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A Rare Case of Adrenoleukodystrophy Masquerading as Progressive Spondylotic Myelopathy Resulting in Unnecessary Surgical Intervention

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INTRODUCTION

Adrenoleukodystrophy (ALD) is an X-lined genetic peroxisomal disorder of beta-oxidation that causes accumulation of very long chain fatty acids in all tissues and leads to demyelination of nerves which leads to progressive muscle weakness, gait dysfunction, and urinary incontinence.[1] Typically, X-linked female carriers remain asymptomatic throughout their life, but some may present with progressive weakness later in their life. We present an interesting case of a patient that that had progressive weakness for 30 years initially attributed to a spondylotic compressive myelopathy that underwent surgical intervention, but then diagnosed as an X-linked adrenoleukodystrophy (X-ALD) carrier only after her grandson was diagnosed with ALD after routine newborn screening.This case brings to the forefront the consideration of ALD genetic analysis in the differential for chronic non-compressive myelopathy.

CASE

A 66-year-old bed-bound female with a significant 30-year history of progressive lower extremity paraparesis, urinary incontinence and decreased lower extremity sensation initially attributed to myelopathy presented to the emergency room with altered mental status secondary to urinary tract infection which eventually resolved with antibiotics. Pertinent physical examination findings include scanning speech, facial masking, subtle bradykinesia and pill-rolling tremor noted on her left arm, slightly increased tone in bilateral upper extremities with no inducible clonus present. The motor exam revealed paraparesis of bilateral lower extremities with 1/5 strength and decreased flexion and extension of bilateral knees. The patient did not respond to any physical pain on sensory exam. Her cranial 2-12 were grossly intact. She has a bilateral Babinski sign. Notable lab findings were creatinine kinase 18 U/L, TSH 1.201 mIU/L, B12 664 pg/mL, and RPR negative. CT imaging of the head was unremarkable, and MRI cervical and thoracic spine without contrast revealed multilevel cervical spondylosis with prominent spinal canal stenosis at C3-C4 levels which was severe and with minimal cord flattening without cord edema. Prominent spinal canal stenosis at C5-C6 and C6-C7 as well. At T1-T2 level there was a diffuse disc bulge and bilateral facet disease causing mild spinal canal stenosis.

A neurology consult was placed to evaluate other causes to explain a 30-year history of progressive weakness.It was discovered that the patient's grandson underwent newborn screening and was found to be positive and hemizygous for the *ABCD1* gene seen with ADL. She noticed that she was having gradually progressive weakness and gait disorder that left her wheelchair bound. At this time the patient was evaluated at the onset of her gait disorder with myelography and imaging and found to have significant lumbar degenerative disk disease with ventral herniation in the mid lumbar segment as well as thoracic disease. During this time, she underwent surgery for a thoracic bone spur and lumbar laminectomy due to concern for an underlying myelopathy causing her symptoms.

Over two decades she had numerous orthopedic evaluations for degenerative disease of the spine involving the thoracic and lumbar regions. She underwent MRIs of the lumbar and thoracic spine, but never got a brain or cervical MRI to test for multiple sclerosis. Records show that at the time of this worsening gait disorder she developed worsening urinary incontinence with spastic and neurogenic bladder for which she was trialed on multiple medications such as Ditropan and Detrol, as well as Oxybutynin, all without significant benefit. Thus, she was recommended to undergo straight catheter intermittently. She was also noted to have progressive tingling, numbness and clumsiness of her right hand and found on electrophysiologic testing to have profound denervation of the median nerve. Similar symptoms developed in the left hand and electromyography showed evidence of median nerve carpel tunnel syndrome and an ulnar nerve neuropathy.

Unfortunately, despite surgery and numerous orthopedic evaluations, over the next two decades, she became wheelchair bound, required straight catheterization, developed complete loss of sensation below T10, spasticity and weakness in the ulnar nerves bilaterally.

The outside hospital neurologist who evaluated her ten years prior to her presentation to our hospital believed that her gait dysfunction was multifactorial in nature due to aging, significant diabetes with peripheral neuropathy, and significant underlying myelopathy, obesity and arthritis. He was concerned about demyelination in the central nervous system higher up at the level of the cervical cord or the brain, and wanted to rule out rarer causes of inflammatory peripheral neuropathy that might exacerbate her current condition. At the time her Vitamin B12 levels were in the lower range of normal and he thought they could conceivably be associated with some of her dysfunction. He recommended that she get an MRI of the cervical cord and MRI of the brain to rule out demyelinating lesions, parasagittal process or compressive myelopathy. In the event that the workup would be unrevealing, he thought it would be reasonable to refer for EMG nerve conductions in the lower extremities particular to workup sciatic discomfort and other peripheral neuropathic changes. He recommended further physical therapy with gait training and aids for ambulation. However, the patient never did get an MRI of the cervical or the bran. Further documents showed that she did get an MRI about a decade later when she presented with a stroke which showed microvascular changes.

Our medical team and neurologist reviewed these extensive medical records with the patient and her daughter. It was revealed that the patient's grandson was diagnosed with ALD from routine newborn screening in the state of New York. The older grandson and daughter both got genetic testing which showed evidence of *ABCD1*mutationconsistent in ALD. The older grandson was tested weeks later and found to have cerebral ALD, and the daughter was found to be a X-ALD carrier. These findings, in light of the patient's extensive clinical history strongly suggested that the patient was a X-ALD carrier. Further investigation warranted an MRI which was ordered for the patient during her hospital visit but was not done due to patient's kyphosis causing discomfort during the MRI. Patient was advised to have further workup done with the neurologist post hospital discharge but she did not get it. However, the patient did undergo genetic testing and found to have *ABCD1* mutation confirming she was a X-ALD female carrier.

DISCUSSION

X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in the *ABCD1* gene encoding a peroxisomal *ABCD1* transporter, which normallyfunctions to transport the very long-chain fatty acid (VLCFA) CoA esters across the peroxisomal membrane.[2] If there is a dysfunction in *ABCD1*, the VLCFA cannot be transported for degradation and this will result in the buildup of VLCFAs in tissue this can have toxic effects on both the myelin sheath of nerves and the adrenal gland.[3,4,5] The accumulation of the VLCFA instigates an inflammatory response to the myelin sheath around the nerve cells of the brain and spinal cord leading to progressive neurological deterioration over time. In addition, the VLCFA can damage the adrenal glands and cause adrenocorticoid insufficiency.[3]

It is estimated that X-ALD affects approximately 1 in 42,000 males[6] and 1 in 28,000 females are heterozygous carriers for the*ABCD1*mutation.[6] ALD is inherited in an X-linked pattern which means that males that carry one altered copy of the *ABCD1*gene will cause ALD. However, females have two copies of the X chromosome, so typically one altered copy of the *ABCD1* gene does not cause symptoms of X-ALD; however, some females who are carriers can exhibit signs and symptoms later in their age then males.[7,8]

The diagnosis of X-ALD is typically found in boys who a positive newborn screen result,[9] and there have been multiple studies on the wide spectrum of phenotypes seen in males which include adrenocortical insufficiency,[10,11]adrenomyeloneuropathy,[12,13]andchild hood cerebral demyelination ALD.[12,9]However, it is much more challenging to diagnose X-ALD in females since 20% of X-ALD female carriers develop mild-to-moderate spastic paraparesis in middle age or later (with typically normal adrenal function),[9]and may have a negative family history for ALD.

A recent large cross-sectional cohort study by Engelen et al. showed that X-ALD female carriers have neurological abnormalities increase with frequency of age (most often after age 60), with the main symptoms consistent with myelopathy and/or peripheral neuropathy, and fecal incontinence. [8] The study suggested that based on the clinical symptoms seen in the cohort that X-ALD female carriers develop an adrenomyeloneuropathy-like phenotype.[8]X-linked adrenoleukodystrophy should be considered in the differential diagnosis in women with chronic myelopathy and/or peripheral neuropathy (especially with early fecal incontinence).The MRI imaging shows a distinct pattern of symmetric enhanced T2 signal in the parieto-occipital region.[9] The Engelen et al. study also reported that X-ALD female carriers had similar disability to those with Parkinson's disease 1 year after the diagnosis, which strongly suggests that the burden of disease in X-ALD carriers has a greater morbidity impact than initially thought.[8]

X-ALD should be strongly considered in the differential for adult women who have chronic myelopathy and develop progressive paraparesis, loss of sphincter control, and sensory disturbances mainly affecting the

legs.[8,9] The diagnosis of X-ALD is important to make as some patients have been reported to have cervical laminectomy for what was initially thought to be a cervical spondylogenic myelopathy, when in fact they were X-ALD female carriers.[14]

Typically, the finding of elevated VLCFA is strongly suggestive for ALD in affected males and carrier females, but exclusion of carrier status biochemically is unreliable.[15] The screening test for ALD is elevated VLCFA, and if positive patients are sent for mutation analysis of the *ABCD1*gene.[15] Most males will possess elevated VLCFA and the finding of the pathogenic mutation *ABCD1*confirms the diagnosis.[16,17] However, 15-20% of X-ALD female carriershave their VLCFA levels within the normal range so this diagnosis can be missed.[17]Typically, those that undergo genetic testing for X-ALD is done for those that have any *ABCD1*pathogenic variant in the family, such as those found in newborn screening.[9]

This case illustrates the importance of keeping a broad differential, such as X-ALD,in the workup for chronic myelopathy and progressive weakness seen in elderly women. Our patient had undergone surgical interventions for what was initially believed to be a compressive spondylotic myelopathy. However, the 30-year history of progressive lower extremity paraparesis, urinary incontinence and decreased lower extremity sensation, with no improvement despite surgical intervention, suggested theinitial diagnosis ofcompressive spondylotic myelopathywas incorrect.

Fortunately, with newborn screening, the patient's grandchildren were found to have elevated VLCFA levels which prompted a genetic test toconfirm presence of the*ABCD1*mutation seen in ALD. However, if this patient were tested for the *ABCD1*mutation decades earlier, she would have been correctly diagnosed as an X-ALD female carrier with symptoms and avoided unnecessary surgical intervention for what was thought to be a spondylotic myelopathy.While there are no screening guidelines for X-ALD in female carriers, this case puts forth the consideration of *ABCD1*mutation analysis in the differential for women with chronic progressive non-compressive myelopathic symptoms.

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