left hip flexor, 4/5 strength in the right hamstring and right tibialis anterior and evertor, and 4+/5 strength in the right extensor hallucis longus and invertor. His left leg had otherwise 5/5 strength. He had spasticity in all 4 extremities and fasciculations in the right arm and bilateral quadriceps. His reflexes were 3+ in the left biceps and 3+ in both knees. His plantar responses were flexor bilaterally and he had no jaw jerks. He had bilateral Hoffmann reflexes and a normal finger-nose-finger test finding. He had spastic gait and slight difficulty in tandem gait. His nerve conduction study findings showed essentially normal motor and sensory nerve conduction studies. Electromyography revealed diffuse fibrillation and fasciculation potentials in many muscles tested. He was diagnosed as having ALS. He did not have any sequence alteration in the familial ALS genes available at the first clinical visit including SOD1, TARDBP, ANG, or FUS assessed by Athena Diagnostics. The patient's condition progressed rapidly and subsequently was treated with tracheostomy and long-term ventilation.

Based on our previous report of the diverse presentations of ataxia and motor neuron disease in a family with full CAG.
repeat expansions of ATXN2 presenting with ataxia and motor neuron disease,11 we sent the blood samples to Athena Diagnostics and determined the CAG repeat expansions of ATXN2. The proband had a normal CAG repeat length 22/22 in the ATXN2 gene. Because the hexanucleotide repeat expansions in C9orf72 can also either present as ataxia or motor neuron disease,7,8 we tested this gene. Both the proband and her brother were found to have hexanucleotide repeat expansions of greater than 44/2 in C9orf72. We also performed Southern blot analysis at the Columbia University research laboratory to determine the size of hexanucleotide repeat expansions4 of C9orf72 and found that both the proband and her brother had repeats of more than 1000 with similar expansion size. In addition, we also excluded the CQ2 sequence variant V343A associated with MSA12 and the pathological repeat expansions13 of SCA36 in the proband.

Discussion

We present a patient and her sibling with cerebellar ataxia and ALS, respectively, with pathological hexanucleotide repeat expansions in C9orf72. C9orf72 hexanucleotide repeat expansion disease has very diverse clinical presentations, ALS and FTD being the most common.4-6 Parkinsonism and corticobasal syndrome can also occur in patients with C9orf72 repeat expansions.4-15 A study investigating the prevalence of C9orf72 hexanucleotide repeat expansions among patients with adult-onset sporadic ataxia found only 1 case out of 209 patients carrying this mutation. Interestingly, this patient also had a strong family history of ALS.8 Another reported case of ataxia with a C9orf72 repeat expansion had a clinical diagnosis of oливopontocerebellar atrophy, a variant of MSA, and the patient also had a family history of ALS.7 Our case adds to the literature of C9orf72 hexanucleotide repeat expansion in a family with both MSA and ALS.

Neuroimaging of patients with C9orf72 hexanucleotide repeat expansions shows brain atrophy in the various parts of the brain. Cerebellar atrophy is much more common in patients with FTD with the C9orf72 expansion than in patients with FTD with mutations in other FTD genes such as MAPT or GRN.16,17 Interestingly, ubiquitin/p62-positive, TDP-43-negative neuronal cytoplasmic inclusions in the granular and molecular layers of the cerebellum have been found to be characteristic of C9orf72 repeat expansion pathology.18 These studies suggested that the cerebellum is commonly involved in the C9orf72 repeat expansion disorders, although clinically cerebellar ataxia might not be apparent in most cases. Other factors, such as environmental factors or genetic backgrounds, could determine the degree of cerebellar involvement. Interestingly, we found that the proband and her brother had similar size of C9orf72 repeat expansions, which indicates that other genetic modifiers or environmental factors might partly account for the phenotypic variability.

Conclusions

C9orf72 hexanucleotide repeat expansion disease can have diverse clinical presentations including ALS, FTD, and cerebellar ataxia. The exact prevalence of C9orf72 hexanucleotide repeat expansions in patients with ataxia with a family history of ALS has not been investigated but clinicians might consider such genetic tests in this specific population.

ARTICLE INFORMATION

Accepted for Publication: November 6, 2013.

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Author Contributions: Ms Goldman and Dr Kuo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kuo. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Kuo. Critical revision of the manuscript for important intellectual content: Goldman, Quinzii, Dunning-Broadbent, Waters, Mitsumoto, Brannagan, Cosentino, Huey, Nagy. Administrative, technical, or material support: Goldman, Quinzii, Dunning-Broadbent, Waters. Study supervision: Cosentino, Huey, Kuo.

Conflict of Interest Disclosures: None reported.

Funding/Support: Ms Goldman received funding from the National Institute on Aging (NIA)/National Institutes of Health (NIH) (grant R01AG087022); principal investigator: Michael Shalemski, MD, PhD), the National Institute of Neurological Disorders and Stroke (NINDS)/NIH (grant RO1NS076837-01A1; principal investigator: Edward D. Huey, MD), and the Parkinson’s Disease Foundation. Dr Mitsumoto received funding from the NIH (grant R01-ES016348), the Spastic Paraplegia Foundation, and the Muscular Dystrophy Association. Dr Cosentino is funded by the NINDS/NIH (grant R01NS075743) and National Multiple Sclerosis Society (grant P30NS083653). Dr Huey is funded by the NINDS/NIH (grants R01NS087380 and R01NS087366), the Florence and Herbert Irving Clinical Research Career Award, and the NIA/NIH (grants P01AG087020, R01AG041795, and R0103873402). Drs Dunning-Broadbent and Nagy are funded by the NINDS/NIH (grant 5R00NS064253-3). Dr Kuo received funding from the NIH (grant K08 NS083738), the Louis V. Gerstner Jr Scholar Award, the Parkinson’s Disease Foundation, the American Academy of Neurology Research Fellowship, and the American Parkinson’s Disease Association.

Role of the Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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