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Clinical Reasoning: A 56-year-old man with progressive spasticity

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SECTION 1

A 56-year-old man presented with progressive neurologic symptoms that developed more than 14 years ago. His symptoms started with numbness in the toes, followed by slowly progressive lower extremity weakness, increase in tone, and imbalance. He also developed bladder and bowel urgency, constipation, and erectile dysfunction. He did not have any symptoms in his arms.

His neurologic examination showed symmetric weakness in the lower extremities, marked spasticity with hyperreflexia, and bilateral Babinski signs. Sensory examination showed loss of vibration and pinprick in his feet on both sides. His gait was spastic. The remainder of the general medical examination had normal results.

Family history revealed 2 nephews who died at ages 12 and 13 years from complications related to an uncategorized progressive neurologic disease, a brother who had progressive spasticity starting at age 20, a mother with mild leg weakness at age 82, and a sister with mild leg weakness at age 62.

Questions for consideration:

1. What are the differential diagnoses of the patient's symptoms and examination findings?
2. How does the family history help in narrowing the differential diagnosis for our patient?
3. What is the likely mode of inheritance based on the family history?

[GO TO SECTION 2](#)

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SECTION 2

The patient's symptoms and signs suggest a progressive myelopathy. The differential diagnosis includes hereditary diseases such as spastic paraparesis and adrenomyeloneuropathy (AMN); autoimmune and inflammatory disorders such as primary progressive multiple sclerosis; metabolic disorders such as vitamin B12 and copper deficiency; mass lesion such as intramedullary spinal cord tumor; neurodegenerative conditions such as primary lateral sclerosis; and cervical spondylosis.

MRI of the brain and spinal cord were normal.

Because of the positive family history, the negative spine MRI, and the chronic and very slow progression of his disease, we strongly suspected an inherited disorder. The likely mode of inheritance is X-linked recessive. The female members are carriers and hence not severely affected or unaffected, while the male members are more severely affected. Based on our pa-

tient's symptoms, examination findings, and family history of X-linked inheritance, the diagnosis of AMN, which is an X-linked disorder, was highest on the differential.

Serum analysis of very long chain fatty acids (VLCFA) was performed. The concentration of C26:0 was at the upper end of normal range while the ratio of C24:0 to C22:0 and ratio of C26:0 to C22:0 were in the AMN range. A CSF examination was not performed. Mutation analysis of the *ABCD1* gene was positive.

Questions for consideration:

1. What is the physiologic basis for abnormal VLCFA in the serum?
2. What is the final diagnosis?
3. What are the other phenotypes of this metabolic disorder?

GO TO SECTION 3

SECTION 3

Peroxisomes are subcellular organelles that play an important role in the oxidation of VLCFA. The gene product of *ABCD1* gene is adrenoleukodystrophy protein (ALDP), involved in the transport of VLCFA across the peroxisome membrane from the cytosol. Mutation in the *ABCD1* gene located on Xq28 is pathogenic in a majority of the individuals.¹ Plasma concentration of VLCFA (concentration of C26:0, ratio of C24:0 to C22:0, ratio of C26:0 to C22:0) is abnormally elevated in this disorder.²

Based on the clinical presentation, family history, abnormal laboratory data, and positive genetic testing, the patient was diagnosed with X-linked AMN. A detailed 3-generation family pedigree is included (figure).

There are 3 main phenotypes in affected males: childhood cerebral form, AMN, and Addison disease only.

Female carriers can also be symptomatic with an AMN-like phenotype with slowly progressive mild spastic paraparesis that can present in adulthood. Cerebral involvement and Addison disease are rare in females, but have been reported.³

Our patient did not have any evidence of brain involvement on the MRI and had no clinical or laboratory evidence of adrenal insufficiency. He did not tolerate Lorenzo's oil. He continued with intensive physical therapy program, bowel and bladder regimen, with good quality of life. At last follow-up, his symptoms have continued to slowly progress.

Question for consideration:

1. What are the surveillance and treatment recommendations and the overall prognosis of this disorder?

[GO TO SECTION 4](#)

Figure Pedigree

ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy.

SECTION 4

Adrenal insufficiency is treatable, but may result in significant morbidity and even death during adrenal crisis. Adrenal crisis can occur during infections or surgery. Surveillance for affected males includes periodic reevaluation (at least annually) of adrenocortical function by measuring ACTH and cortisol levels.⁴ In select circumstances, an ACTH stimulation test may be necessary, but it should be noted that most individuals (>70%) will develop adrenal insufficiency.

MRI of the brain should be performed every 6 months in males at risk for childhood cerebral disease and yearly in older individuals (>13 years).

In terms of treatment, corticosteroid replacement therapy is essential for those with adrenal insufficiency. Bone marrow transplantation has been performed in males who have developed mild cerebral disease.⁵ General supportive measures like physical therapy and management of urologic and gastrointestinal complications should be continued.

The use of Lorenzo's oil remains an investigational therapy based upon an open-label study without a placebo arm that showed that reduction of hexacosanoic acid (C26:0) by Lorenzo's oil was associated with a reduced risk of developing brain MRI abnormalities.⁶

Recently, an ex vivo gene therapy has been developed and has demonstrated promise in arresting cerebral disease.⁷

Genetic counseling should be provided. Evaluation of relatives at risk is essential as early identification of asymptomatic or minimally symptomatic patients is important.

DISCUSSION Adrenoleukodystrophy (ALD) is an X-linked recessive and the most common peroxisomal disorder. All ethnic groups are equally affected. It is caused by mutations in the *ABCD1* gene.¹ Abnormal protein prevents normal transport of VLCFA into peroxisomes, thereby preventing β -oxidation and breakdown of VLCFA. Accumulation of abnormal VLCFA in affected organs is presumed to underlie the pathologic process of the ALDs.^{2,8}

Neuropathology shows 2 main forms: inflammatory demyelination affecting the cerebral white matter and noninflammatory axonal disorder of peripheral nerves and spinal cord tracts.⁹

ALD has 3 main phenotypes in affected males. The first form is the childhood cerebral form that presents most commonly between the ages of 4 and 10 years. Prior to this age, boys typically have normal development. Neurologic symptoms include attention-deficit disorder, progressive cognitive and behavior impairment, deterioration in motor function and vision, and finally neurologic disability with spasticity within a few years. Bilateral occipitoparietal region demyelination is typically seen first on the MRI scan of the brain,

though frontal lobe involvement can be seen in a minority of cases. Other distinctive neuroimaging features include involvement of corpus callosum and corticospinal tracts and T1 postgadolinium enhancement of the outer rim of the lesion. The MRI abnormality precedes clinical disease onset.⁹ The second phenotype is the AMN that manifests most commonly in the second decade or later as slowly progressive paraparesis, sphincter and erectile dysfunction, and often accompanied by impaired adrenocortical function. The third phenotype is Addison disease, with onset of primary adrenocortical insufficiency in the first decade, without evidence of neurologic abnormality initially; however, some degree of neurologic disability (most commonly AMN) usually develops later.¹⁰ Close to half of the patients with AMN have MRI evidence of brain involvement at some point. A minority of them can have progressive cerebral disease.

Female carriers can also be symptomatic with an AMN-like phenotype in about 50%, with slowly progressive mild spastic paraparesis that can present in adulthood. Cerebral involvement and Addison disease are rare in females, but have been reported.³

The phenotype can be variable in affected families. Our patient's family highlights the clinical variability of phenotypes and highlights that neither the gene defect nor biochemical abnormality predicts the presentation.

The plasma concentration of VLCFA is elevated in all males with the ALD and AMN. The diagnosis can be confirmed by mutation analysis of the *ABCD1* gene.⁸ All individuals with suspected or confirmed ALD or AMN should be evaluated for adrenal insufficiency, and re-evaluated periodically. Hemopoietic stem cell transplant is an emerging therapy of choice for early disease. It is most appropriate for boys with neurologic abnormalities and evidence of early CNS involvement on MRI. It is not recommended in late disease or in males without MRI evidence of CNS involvement.⁵ The use of other therapies including Lorenzo's oil remains investigational.

AUTHOR CONTRIBUTIONS

Dr. Dhamija: preparation of initial manuscript, revision of the manuscript. Dr. Gavrilova: acquisition of data, critical revision of the manuscript for important intellectual content, supervision. Dr. Raymond: acquisition of data, critical revision of the manuscript for important intellectual content, supervision.

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