Slowly Progressive Ataxia, Neuropathy, and Oculomotor Dysfunction

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A 54-year-old white man presented with slowly progressive incoordination and weakness. He had normal motor development until, at 16 years of age, he noted difficulty walking and difficulty reading despite normal visual acuity. By the fourth decade of life, he developed poor coordination and balance, as well as inability to walk. In subsequent years, he developed progressive, painless sensory loss, weakness, and atrophy in his distal arms and legs. His vision problems progressed and he also developed dysarthria without dysphagia. Family history was negative except for an uncle who was described as “clumsy.” Results of an oculomotor examination were notable for increased square-wave jerks, persistent bilateral gaze-evoked nystagmus with saccadic pursuit, intact vestibulo-ocular reflex, and saccadic dysmetria. He had a mixed dysarthria with flaccid and ataxic characteristics and severe weakness and atrophy in the distal limb muscles. Sensation was diminished to the midforearms and midthighs in all modalities. Deep tendon reflexes were absent throughout, with no response to plantar stimulation. He had marked appendicular ataxia with mild axial ataxia. Magnetic resonance imaging of the brain revealed severe cerebellar atrophy. Results of an electrodiagnostic study suggested a severe axonal sensorimotor polyneuropathy with active and chronic denervation. The differential diagnosis in a patient with ataxia, neuropathy, and oculomotor features is discussed; a methodical approach to the diagnostic workup is suggested; and the final diagnosis is revealed.

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We herein describe a patient with slowly progressive ataxia, neuropathy, and oculomotor dysfunction. We discuss the differential diagnosis, suggest a methodical approach to the diagnostic workup, and reveal the final diagnosis.

REPORT OF A CASE

A 54-year-old white man with no other significant medical history presented to our clinic for evaluation of slowly progressive incoordination and weakness. In childhood, he had normal motor development, although he described himself as “clumsy.” At 16 years of age, he first noted difficulty walking and, despite normal visual acuity, reading. His coordination deteriorated slowly during the next decade, and he began using a cane. At 28 years of age, he accidentally ingested ethylene glycol, and on recovery, his balance was worse and he could no longer ambulate. During the following years, he developed progressive, painless sensory loss, weakness, and atrophy in his distal arms and legs. His vision problems progressed to include diplopia on primary and eccentric gaze, and he developed dysarthria without dysphagia. He had no bowel or bladder dysfunction. For 3 years before this evaluation, his symptoms were stable. He used a manual wheelchair and was independent with activities of daily living. Family history was negative for similar conditions except for

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an uncle who was described as “clumsy” but who carried no specific neurological diagnosis.

Results of general medical and mental status examinations were normal. The ocular examination demonstrated normal pupils and normal funduscopic findings. Visual acuity was normal in each eye, but he reported blurring with binocular vision. The oculomotor examination was notable for increased square-wave jerks, persistent bilateral gaze-evoked nystagmus with saccadic pursuits, intact vestibulo-ocular reflex, and saccadic dysmetria. He had a mixed dysarthria with flaccid and ataxic characteristics. Muscle tone was normal with symmetric, severe distal atrophy in the hands and distal lower extremities. Motor strength (rated using the Medical Research Council Scale) was 5 of 5 proximally in the arms and legs, 4 of 5 in wrist extensors and flexors, 2 of 5 in finger extensors and intrinsic hand muscles, and 0 of 5 in the ankles and toes. Sensation was diminished to the midforearms and midthighs to all modalities. Vibratory sensation was absent at the toes and ankles and decreased to 2 seconds at the knees and 5 seconds at the fingers. Deep tendon reflexes were absent throughout, with no response to plantar stimulation. He had marked appendicular ataxia, with only mild axial ataxia. He could stand with assistance but could not walk. (See the video for highlights of the neurological examination and speech at http://www.archneurol.com.)

LABORATORY AND IMAGING STUDIES

Initial laboratory studies revealed levels of vitamin B12, methylmalonic acid, vitamin E, zinc, copper, and erythrocyte sedimentation rate within the reference range. Hepatitis serology findings were negative and serum protein electrophoresis demonstrated no abnormal protein production. Magnetic resonance imaging of the brain revealed severe cerebellar atrophy or hypoplasia (no prior study was available for comparison). An electrocardiogram showed an incomplete right bundle branch block with left axis deviation. An echocardiogram showed normal cardiac structure and function.

ELECTRODIAGNOSTIC STUDIES

Median and ulnar motor responses revealed severely diminished amplitudes with prolonged distal latencies and moderately slowed conduction velocity. Motor responses in the lower limbs were absent, as were sensory responses in the upper and lower limbs. Needle electromyography revealed changes consistent with mild active denervation and chronic reinnervation. This study indicated severe axonal sensorimotor polyneuropathy with active and chronic denervation.

CLINICAL DISCUSSION

The patient presented with slowly progressive neurological symptoms since adolescence, including ataxia, weakness, sensory loss, and oculomotor difficulties. Neuropathological localization should precede the discussion of the differential diagnosis. First, it is unlikely that cortical or subcortical regions are affected, because no upper motor neuron findings were revealed on examination and cognition was normal. Cerebellar dysfunction is a strong consideration to explain dysarthria, ataxia, and nystagmus, but distal weakness and sensory loss suggest additional or alternative localization. Posterior column involvement of the spinal cord may also be considered as a cause of ataxia and large-fiber sensory loss, but the degree of weakness and distal muscle atrophy is not compatible with such involvement. Anterior horn cell involvement is less likely given the extensive sensory loss. Length-dependent peripheral nerve dysfunction would explain weakness that is worse distally, length-dependent sensory loss, and absent reflexes. Speech and eye movement abnormalities, however, are unlikely to be secondary to isolated peripheral neuropathy. Overall, the clinical findings do not easily localize to 1 area within the nervous system. The best explanation is a pathological process that involves the cerebellum with additional involvement of the oculomotor system and peripheral nerves. The temporal relationship of the symptoms suggests a unifying cause rather than multiple independent processes. The chronic and progressive nature of this patient’s disease is supported by neuroimaging findings of severe cerebellar atrophy and severe axonal polyneuropathy with acute and chronic denervation on electrodiagnostic findings. The lack of associated family history makes autosomal dominant diseases unlikely and suggests an autosomal recessive disorder or a metabolic disorder. The gradual onset and chronic, slowly progressive nature of these symptoms make inflammatory, toxic, or vascular causes less likely.

In an effort to narrow the list of potential causes, one can consider each of the cardinal symptoms of ataxia, neuropathy, and oculomotor deficit. Focusing on disorders fitting the time course and potential mode of inheritance, one might determine if and where the differential diagnoses of each symptom overlap for a narrowed differential diagnosis (Figure 2).

An important consideration in any case of sporadic or recessive ataxia is Friedreich ataxia (FA). This autosomal recessive GAA trinucleotide-repeat disorder within the FRDA gene encodes the protein frataxin. The incidence of FA is 1 in 30,000 to 50,000, making it the most common form of hereditary ataxia. Typical presentation of FA is at younger than 25 years and involves progressive ataxia, absent knee and ankle reflexes, extensor plantar responses, dysarthria, and sensory loss to vibration and proprioception, especially in the lower extremities. Oculomotor abnormalities are common in FA. In a large FA cohort, macro square-wave jerks were present in about two-thirds of patients. Gaze-evoked nystagmus, impaired smooth pursuit, and saccadic dysmetria were also common. Hypertrophic cardiomyopathy and cardiac conduction abnormalities develop in most of these patients, in addition to scoliosis, pes cavus, optic atrophy, deafness, and diabetes mellitus. Typically, imaging does not show cerebellar atrophy, except in rare cases of late-onset FA. Cervical spinal cord atrophy, however, is a common feature. Friedreich ataxia is a progressive disease, and the most common cause of death is cardiomyopathy at an average age of 37.5 (range, 21-69)
years. Given our patient’s time course and symptom complex, FA is a strong consideration in this case, although cerebellar atrophy and normal cardiac function do not favor this diagnosis.

Ataxia telangiectasia (AT) is another important consideration and the second most common autosomal recessive ataxia. This syndrome, which is related to a mutation of the ATM gene that is involved in DNA repair, typically presents with early-onset ataxia by 2 to 3 years of age and is severe and progressive. Late-onset symptoms have been described in a minority of cases. Ocular motor apraxia and dysarthria are common in AT, followed later by choreoathetosis and oculocutaneous telangiectasias. Serum α-fetoprotein (AFP) levels are elevated, and magnetic resonance imaging demonstrates cerebellar atrophy. In addition, most patients have immunodeficiencies, with low levels of serum IgA, IgE, and IgG2, and impaired responses to pneumococcal polysaccharides. Often a reciprocal translocation between chromosomes 7 and 14 occurs in lymphocytes, with in vitro radiosensitivity and increased risk of lymphoid tumors owing to poor DNA mutation repair. A separate disor-

Figure 1. Magnetic resonance imaging of the brain demonstrating severe cerebellar hypoplasia or atrophy. A, T2-weighted axial images; B, T1-weighted sagittal images.
coenzyme Q10 (CoQ10) deficiency. Ataxia with vitamin E deficiency (AVED), abetalipoproteinemia, and treatable syndromes. Three such disorders are ataxia with vitamin E deficiency frequently causes head titubation and retinitis pigmentosa but no oculomotor dysfunction. Abetalipoproteinemia is also treated with α-tocopherol supplementation based on serum vitamin E levels. Coenzyme Q₁₀ deficiency is caused by a variety of mutations in CoQ₁₀ biosynthesis pathways, including mutations in CABC1/ADCK3, and causes heterogeneous ataxia syndromes. Common presentations include adolescent-onset ataxia with frequent epilepsy, tremor, muscle complaints, and migraine. Neuropathy and oculomotor dysfunction are less frequently described in CoQ10 deficiency. Supplementation of CoQ₁₀ may provide transient clinical improvement. These treatable causes of ataxia syndromes are unlikely in our patient with a vitamin E level within the reference range, normal findings of the retinal examination, and no epilepsy, tremor, muscle complaints, or gastrointestinal tract dysfunction. Further, cerebellar atrophy and severe neuropathy would not be encountered in these diseases.

Tay-Sachs disease is a GM₂ gangliosidosis related to a deficiency of β-hexosaminidase A, which typically causes severe neurological devastation in infancy. In patients with late-onset Tay-Sachs disease, related to more favorable genetics, symptoms may begin in adolescence or adulthood and may more closely resemble FA. Typically, patients develop cerebellar dysfunction with severe cerebellar atrophy, areflexia, neuropathy, and proximal muscle weakness with subsequent muscle atrophy. Late-onset Tay-Sachs disease also frequently includes spasticity, seizures, and dementia. Case reports of oculomotor disturbances have been published, although this manifestation is not common. Our patient is less likely to have this disorder owing to his normal cognitive function and no clear evidence of seizures or spasticity.

**Figure 2.** Venn diagram demonstrating the systematic process by which the differential diagnosis was constructed. The 3 cardinal symptoms of cerebellar dysfunction, oculomotor dysfunction, and neuropathy were listed, and differential diagnoses for each symptom were narrowed by time course and heredity. Those diagnoses correlating with multiple symptoms were explored further. DRPLA indicates dentatorubral-pallidoluysian atrophy; POLG, polymerase-γ gene; and SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.
Mutations in the mitochondrial DNA polymerase γ (POLG) gene cause disruptions in mitochondrial DNA replication. Individuals with mutations in POLG may show various clinical phenotypes, often including ataxia, neuropathy, and progressive external ophthalmoplegia. Within this group of disorders, a syndrome of sensory ataxic neuropathy, dystrophy, and ophthalmoplegia causes an ataxic syndrome related to neuropathy without out cerebellar dysfunction. A mitochondrial disorder with a POLG mutation should be considered, but the lack of seizures, headaches, and cognitive impairment argues against this diagnosis.

Several additional neurodegenerative disorders are similar to AT and are associated with impaired repair mechanisms of damaged DNA. Whereas AT causes systemic and neurological symptoms, including cerebellar ataxia, ataxia with oculomotor apraxia types 1 (AOA1) and 2 (AOA2) and spinocerebellar ataxia with axonal neuropathy 1 reside within this category. Ataxia with oculomotor apraxia type 1 is caused by mutation of the APTX gene encoding the aprataxin protein and is associated with impaired DNA repair of single-strand breaks. The mean (SD) age of onset of AOA1 is 6.8 (4.8) years (range, 2-18 years), and nearly all patients have cerebellar ataxia with cerebellar atrophy and severe axonal sensorimotor neuropathy. Oculomotor apraxia is present in most patients (86%), as is chorea (79%), which tends to remit as the disease progresses. On laboratory investigation, AOA1 is associated with hyperalimentemia and hypercholesterolemia in most patients. But AFP levels are within the reference range. On the other hand, AOA2 results from mutation of the SETX gene encoding the senataxin protein, which is also believed to be involved in DNA repair and/or RNA metabolism. The mean (SD) age of onset of AOA2 is 14 (3) years (range, 8-19 years), and most patients present with severe ataxia of gait with milder limb and trunk ataxia. Ninety percent of patients have motor and sensory neuropathy with distal weakness and areflexia. Cerebellar dysarthria is present in most patients. Oculomotor difficulties vary, with oculomotor apraxia in 32%, convergent strabismus in 37%, and nystagmus in 42%. Magnetic resonance imaging demonstrates cerebellar atrophy, and laboratory investigation nearly always reveals elevated AFP levels. Spinocerebellar ataxia with axonal neuropathy 1, caused by mutation of the TDP1 gene encoding tyrosyl-DNA phosphodiesterase 1, is also associated with impaired repair of single-strand DNA breaks. This disorder begins with ataxia in adolescence, which is slowly progressive and followed by areflexia and peripheral neuropathy. Nystagmus is described with spinocerebellar ataxia with axonal neuropathy 1, but no other oculomotor dysfunction is reported. Although the overall presentations are similar among these 3 disorders, our patient’s findings fit best with AOA2 based on the age of onset, the description of oculomotor dysfunction, and the lack of chorea. Measurement of serum AFP levels would be useful.

A few other rare disorders should also be considered for the sake of completeness. First, autosomal recessive spastic ataxia of Charlevoix-Saguenay, caused by a mutation in the SACS gene encoding the sacsin protein, should be mentioned. This disorder presents with spastic paraparesis in infancy, followed by ataxia, dystrophy, saccadic pursuit, and nystagmus in adolescence and later a demyelinating polyneuropathy with absent ankle jerks. Cerebellar atrophy has been described with autosomal recessive spastic ataxia of Charlevoix-Saguenay. Next, mitochondrial respiratory chain defects, such as cytochrome-c oxidase deficiency, are a heterogeneous group of disorders that may also cause ataxia syndromes. Commonly, cytochrome-c oxidase deficiency presents with ataxia, dystrophy, myopathy, external ophthalmoplegia, and movement disorders. Finally, a rare subset of patients presenting with a clinical phenotype suggestive of Charcot-Marie-Tooth disease 2 with foot deformity, distal areflexia, areflexia, and sensory loss have been described to subsequently develop cerebellar ataxia with cerebellar atrophy, dystrophy, nystagmus, and spastic paraplegia. Our patient is not likely to have these disorders due to his age of onset, the progression of his symptoms, and the lack of spasticity or movement disorder.

In their review of autosomal recessive ataxia syndromes, Fogel and Perlman propose a diagnostic algorithm that begins with screening for FA. After this test, phenotypic presentation and serological testing may further direct genetic testing for specific diagnoses.

**LABORATORY TESTING**

Genetic testing performed for FA demonstrated 6 CAG repeats (normal, 7-34) within the FRDA gene, which was not suggestive of FA. The AFP level was elevated at 39.3 (reference range, 0-8) ng/mL, and the serum albumin level was decreased at 3.21 (reference range, 3.9-5.1) g/dL (to convert to grams per liter, multiply by 10). Genetic testing for AOA2 demonstrated 2 frameshift mutations in the SETX gene (3496delG and 7121_7122delTG) confirming the diagnosis of AOA2.
This case provides a unique learning opportunity, because it requires recognition of a disease affecting multiple neurological systems and should trigger an investigation for a single, unifying cause. Slowly progressive ataxia and neuropathy, with no significant family history, leads one to consider autosomal recessive ataxias as potential causes. Because this group of diseases is heterogeneous and it is not practical or cost-efficient to perform genetic testing for all autosomal recessive ataxias, a diagnostic approach based on the prevalence and potential severity of disease should be considered. Because FA is the most common cause, and because it is associated with cardiomyopathy, this diagnosis should be considered in all such patients. If results of genetic testing for FA are negative, one should consider other diagnoses. Serum albumin, AFP, vitamin E, and cholesterol levels are useful in narrowing the list of possible diagnoses. In our patient, an elevated AFP level suggested AT or AOA2. Because he did not have the typical associated symptoms of AT, we favored the diagnosis of AOA2. This case emphasizes the importance of a methodical approach to complex syndromic diagnoses.

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REFERENCES


