Resident's Clinic

26-Year-Old Man With Hyperpigmentation of Skin and Lower Extremity Spasticity

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A 26-year-old man came to our neurology clinic because of progressive difficulty with ambulation. Two months before this examination, he had first noted stiffness in his legs and difficulty with walking as well as mild fatigue and nausea. During the ensuing weeks, his ability to ambulate gradually deteriorated; 2 weeks before the current assessment, he could not run. In addition, during this period, he became more nauseated and began vomiting. He also noticed decreased sensation in his lower extremities, a 4.5-kg weight loss, and darkening of his skin. He had no complaints of headache, visual or auditory troubles, bowel or bladder incontinence, incoordination or weakness of his hands, or neck trauma or pain. He had been examined by his local physician 1 week before coming to Mayo Clinic Scottsdale, at which time laboratory studies revealed a serum sodium level of 122 mEq/L and a potassium level of 5.1 mEq/L. On our initial examination, he was wheelchair-bound and nauseated, and he appeared extremely ill. He was unable to stand for more than 10 to 15 seconds because of severe light-headedness.

The past medical history of the patient was notable for developmental delay. His mother described him as not being as coordinated as others his age while growing up. Except for a brief time in special education in elementary school, he progressed through mainstream high school, graduated, and attended community college. He had undergone surgical reconstruction for micrognathia at the age of 20 years.

The patient had recently stopped working in the food service area because of his illness. He did not smoke and had no history of illicit drug use or risk factors for human immunodeficiency virus (HIV). He rarely used alcohol. He has a maternal grandmother with amyotrophic lateral sclerosis and a maternal uncle with Parkinson's disease. He had no allergies and took no medications.

On physical examination, the patient’s blood pressure was 74/40 mm Hg, pulse was 100 beats/min, and respiratory rate was 16 breaths/min. His skin was slightly hyperpigmented, particularly over the elbows, knees, and knuckles. He had thin facies, micrognathia, and a receding hairline. He had no carotid bruits. Cardiopulmonary findings were normal. Bowel sounds were normal; he had no tenderness, masses, or hepatic or splenic enlargement. No testicular atrophy, lymphadenopathy, cyanosis, clubbing, or edema was noted. The neurologic examination disclosed that the patient was alert and oriented. His cranial nerves were intact. He had symmetric weakness graded as −1 (on a 0 to −4 scale) in all distal muscle groups. In his lower extremities, symmetric hyperreflexia, increased muscle tone, and bilateral Babinski signs were noted. Alternating motion rates were slightly decreased throughout. Sensory testing disclosed diminished ability to perceive pinprick and vibration in the lower part of the legs and absent proprioception in the toes. Results of Romberg testing were profoundly abnormal. His gait was spastic, with stiff, scissoring steps; consequently, he was unable to perform tandem walking.

Initial laboratory testing revealed a normal complete blood cell count, an erythrocyte sedimentation rate of 18 mm in 1 hour, and a chemistry panel as follows: sodium 115 mEq/L, potassium 6.1 mEq/L, chloride 82 mEq/L, carbon dioxide 22 mEq/L, creatinine 1.6 mg/dL, blood urea nitrogen 35 mg/dL, glucose 101 mg/dL, and calcium 9.4 mg/dL. Further testing showed normal values for thyrotropin, vitamin B₁₂, and folate. HIV testing was negative; no test was done for human T-cell lymphotropic virus type I. Because of hyponatremia, hyperkalemia, hypotension, and hyperpigmentation, the possibility of adrenal insufficiency was considered. The corticotropin level was 240 pg/mL (normal, 0 to 60). A baseline cortisol level (while the patient was acutely ill) was 17 µg/dL and did not increase after corticotropin stimulation. Antirenal antibodies were negative; abdominal computed tomography showed no adrenal masses.

Magnetic resonance imaging (MRI) of the brain and spinal cord of the patient showed normal findings. Cerebrospinal fluid (CSF) analysis disclosed the following: glucose 58 mg/dL, protein 21 mg/dL, erythrocytes 1/µL, leukocytes 1/µL, and negative results of cultures for bacteria and acid-fast bacilli, India ink staining, the Venereal Disease Research Laboratory test, and cryptococcal antigen. The IgG synthesis rate and CSF index were normal, and both oligoclonal banding and myelin basic protein were absent.
1. Which one of the following entities is most likely responsible for this patient’s neurologic symptoms?
   a. Multiple sclerosis
   b. Central pontine myelinolysis (CPM)
   c. Hereditary spastic paraplegia
   d. Adrenoleukodystrophy (ALD)
   e. Adrenomyeloneuropathy (AMN)

   Multiple sclerosis is a demyelinating disorder that typically manifests between 20 and 50 years of age (female: male ratio, 2:1). Initial symptoms are paresthesias, motor weakness, spasticity, visual disturbances (optic neuritis, diplopia, or nystagmus), bladder dysfunction, or fatigue. The diagnosis necessitates a history of remission and relapse of neurologic symptoms and evidence on examination of more than one discrete lesion in the central nervous system (CNS). MRI commonly shows areas of increased T2 signal in the periventricular white matter, brain stem, spinal cord, or optic nerves. CSF studies may reveal mononuclear pleocytosis (less than 50 cells/μL) during an acute exacerbation. In about 40%, the CSF protein is increased as well, usually to no more than 100 mg/dL. In 90%, either the IgG synthesis rate or oligoclonal banding is abnormal. Lastly, myelin basic protein may be abnormal (because of breakdown of CNS myelin) during an acute exacerbation of multiple sclerosis. CPM can be caused by several illnesses that lead to destruction of myelin sheaths in the midline pons. It manifests as flaccid paralysis or pseudobulbar palsy, and it can progress to a “locked-in” state. Most often, it is associated with rapid correction of severe hyponatremia, but it is also seen in patients with alcoholism (and chronic malnutrition), chronic renal failure, hepatic failure, lymphoma, and bacterial infections. Because of the risk of CPM in reversal of severe hyponatremia, the serum sodium should be increased by no more than 12 mEq/L per day. Hereditary spastic paraplegia, typically an autosomal dominant disorder, is characterized by onset of spasticity and mild weakness in the lower extremities during the second to fourth decade of life. Some degree of distal loss of vibratory sense and proprioception may be noted. Typically, MRI of the brain and spinal cord shows normal findings. Without a known family history of this disease (although one may speculate about the patient’s grandmother), and especially in this clinical context, it is an unlikely diagnosis. X-linked ALD is a disorder of fatty acid metabolism that leads to accumulation of very-long-chain fatty acids (VLCFA) in the adrenal gland, testes, brain, and spinal cord. Of the several variants of this disorder, the most frequent is the childhood cerebral form, commonly called “adrenoleukodystrophy.” Typical manifestations are personality changes, attention deficit, and visual or auditory impairment, which occur about age 7 years. The second most common type is AMN, which is the “spinal cord” form of X-linked ALD. It usually first appears as spastic gait, sensory impairment in the legs, and bladder dysfunction in men in their mid-20s. Because the adrenal gland is often affected in either type of X-linked ALD, AMN is a possible diagnosis in our patient.

2. Which one of the following tests is most likely to confirm the diagnosis?
   a. Arylsulfatase A level
   b. Electromyography (EMG)
   c. DNA analysis for X-linked adrenoleukodystrophy
   d. Serum very-long-chain fatty acid level
   e. Fibroblast very-long-chain fatty acid level

   Arylsulfatase A is deficient in metachromatic leukodystrophy, a disease that leads to accumulation of sulfatides within tissues. When it occurs in adults, it manifests as spastic weakness, dementia, blindness, and deafness; these patients seldom have associated adrenal insufficiency. Although EMG will help clarify the nature and extent of nerve or muscle damage (or both), it is unlikely to confirm the diagnosis of AMN. In X-linked ALD, a genetic mutation on the X chromosome leads to a deficiency in a peroxisomal enzyme that normally oxidizes VLCFA into their coenzyme A (CoA) esters. Increased levels of VLCFA are thought to lead to abnormal accumulation in tissues and hence to manifestation of the various phenotypes. Although 20% of the mutations within the ALD gene occur at one site, the rest are spread throughout the gene. Thus, no standard DNA test can detect X-linked ALD. The diagnosis of X-linked ALD is based on serum VLCFA, especially in men. In assessment of women who are potential carriers, the false-negative rate is 15%, and testing of cultured fibroblasts for VLCFA is more sensitive. In our patient, an EMG showed a peripheral neuropathy with features of both axonal degeneration and demyelination. On examination of serum levels of VLCFA, both C25:0 (0.040; normal, less than 0.034) and C26:0 (0.027; normal, less than 0.011) were above normal; in conjunction with the clinical manifestations, these findings confirmed the diagnosis of X-linked ALD—specifically, AMN.

3. Which one of the following statements is not true about the neurologic disease in our patient?
   a. The patient’s mother has a 50% chance that neurologic symptoms will develop
   b. Adrenomyeloneuropathy will develop among 50% of his male siblings
   c. The rate of progression of the disease during the first 3 years is 35%
   d. Cerebral manifestations will eventually occur in about 50% of patients with this disease
   e. The presence and severity of adrenal insufficiency do not correlate with the severity of neurologic disease
X-linked ALD is a clinically heterogeneous disorder. AMN occurs in 28 to 40% of those with the genetic defect for X-linked ALD. The cerebral variant of X-linked ALD occurs in 35 to 50%. Those cases that manifest only as idiopathic Addison's disease constitute 8%, and another group of patients (10%) is completely asymptomatic at diagnosis, many of whom will have some form of the disease later in life. Lastly, up to 50% of female heterozygotes may have symptoms that resemble those of AMN; however, they tend to manifest up to 10 years later, and the spasticity and sensory deficits in the lower extremities may be milder. Although the patient's male siblings have a 50% risk of receiving the ALD gene from their mother, this risk is distributed over the various phenotypes because X-linked ALD is a clinically heterogeneous disorder. Thus, the risk of development of AMN in his male siblings is less than 50%. Approximately 35% of patients with AMN will have substantial neurologic progression during a 3-year period, and cerebral involvement may develop in up to half at some point. Typically, a patient's neurologic status deteriorates slowly over decades. Neither the fact that a patient has adrenal insufficiency nor its severity has any bearing on the severity of the neurologic disease.

Our patient's two younger sisters, his parents, and a 10-year-old nephew were asymptomatic. Screening of other young male relatives is under way. Persons can be identified who may benefit from therapy (see question 5 and Discussion), and female carriers can be offered genetic counseling and data on the disease and its potential complications. Because our patient had normal findings on MRI of the brain and no decline in mental functioning or behavior, apparently he has no cerebral involvement by AMN thus far.

4. Which one of the following statements is not true with respect to our patient's X-linked neurologic disease?

a. It is caused by a deficiency of lignoceroyl-coenzyme A ligase
b. A putative gene has been identified
c. The putative gene codes for lignoceroyl-coenzyme A ligase
d. A single mutation can lead to several different phenotypes
e. Cytokines have a role in the pathogenesis of the cerebral form of the disease

The biochemical defect in X-linked ALD is the degradation of VLCFA within the peroxisome. The enzyme that normally catalyzes this reaction is lignoceroyl-CoA ligase. The search for the genetic defect led to the discovery of the ALD gene that codes for a peroxisomal membrane protein, not lignoceroyl-CoA ligase. Introduction of the ALD gene by means of complementary DNA into fibroblasts from patients with ALD lacking both the gene product and the ability to degrade VLCFA leads to not only the appearance of the ALD protein but also the ability to degrade VLCFA. The link between the genetic defect and the deficiency in the enzymatic mechanism is not clearly understood, but the gene product is thought to operate in the transport or function of the enzyme. As noted earlier, the genetic mutations occur throughout the gene. No correlation seems to exist between the type of mutation, or genotype, and the clinical phenotype. Specifically, in one family, one mutation was found in six siblings, who expressed five separate types of X-linked ALD.

In the cerebral variant of X-linked ALD, the pathologic findings in the CNS consist of lymphocytic inflammatory demyelination and prominence of macrophages and reactive astrocytes. The accumulation of VLCFA within the membranes of the myelin is thought to cause the myelin to become unstable and deteriorate—so-called myelinolysis. In patients with the cerebral form of the disease, macrophages and astrocytes react to this myelinolysis by producing tumor necrosis factor-α and interleukin 1, which disrupt the blood-brain barrier and lead to the lymphocytic inflammation seen pathologically. The question arises, Why do only some patients have this inflammatory cerebral disease when all have the same biochemical defect? At this time, the most likely explanation is the interplay of an autosomal modifier gene that modulates the cytokine- and immune-mediated reaction to the myelinolysis in the CNS.

Our patient's family is interesting in that his mother had only two sisters, neither of whom had children. His maternal grandmother, who also had only two sisters, was the only other family member with neurologic disease (amyotrophic lateral sclerosis). Whether this may, in fact, have been a misdiagnosed case of X-linked ALD is unknown.

5. Which one of the following treatments is most likely to benefit our patient?

a. Diet low in very-long-chain fatty acids
b. Lorenzo's oil
c. Bone marrow transplantation
d. Interferon-β
e. Treatment of adrenal failure

Much has been written and even portrayed in Hollywood about treatments for X-linked ALD. Interest was first focused on alteration of the diet. Radiolabeled C26 from a patient's diet was found to accumulate within the demyelinating lesions in the brain. A diet low in C26, however, failed to alter the rate of progression of the cerebral variant of X-linked ALD. Certain monounsaturated fatty acids in excess compete for the microsomal elongation system that builds VLCFA and thus decrease their production. Two of these monounsaturated fatty acids, glyceryl trioleate (GTO) and the more potent glyceryl trierucate (GTE), combined in a GTE:GTO ratio of 4:1 is called Lorenzo's oil. Its cost is $180 to $200 per month; in addition, one must maintain a...
diet low in saturated long-chain fatty acids while taking Lorenzo’s oil. Although treatment with Lorenzo’s oil can normalize plasma VLCFA in 4 weeks, the GTE component does not seem to enter the CNS in substantial amounts. This limitation may be the reason for the overall disappointing response to this therapy. Studies of the use of Lorenzo’s oil in patients with AMN have failed to demonstrate appreciable benefit. Of 14 patients with AMN who were treated for a mean of 33 months, none improved clinically and 9 actually deteriorated. Bone marrow transplantation is considered in children with the cerebral form of the disease. The rationale is that by providing new microglial cells within the CNS that contain the functional capacity to degrade VLCFA, the disease can be reversed. The first such transplantation in 1990 yielded complete reversal of neurologic signs and symptoms and radiographic lesions by 18 months. Most of these patients now have both clinical stabilization or improvement and increased survival. The indications for bone marrow transplantation include the following: neuropsychologic deterioration, but not below normal; dietary normalization of VLCFA before and during transplantation; absence of severe neurologic deficits; and the ability to minimize the risk of graft-versus-host disease by special filtration techniques (elutriation). Other new experimental treatments are interferon-β and thalidomide, which are currently being studied in those patients who are not candidates for bone marrow transplantation. The theory for use of interferon-β is based on the pathologic similarities between X-linked ALD and multiple sclerosis. Thalidomide is a down-regulator of tumor necrosis factor-α and thought possibly to exert some benefit in this disease. Because our patient is symptomatic with AMN, no available data support treating him with either Lorenzo’s oil or bone marrow transplantation. Of the listed therapeutic alternatives, our patient is most likely to benefit from optimal treatment of adrenal failure.

Because of life-threatening adrenal failure, our patient was admitted to the hospital. His electrolyte abnormalities were corrected during a 3-day period. He was given appropriate steroid replacement and dismissed from the hospital after 6 days. His neurologic status improved to the point of being able to walk without much difficulty at dismissal. Two months later, he continued to function well neurologically, with only running being affected.

**DISCUSSION**

In our patient with AMN, no neurologic treatment is thought to be beneficial at this time, but a search for family members who are carriers of the biochemical defect of X-linked ALD is warranted. Moser showed that treatment with Lorenzo’s oil in asymptomatic children with the biochemical defect of X-linked ALD is beneficial in prolonging disease-free survival. In that study of 53 children with a mean age of 7.48 years who underwent follow-up for a mean of 38.8 months, serum C26 levels were normalized or substantially reduced in 65%, and only 11% of the group had deterioration to severe neurologic disability or death (only 8% of those in whom this treatment was begun before the age of 10 years). Although the study had no control arm, we know that the childhood cerebral form of the disease will develop in 35 to 50% of all those with the known biochemical defect in X-linked ALD. Therefore, treatment with Lorenzo’s oil in asymptomatic children who are at risk for the cerebral variant of the disease seems warranted.

Overall in patients with AMN, approximately 70% will have adrenal insufficiency, and 80% will show evidence of a peripheral neuropathy—typically, a mixed picture of demyelination and axonal degeneration. Indeed, up to 35% of young male patients with idiopathic adrenal insufficiency may have occult AMN.

**ACKNOWLEDGMENT**

We thank Michael D. Whitaker, M.D., for valuable help in managing the endocrinologic problem in our patient.

**REFERENCES**


Correct answers: 1, e, 2, d, 3, b, 4, c, 5, e