

# X-linked adult-onset adrenoleukodystrophy: Psychiatric and neurological manifestations

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## Abstract

Adult-onset adrenoleukodystrophy is a rare x-linked inborn error of metabolism occurring predominantly in males with onset in early 30s. Here, we report a 34-year-old male with first signs of disease in early 20s manifesting as a pure psychiatric disorder. Prior to onset of neurological symptoms, this patient demonstrated a schizophrenia and bipolar-like presentation. The disease progressed over the next 10–13 years and his memory and motor problems became evident around the age of 33 years. Subsequently, diagnostic testing showed the typical magnetic resonance imaging and lab findings for adult-onset adrenoleukodystrophy. This case highlights adult-onset adrenoleukodystrophy which may present as a pure psychiatric disturbance in early adulthood and briefly discusses the prolonged time between the onset of psychiatric symptoms and the onset of neurological disease.

## Keywords

Adrenoleukodystrophy, x-linked, clinical manifestations, neurological, psychiatric

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## Introduction

X-linked adult-onset adrenoleukodystrophy (ALD) is a rare genetic disorder of peroxisomal fatty acid beta oxidation which results in the accumulation of very-long-chain fatty acids (VLCFA), defined as having greater than 22 carbons.<sup>1–3</sup> The deposition most notably affects the central nervous system (CNS), adrenal cortex, and testes<sup>4</sup> which brings about the various clinical symptoms seen in this disorder, depending on the site of deposition of VLCFA.

ALD has three main phenotypes: Addison-only, adrenomyeloneuropathy, and cerebral ALD.<sup>5</sup> Cerebral ALD can be further divided into childhood and adolescent/adult onset. Of these two, the adult form of cerebral ALD is the more uncommon presentation of the disease and is known to have psychiatric manifestations that precede the neurological deterioration seen in this disorder.<sup>4</sup> These psychiatric symptoms are possibly the result of deposition of VLCFA in the brain and secondary neuronal injury. This case report discusses these psychiatric and neurological manifestations of the adult cerebral form of ALD.

## Case report

This is a 34-year-old male who presented primarily with behavioral and psychiatric problems which later progressed to involve memory and motor functions.

## Behavioral

Prior to the start of his psychiatric problems, he had behavioral issues which included serving jail time for trespassing, car accidents, and parking ticket violations. He also had a history of illicit drug use. He was fired from his job as a programmer that resulted in him losing his apartment and becoming homeless.

## Psychiatric

His mother reported that his psychiatric problems started in his early 20s and he subsequently received a diagnosis of schizophrenia. His roommate in college described him as “manic.” The patient reported having racing thoughts but denied any hallucinations, depression, or anxiety. His mother also reported poor upkeep of his previously clean apartment and described his behavior as belligerent and demanding.

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He subsequently also received a diagnosis of bipolar disorder in addition to the diagnosis of schizophrenia. He was prescribed risperidone 2 mg PO QHS and mirtazapine 15 mg PO QHS, but compliance could not be verified.

### **Substance abuse**

Approximately the same time of receiving this diagnosis, he reported the use of multiple recreational drugs: nicotine, marijuana, K2, cocaine, and methamphetamine. His last use was prior to his admission to the emergency psychiatric unit, approximately 1 year ago.

Upon admission, he was observed to be responding to internal stimuli with delusional and disorganized thought processing. He continued to display patterns of odd thinking with ideas of reference (the television was talking to him), grandiose delusions (believed he had special spiritual powers), auditory hallucinations, thought blocking, and disorganized speech. Importantly, he also displayed signs of disinhibition.

### **Memory**

Collateral information obtained from his mother suggested that his memory problems began approximately a year ago. He scored 24/30 on the Mini Mental State Examination (MMSE) which was below the normal range (27/30) and 17/30 on the Montreal Cognitive Assessment (MoCA) also below the normal range (26/30).

### **Physical exam**

His neurological problems also started a year prior to presentation with initial symptoms of urinary and fecal incontinence. This progressed to difficulty walking and an ataxic gait. He was unable to perform tandem gait, and spasticity was noted in upper and lower limbs. Subsequently, he also developed speech abnormalities where his speech was strained, loud, and slow in rate. He was also noted to have anisocoria.

Of note, he developed stereotypical, circular head motion after starting on 50 mg of Risperdal Consta. His medication was therefore switched to quetiapine 400 mg PO QHS, but this did not stop the head movements.

### **Reflexes**

Positive Myerson's sign and Babinski sign. Hyperstartle was present. Palmar grasp was negative.

### **Magnetic resonance imaging**

Confluent deep white matter T2 hyperintensity involving bilateral occipital and parietal lobes, splenium of corpus callosum, bilateral occipital medial subcortical U fibers,

posterior limb of the bilateral internal capsules, deep white matter adjacent to the body of the bilateral lateral ventricles, pyramidal tracts, bilateral middle cerebellar peduncles, and the bilateral cerebellar white matter were observed. Gray matter and deep nuclei were preserved. There was mild heterogeneous enhancement at the T2 hyperintensity of the deep white matter of the left frontal lobe adjacent to the left lateral ventricle and T2 hyperintensity of the bilateral cerebellar white matter. The pattern was consistent with demyelinating disorder of ALD.

### **Labs**

ACTH: Plasma 53 pg/mL (N=6–50);

Morning cortisol: 17.9 (N=4–22);

Afternoon cortisol: 5 (N=4–22);

Discriminant function of VLCFA: 22.3 (N<7.5).

### **Diagnosis**

His current diagnosis is frontal lobe dementia due to X-linked ALD. Diagnosis was suggested by history, physical exam, magnetic resonance imaging (MRI) pattern of demyelination, and confirmed by gel electrophoresis for VLCFA.

### **Discussion**

Although previously thought to occur only in childhood, cerebral ALD is now known to have an adult form which has a different presentation from its childhood-onset counterpart. The childhood form of ALD is predominantly neurological and rapidly progressive leading to complete disability and death within 3–5 years of symptom onset.<sup>6,7</sup> In contrast, the adult form follows a more indolent course and can manifest first with non-specific psychiatric disturbances that may mimic the symptoms of schizophrenia and the manic phase of bipolar disorder.<sup>8</sup> ALD has considerable clinical heterogeneity and may present with any combination of psychiatric, neurological, adrenal, and gonadal symptoms. However, the majority of patients with ALD will have neurological problems at some point during the course of their illness.<sup>9,10</sup>

ALD follows an X-linked recessive pattern of inheritance, and thus, the majority of patients who have this disease are males. Of note, 20%–50% of women heterozygous for the ALD gene defect have a mild form of the disease with neurological problems that can be misdiagnosed as multiple sclerosis.<sup>11</sup>

Most cases of ALD are diagnosed based on neurological symptoms, which typically appear 3–4 years after the development of psychiatric symptoms.<sup>4</sup> Interestingly, the neurological symptoms (urinary and fecal incontinence) that prompted diagnosis of ALD in our patient developed almost 10 years following the onset of psychiatric symptoms. After

receiving the diagnosis of schizophrenia and bipolar disorder in his early 20s, the patient was followed in an outpatient psychiatric setting, and to our knowledge, there were no reports of neurological symptoms prior to his current presentation at our facility. Although the course of his psychiatric illness was longer than usual for ALD, published literature suggests that his refractoriness to treatment and aggressive clinical course were typical for psychiatric symptomology of ALD.<sup>4</sup>

The case is further complicated by the concomitant drug abuse which makes it difficult to tease apart the etiology of his psychiatric symptoms. An important question to ask then is as follows: “Were his psychiatric symptoms due to drug abuse or due to schizophrenia?” or “Were these symptoms due to ALD all along?”

For our patient, it could not be verified whether the drug abuse or psychiatric symptoms came first. Nonetheless, the fact that the patient continued to experience the classical symptoms of schizophrenia such as ideas of reference, grandiose delusions, and auditory hallucinations even after the cessation of illicit drug abuse led to his initial diagnosis of schizophrenia. Because his symptoms started much in advance of his neurological deterioration and responded only partially to antipsychotic medications, a diagnosis of ALD with comorbid schizophrenia can also be argued for. However, it is important to note that in the majority of cases, the psychiatric manifestations in ALD may be clinically indistinguishable from a pure psychiatric disorder.<sup>4</sup>

The only definitive treatment option for ALD is bone marrow transplant to provide the patient with healthy cells that have the ability to breakdown VLCFA.<sup>12</sup> It must be noted that bone marrow transplant as a treatment option is less effective once the individual has developed neurological symptoms.<sup>13</sup> Thus, early diagnosis and genetic testing of family members are crucial to successful treatment.<sup>4</sup>

The treatment of psychiatric symptoms is complicated by atypical responses in patients with metabolic disorders. Furthermore, these patients are more vulnerable to developing side effects.<sup>14</sup> Our patient developed the side effect of stereotypic head wringing movements after administration of antipsychotic medication. However, it is also possible that these movements were a manifestation of his disease process or a result of his psychiatric condition.

The initial investigation for suspected ALD is an MRI.<sup>15,16</sup> In addition to their presence in ALD, T2-weighted densities are also found in multiple sclerosis,<sup>17</sup> Krabbe disease,<sup>18</sup> metachromatic leukodystrophy,<sup>19</sup> vitamin B deficiency,<sup>20</sup> and solvent abuse.<sup>21</sup> Since these metabolic disorders are also associated with psychiatric symptoms,<sup>22</sup> they must be ruled out by measurement of VLCFA in the serum which is the definitive diagnostic test for ALD.<sup>23</sup>

In conclusion, while it is important to assess psychiatric patients for inborn errors of metabolism at the time of their presentation, it may also be worthwhile to consider a comorbid diagnosis especially when the time from psychiatric to

neurological symptoms is longer than expected. Assessment in all suspected cases should include a family history of neurological and psychiatric disorders, a neurological exam, and neuroimaging if indicated. Things that warrant further assessment for metabolic disorders in a young adult psychiatric patient are refractoriness to treatment, unusual side effects to psychotropic medications, development of neurological symptoms, or cognitive decline. Because metabolic disorders such as ALD are considered to be childhood diseases, they can often go underdiagnosed in adulthood. Early diagnosis of adult cerebral ALD has important implications for genetic counseling and treatment options.

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### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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### Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

### References

1. Ho JK, Moser H, Kishimoto Y, et al. Interactions of a very long chain fatty acid with model membranes and serum albumin. Implications for the *pathogenesis* of adrenoleukodystrophy. *J Clin Invest* 1995; 96: 1455–1463.
2. Singh I, Moser HW, Moser AB, et al. Adrenoleukodystrophy: impaired oxidation of long chain fatty acids in cultured skin fibroblasts an adrenal cortex. *Biochem Biophys Res Commun* 1981; 102: 1223–1229.
3. Igarashi M, Schaumburg HH, Powers J, et al. Fatty acid abnormality in adrenoleukodystrophy. *J Neurochem* 1976; 26: 851–860.
4. Rosebush PI, Garside S, Levinson AJ, et al. The neuropsychiatry of adult-onset adrenoleukodystrophy. *J Neuropsychiatry Clin Neurosci* 1999; 11: 315–327.
5. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis* 2012; 7: 51.
6. Cappa M, Bizzarri C, Vollono C, et al. Adrenoleukodystrophy. *Endocr Dev* 2011; 20: 149–160.
7. Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. *Lancet* 2000; 356: 713–718.
8. Kitchin W, Cohen-Cole SA and Mickel SF. Adrenoleukodystrophy: frequency of presentation as a psychiatric disorder. *Biol Psychiatry* 1987; 22: 1375–1387.

9. Moser HW, Moser AB, Naidu S, et al. Clinical aspects of adrenoleukodystrophy and adrenomyeloneuropathy. *Dev Neurosci* 1991; 13: 254–261.
10. Schaumburg HH, Powers JM, Raine CS, et al. Adrenoleukodystrophy. A clinical and pathological study of 17 cases. *Arch Neurol* 1975; 32: 577–591.
11. Jangouk P, Zackowski KM, Naidu S, et al. Adrenoleukodystrophy in female heterozygotes: underrecognized and undertreated. *Mol Genet Metab* 2012; 105: 180–185.
12. Loes DJ, Stillman AE, Hite S, et al. Childhood cerebral form of adrenoleukodystrophy: short-term effect of bone marrow transplantation on brain MR observations. *AJNR Am J Neuroradiol* 1994; 15: 1767–1771.
13. Baumann M, Korenke GC, Weddige-Diedrichs A, et al. Haematopoietic stem cell transplantation in 12 patients with cerebral X-linked adrenoleukodystrophy. *Eur J Pediatr* 2003; 162: 6–14.
14. MacQueen GM, Rosebush PI and Mazurek MF. Neuropsychiatric aspects of the adult variant of Tay-Sachs disease. *J Neuropsychiatry Clin Neurosci* 1998; 10: 10–19.
15. Melhem ER, Loes DJ, Georgiades CS, et al. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. *AJNR Am J Neuroradiol* 2000; 21: 839–844.
16. Steinberg SJ, Moser AB and Raymond GV. X-linked adrenoleukodystrophy. In: Pagon RA, Adam MP, Ardinger HH, et al. (eds). *GeneReviews*<sup>®</sup>. Seattle, WA: University of Washington, 1993, <https://www.ncbi.nlm.nih.gov/books/NBK1315/>
17. Wiebe S, Lee DH, Karlik SJ, et al. Serial cranial and spinal cord magnetic resonance imaging in multiple sclerosis. *Ann Neurol* 1992; 32: 643–650.
18. Kapoor R, McDonald WI, Crockard A, et al. Clinical onset and MRI features of Krabbe’s disease in adolescence. *J Neurol Neurosurg Psychiatry* 1992; 55: 331–332.
19. Lee TG, Solomon GD, Kunkel RS, et al. Reversible cerebellar perfusion in familial hemiplegic migraine. *Lancet* 1996; 348: 1383.
20. Chatterjee A, Yapundich R, Palmer CA, et al. Leukoencephalopathy associated with cobalamin deficiency. *Neurology* 1996; 46: 832–834.
21. Filley CM, Heaton RK and Rosenberg NL. White matter dementia in chronic toluene abuse. *Neurology* 1990; 40: 532–534.
22. Hyde TM, Ziegler JC and Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Arch Neurol* 1992; 49: 401–406.
23. Valianpour F, Selhorst JJ, van Lint LE, et al. Analysis of very long-chain fatty acids using electrospray ionization mass spectrometry. *Mol Genet Metab* 2003; 79: 189–196.