X-linked adrenoleukodystrophy in a 6-year-old boy initially presenting with psychiatric symptoms

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X-linked adrenoleukodystrophy (ALD) leads to demyelination of the nervous system, adrenal insufficiency and accumulation of long-chain fatty acids. Most young patients with X-linked ALD develop seizures and progressive neurologic deficits, and die within the first two decades of life. We present the case of a 6-year-old with childhood-onset ALD, first presenting with psychiatric symptoms and progressive gait difficulties, slurred speech and cognitive impairment. Genetic testing was performed and a p.R401Q (c.1202G>A) mutation detected in the ABCD1 gene. ALD should be considered in the differential diagnosis of patients presenting with behavior changes and white matter disease in neuroimaging.

Key words: X-linked adrenoleukodystrophy, clinical presentation, childhood.

X-linked adrenoleukodystrophy (ALD) is the most common severe, recessively inherited peroxisomal neurodegenerative disorder, characterized by progressive demyelination of the central nervous system and adrenocortical insufficiency. It is also characterized by great clinical variability, with an incidence of 1:21,000 in males. The major phenotypes include childhood cerebral ALD, adrenomyeloneuropathy, Addison-only, and asymptomatic.

It is caused by mutations in the ABCD1 gene located on the X chromosome. The most severe clinical manifestation of ALD is the cerebral variant (cALD). Childhood-onset cALD develops at a median of 7 years of age and features rapid and profound neurological decline due to demyelination within cerebral white matter. In the present report, we describe a 6-year-old boy with the cerebral form of X-ALD who presented with behavioral changes, progressive gait difficulties, slurred speech and cognitive impairment.

Case Report
A previously healthy 6-year-old boy presented with progressive difficulty in walking, unsteady gait, progressively slurred speech, cognitive impairment and behavioral changes. His first symptom, a change in behavior, was noted one year previously, at the time he started nursery school. The child’s teacher had reported to his parents that he had developed symptoms of anxiety and emotional withdrawal. However, the parents thought that this was related to the start of schooling. Six months later, additional symptoms progressive difficulty in walking, unsteady gait, slurred speech and cognitive impairment were noted by the parents. The child had no history of seizures. The parents were not consanguineous, and there was no family history of neurologic disease. The patient’s early development was normal, and he appeared to be healthy during his first five years.

On examination, his height was 115 cm (25th-50th percentile), weight 20 kg (25th-50th percentile), pulse 80/min and blood pressure 100/70 mmHg. He was not alert or cooperative during physical examination. Neurologic examination revealed moderate cognitive impairment and slurred speech.
He could not walk unaided. Cranial nerve examination was normal. He had moderate spastic paraparesis. The lower extremity deep tendon reflexes were increased, with ankle clonus and bilateral Babinsky signs. Eye fundus examination was normal. The remainder of the physical examination was normal, except for mild hyperpigmentation of his oral mucosa, gum, tongue and lips.

In the laboratory results, serum electrolytes showed sodium of 134 mEq/L, potassium of 3.8 mEq/L, bicarbonate of 18 mEq/L and chloride of 91 mEq/L; blood sugar was 98 mg/dl. Serum cortisol was 7.89 µg/dl (normal range, 6.7-22.6 µg/dl) and ACTH was 8.23 pg/ml (normal range, 10-50 pg/ml) early in the morning. The plasma levels of very long chain fatty acids were C22: 48.40 µmol/L (normal range, <105), C24: 80.20 µmol/L (normal range, <80), C26: 2.97 µmol/L (normal range, <0.92), C24:0/C22:0 ratio of 1.66 (normal range, 0.51-1.19) and C26:0/C22:0 ratio of 0.061 (normal range, 0.006-0.014). T2-weighted magnetic resonance imaging of the brain showed bilateral symmetrical, high signal intensity on the white matter of both temporo-parieto-occipital lobes, including the internal capsules, the splenium of the corpus callosum, and the brainstem (Fig. 1).

Based on the clinical, biochemical and radiological findings with central nervous involvement, the diagnosis of X-ALD (childhood cerebral form) was made. He was treated with oral prednisone and antioxidants.

To confirm the diagnosis of X-linked ALD, we analyzed the \textit{ABCD1} gene sequencing in the patient, revealing a p.R401Q (c.1202G>A) mutation. After a few months, the oral mucosa, gum, tongue and lip hyperpigmentation was reversed. The patient was also referred for bone marrow transplant evaluation.

**Discussion**

X-linked ALD leads to demyelination of the nervous system, adrenal insufficiency and accumulation of long-chain fatty acids\(^4\). The clinical course in ALD is characterized by behavioral disorders, ataxia, visual loss, decreased hearing and epileptic seizures, followed by mental deterioration, psychosis and death\(^5,6\). Adrenal insufficiency is a usual finding, but does not always precede neurologic disease. Abnormal skin pigmentation and other features of adrenal insufficiency may become apparent before neurological symptoms. In some cases, adrenal symptoms never appear. The diagnosis of X-ALD is confirmed by analyzing the plasma levels of VLCFAs and identifying aberrant mutations in the \textit{ABCD1} gene\(^2\).

X-linked ALD is a white matter disease, which can initially present with psychiatric symptoms and thus be misdiagnosed as a primary psychiatric disorder. Behavioral and emotional changes develop prior to progressive deterioration of vision, hearing and motor functions\(^7\). In our patient, the first symptoms were anxiety and emotional withdrawal. His parents considered these a consequence of his starting. Within a few months, the child's cognitive abilities and speech had deteriorated and difficulty in walking had developed to accompany the behavior changes.

In ALD, demyelination typically begins bilaterally in the occipital region, extending across the splenium of the corpus callosum. Gradually the process spreads outward and forward as a confluent lesion, affecting the...
parietal, temporal and finally, the frontal white matter, cerebellar white matter, cerebellar peduncles and corticospinal and corticobulbar tracts. MRI showed a hypointense signal on T1 and a hyperintense signal on T2 and FLAIR images. Post-contrast study showed contrast enhancement at the outer margins due to active demyelination and disruption of the blood brain barrier\textsuperscript{8,9}. We confirmed the diagnosis of X-linked ALD in our patient based on the pathognomonic pattern of distribution of leukodystrophy on cranial MRI.

Treatment is symptomatic; for example, steroid use for adrenal insufficiency and psychotropics for psychiatric symptoms. No clearly effective treatments are available, although Lorenzo’s oil (4:1 glyceryl trioleate and glyceryl erucate) used before the age of 6 may reduce the probability of developing neurological deficits in later life\textsuperscript{10}. Statins can reduce VLCFA levels, but have no influence on neuronal and endocrine functions\textsuperscript{11}. Fatty items in the diet should be restricted\textsuperscript{12}. Bone marrow transplantation is an option in patients with early neurological features, abnormal magnetic resonance imaging scans and neuropsychological dysfunction, but is not recommended in the severely affected group, where it has a significant morbidity and mortality\textsuperscript{13}. We treated our patient with oral prednisone and antioxidants. After prednisone treatment, his hyperpigmentation showed improvement. He was also referred to another hospital for bone marrow transplant evaluation.

In conclusion, ALD is an X-linked recessive disorder, so genetic counseling of family members may be advisable. Early diagnosis brings with it the possibility of genetic counseling, carrier detection and antenatal diagnosis, thus enabling us to reduce the incidence of this devastating disease. Clinicians should consider the possibility of white matter disease and include neuroimaging in their medical workups of children who have a gait difficulty or behavior changes.

**REFERENCES**