A Case of Adrenoleukodystrophy Presenting as Progressive Cerebellar Dysfunction

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X-linked adrenoleukodystrophy (X-ALD) is a hereditary neurological disorder affecting the nervous system and adrenal cortex. The phenotype of X-ALD ranges from the rapidly progressive cerebral form to milder adrenomyeloneuropathy. However, cerebellar manifestations are rare. We report a case of adrenoleukodystrophy presenting as progressive cerebellar dysfunction resembling olivopontocerebellar degeneration, with a review of the literature.

Key Words: X-linked adrenoleukodystrophy, Phenotype, Olivopontocerebellar degeneration.

Adrenoleukodystrophy (ALD) is an X-linked hereditary disorder caused by a genetic problem in Xq28 affecting the peroxisomal membrane. The resulting peroxisomal dysfunction causes very long-chain fatty acids (VLCFA) with more than 22 carbons to accumulate in various tissues, including the nervous system, adrenal cortex, and testis. Depending on the areas involved, this results in a variety of symptoms. The most common types of ALD are cerebral ALD and adrenomyeloneuropathy (AMN). Although adult-onset ALD takes the form of AMN in most cases, several studies have reported progressive cerebellar dysfunction such as olivopontocerebellar degeneration. We report a case of ALD presenting as progressive cerebellar dysfunction, with a review of the literature.

Case Report

A 39-year-old man presented with dizziness and gait disturbance of 2-years duration. The onset and progression were gradual. Over the past year, dysarthria and liquid dysphagia developed and progressed. He had been a problem alcohol drinker for the past 7 years. Over the past 3 years, he had become impatient and was easily angered. One year earlier, he was admitted to a local psychiatric hospital because of abnormal behavior, such as stealing alcohol from a store. He was told that the results of brain magnetic resonance imaging (MRI) performed during that admission were abnormal, but this was not followed up. He continued to drink after discharge. In his family history, his elder brother had alopecia and a similar neurological condition, and died at the age of 46 years.

The physical examination revealed near-total alopecia. On neurological examination, he was alert and oriented. Gaze-evoked nystagmus was observed in both directions and was worse when looking to the right. He also had dysarthria and dysphagia. His motor strength was normal, as were the results of the sensory examination. The deep tendon reflexes were decreased slightly in both the lower and upper limbs. There was no Babinski’s sign or ankle clonus. He had marked dysmetria in both upper limbs that was worse on the right. He was barely able to walk, with a broad-based gait.

A review of the previous brain MRI results showed mild brainstem and cerebellar atrophy, with a subtly increased signal intensity in the right middle cerebellar peduncle on fluid attenuated inversion-recovery (FLAIR) imaging. Cerebral cortical atrophy was also present. The MRI was repeated and showed worsening of the brainstem and cerebellar atrophy. The FLAIR images showed symmetric high-intensity signals in the posterior limbs of the
internal capsule, right middle cerebellar peduncle, and brachia of the inferior colliculus where it joins the medial geniculate body (Figure 1).

Complete blood counts, erythrocyte sedimentation rate (ESR), urinalysis, plasma electrolytes, and kidney, liver, and thyroid function tests were normal. Vitamin B12 was somewhat low at 196 pg/mL (normal range, 200-1,000 pg/mL), and the folate level was low at 1.3 ng/mL (normal range, 3-15 ng/mL). An intramuscular vitamin B12 injection and oral folate did not improve his condition. A Venereal Disease Research Laboratory (VDRL) test for syphilis was negative. An electrocardiogram and a chest X-ray were normal. Gene tests for spinocerebellar ataxia types 1-3, 6, 7, and 17; dentatorubropallidoluysian atrophy; fragile X syndrome; and Friedreich’s ataxia were all negative. The plasma levels of pyruvate, lactic acid, homocysteine, and tumor markers were all normal. The adrenocorticotropic hormone (ACTH) level at 8 a.m. was 90 pg/dL (normal range, 0-60 pg/dL) and the cortisol level was normal at 10.2 μg/dL (normal range, 5-25 μg/dL). An adrenocorticotropic hormone (ACTH) stimulation test resulted in a defective rise in the cortisol level. A very long-chain fatty acid assay showed a C22 : 0 of 2.565 μM/L (normal, <1.310 μM/L), C24 : 0/C22 : 0 of 1.785 (normal, <1.390), and C26 : 0/C22 : 0 of 0.114 (normal, <0.023).

Discussion

ALD has various clinical symptoms depending on the areas involved. A published classification divides the condition into child-onset cerebral, adolescent-onset cerebral, AMN, adult-onset cerebral, Addison’s disease only, and non-symptomatic ALD, based on the onset time and organs involved. The most common adult-onset ALD is AMN. However, rare cases presenting as progressive cerebellar dysfunction have been reported.

One study analyzed the MRI scans of 164 adult-onset ALD patients who were classified into four subgroups based on their symptoms and patterns of brain involvement: AMN with normal brain, AMN with brain abnormalities limited to the long tract (ALMN I), AMN with diffuse lobar cerebral involvement (ALMN II), and adult-onset cerebral ALD. Our patient had progressive cerebellar ataxia. On MRI, demyelination lesions were observed in the cerebellar white matter, including the dentate nuclei and right cerebellar peduncle, posterior limbs of both internal capsules, and auditory pathway. There is a report of a patient who had clinical symptoms similar to our case, and that patient was classified as AMNM I, or somewhere between AMNM I and II. In another case of adult-onset ALD showing slowly developing gait ataxia over 7 years, demyelination lesions were observed in the dentate nucleus, middle cerebellar peduncle, decussation of the superrior cerebellar peduncles, and posterior limbs of both internal capsules on brain MRI; two years later, new white matter lesions were seen in the right frontal lobe, left occipital lobe, and both temporal lobes on brain MRI. The brain MRI findings in other cases of ALD presenting as progressive cerebellar dysfunction are summarized in Table 1.

Our patient had a history of alcohol abuse, aggression, and...
abnormal behavior before the onset of cerebellar ataxia. Preceding psychiatric symptoms have often been reported in adult-onset ALD. In a review of 109 cases of ALD, six cases presented after the age of 20 years, and four patients had psychiatric symptoms at the time of presentation. Among 34 adult-onset ALD cases, 19 (56%) were reported to have psychiatric symptoms. In 13 of these cases, the psychiatric symptoms were assessed relatively thoroughly, and eight cases showed changes in behavior and character. These symptoms appeared between 2 months and 8 years before the onset of other neurological symptoms. Of the 13 patients, 12 were reported to have bipolar disorder, including disinhibition and emotional lability, with two of them reported to abuse alcohol or other substances.

When brain MRI shows brainstem and cerebellar atrophy and demyelination lesions along the long tracts, the possibility of ALD should be considered. Accompanying adrenal insufficiency may be an important clue, but 30% of adult-onset ALD cases have normal adrenal function. Hyperpigmentation of the skin, alopecia, and prior psychotic symptoms are further clues to the diagnosis of ALD.

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