Clinical Case Report

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Unusual brain images of a boy with adolescent cerebral X-linked adrenoleukodystrophy presenting with exhibitionism

A CARE-compliant case report

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Abstract

Rationale: The respective involvements of both the thalamus and exhibitionism in cerebral X-linked adrenoleukodystrophy (X-ALD) have not been reported.

Patient concerns: An 11-year-old boy initially presented with exhibitionism and progressive neurobehavioral symptoms. He subsequently developed transient urinary and fecal incontinence, and an unwillingness to eat or communicate.

Diagnoses: We conducted contrast-enhanced brain magnetic resonance imaging (MRI), which revealed symmetrical altered signal intensities in bilateral frontal white matter, the basal ganglia, and dorsal thalami, as well as a peripheral rim of contrast enhancement. Diagnosis of adolescent cerebral X-ALD was confirmed on the basis of next generation genetic sequencing analysis.

Interventions: We initiated the patient on hormonal replacement therapy.

Outcomes: We observed rapidly progressive neurologic deterioration in this patient, and the boy fell into a vegetative state 10 months after discharge.

Lessons: We recommend that physicians should not disregard X-ALD in patients with isolated psychiatric symptoms, including hypersexual behavior. The combination of detailed clinical evaluation, MRI, and next generation genetic sequencing can expedite the diagnostic process of atypical variant of X-ALD.

Abbreviations: AdolCALD = adolescent cerebral X-ALD, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, X-ALD = X-linked adrenoleukodystrophy.

Keywords: adolescence, basal ganglia, exhibitionism, thalamus, X-linked adrenoleukodystrophy

1. Introduction

X-linked adrenoleukodystrophy (X-ALD) is a rare (1:17,000) metabolic disorder caused by mutations in the *ABCD1* gene that encodes the peroxisomal membrane adrenoleukodystrophy protein, which is involved in transmembrane transport of very long-chain fatty acids.[1,2] The common cerebral forms (childhood, adolescent, and adult) manifest with hyperactivity or inattention, followed by progressive deterioration in cognition, hearing, vision, and motor function.[3] These phenotypes are the most rapidly progressive and devastating phenotypes of X-ALD. Adolescent cerebral X-ALD (AdolCALD) has an onset between 10 and 21 years of age and occurs rarely (4–7% of X-ALD cases). Other clinical phenotypes include adrenomyeloneuropathy, which occurs in men in their 20s or older, and Addison disease.[1,2,4] Generally, exhibitionism has not been reported in X-ALD.

Magnetic resonance imaging (MRI) of the brain in AdolCALD typically shows extensive involvement of parieto-occipital areas. Occasionally, a more atypical presentation has been reported with bilateral frontal demyelization or a combination of parieto-occipital and frontal alterations.[5] Involvement of the basal ganglia has very rarely been reported in cerebral X-ALD,[6,7] while involvement of the thalamus has not previously been reported in the condition. Here, we report a young boy with AdolCALD who presented with an atypical frontal variant that had rare involvement of the basal ganglia and thalamus.

2. Case report

An 11-year-old Chinese adolescent boy was admitted to our hospital following a history of neurobehavioral symptoms and more recently, an unwillingness to eat or communicate. One year prior to hospitalization, he had been found exposing his penis to strangers and masturbating in public. Concurrently, his school teachers noticed that he presented with progressive difficulties in concentration and reasoning, hyperactivity, outbursts of aggressiveness (impulsiveness), and mild cognitive decline. He was diagnosed with exhibitionism and attention deficit hyperactivity disorder. Subsequently, the patient was initiated on Concerta (methylphenidate hydrochloride prolonged-release tablets, ALZA;

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18 mg/d), but the complaints continued to slowly progress. Two weeks prior to hospitalization, the complaints had rapidly increased, with previous behaviors accompanied by transient urinary and fecal incontinence, and an unwillingness to eat or communicate.

The patient was born to healthy non-consanguineous parents following an uncomplicated pregnancy and birth. There was no family history of genetic or psychiatric illness. Before presentation, he had been a healthy boy with normal development and growth.

Clinical examination confirmed the presence of hyperactive behavior and attention deficit. There were no other positive clinical findings. Electroencephalogram showed no abnormal findings. Magnetic resonance imaging (MRI) of the cerebrum (Fig. 1) revealed symmetrical alterations in signal intensity in bilateral frontal white matter, the basal ganglia, internal capsules (predominantly involving anterior limb and genu), and dorsal thalamus. Similar signal intensity was seen involving the genu and body of corpus, insular white matter, and pedunculus cerebri. These regions were confluent and appeared significantly hypointense on T1-weighted images, significantly hyperintense on T2-weighted-, and fluid-attenuated inversion recovery sequence images, and isointense to slightly hyperintense on diffusion-weighted images (DWI). Typical peripheral enhancement appeared after administration of gadolinium on T1-weighted images. The rim appeared to show restricted diffusion on DWI. On spectroscopy, the N-acetyl aspartate peak was decreased resulting in a decreased N-acetyl aspartate/creatine ratio. The choline peak was increased compared with that of creatine and there was a prominent lactate peak.

We observed elevated levels of adrenocorticotropic hormone (177.00 pg/mL; normal: 0–46 pg/mL), but serum cortisol levels were normal. Cerebrospinal fluid was clear and had an elevated protein level (0.75 g/L), 2 leukocytes/μL, and normal glucose level.

We conducted a gene mutation analysis with next-generation sequencing in the patient. In the patient, we detected hemizygote missense mutations of c.443A>G and p.N148S in exon 1 of the *ABCD1* gene (NM_000033). Sanger sequencing confirmed this mutation and detected similar heterozygous missense mutations of c.443A>G and p.N148S in his mother (Fig. 2). The Human Gene Mutation Database reported this mutation as the pathogenic mutation of X-ALD.[8] Therefore, the diagnosis of AdolCALD was confirmed in the patient on the basis of gene mutation analysis, brain MRI, and age of onset. The boy was not eligible for hematopoietic stem cell transplant given the advanced

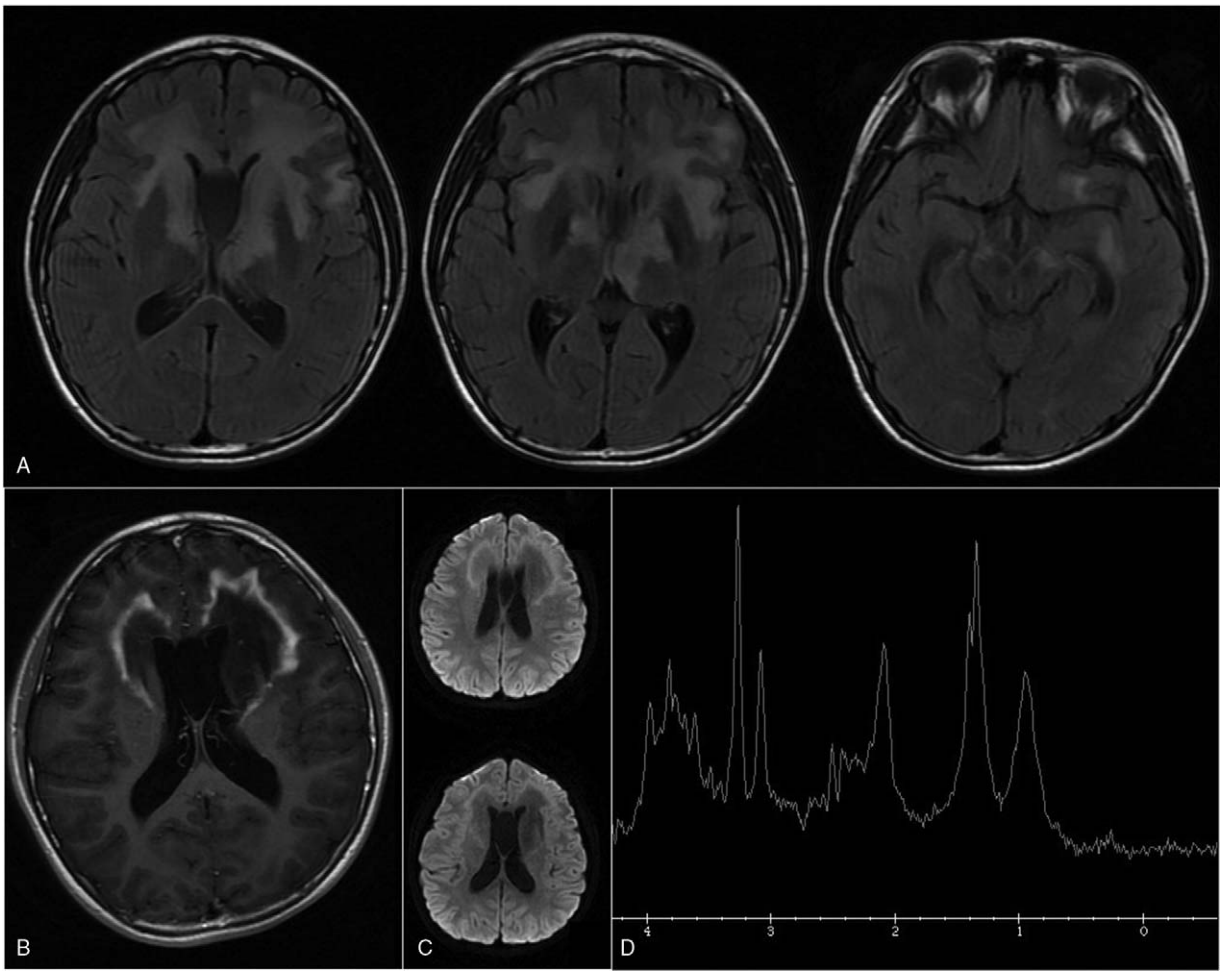

Figure 1. (A) Axial brain fluid-attenuated inversion recovery MRI showing confluent high signal intensities in bilateral frontal and insular white matter, the genu of the corpus callosum, basal ganglia, and dorsal thalami. (B) T1-axial contrast-enhanced MRI showing prominent enhancement at the periphery of the signal changes. (C) The rim appeared to show restricted diffusion on DWI. (D) Spectroscopy showed decreased NAA, increased Cho, and prominent lactate peaks. Cho = choline, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, NAA = N-acetylaspartic acid.

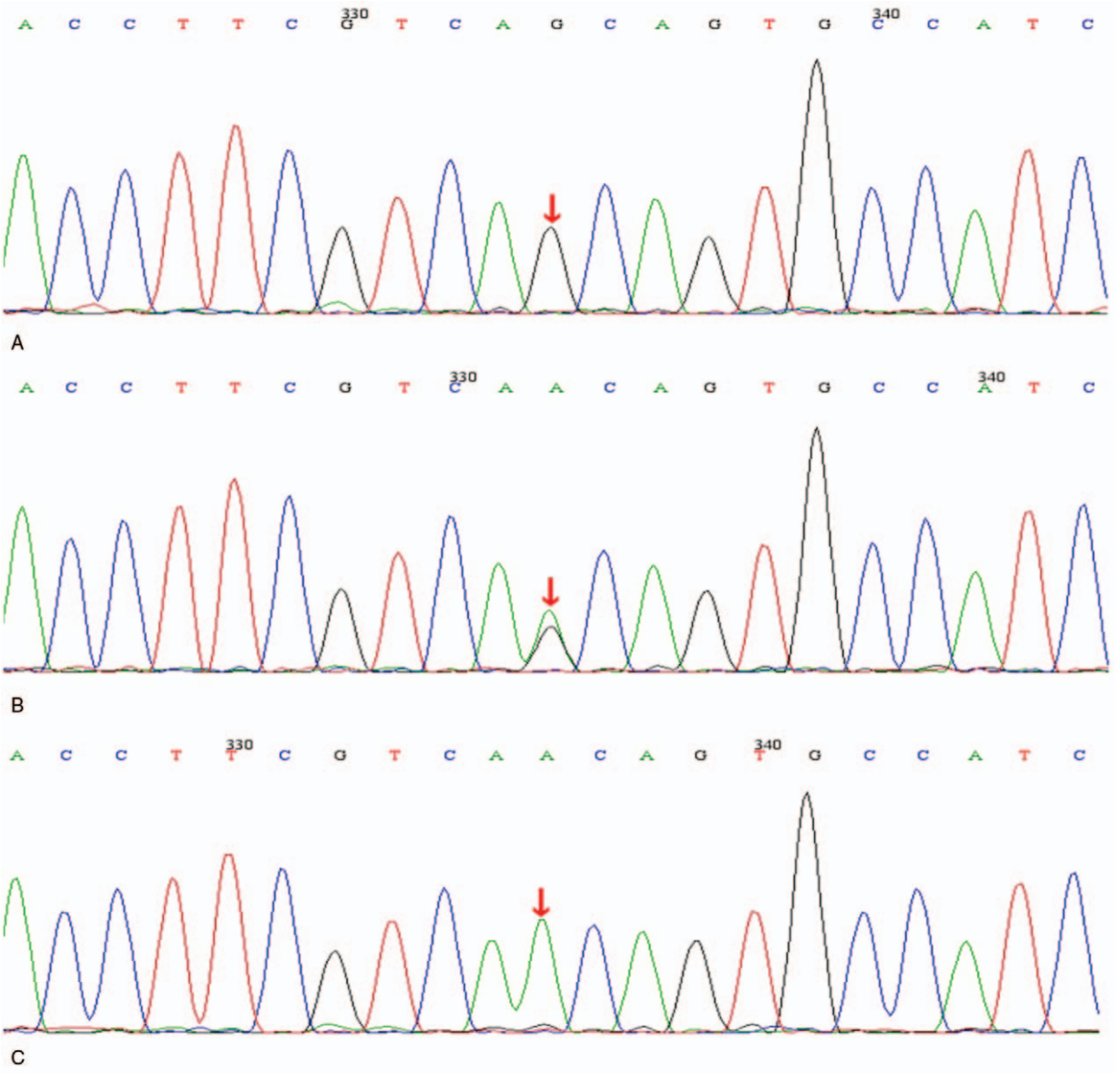

Figure 2. Sanger sequencing of the patient and his parents. (A) The patient has hemizygote missense mutations of c.443A>G and p.N148S in the *ABCD1* gene. (B) The mother has heterozygous missense mutations of c.443A>G and p.N148S. (C) No mutations were found in the father.

cerebral involvement observed on MRI. Therefore, he was discharged with hormonal replacement therapy (prednisone, 5 mg/d).

Following discharge, the patient's symptoms continued to progressively worsen. Four months after discharge, these were accompanied by generalized seizures, impaired vision, and motor function deterioration. At 10 months after discharge, the boy was in a vegetative state and he died 1 month later.

This report just reviewed previous data and did not involve any human trials, so there was no need to conduct special ethic review and ethical approval was not necessary. Informed consent was provided by the patient's mother for the publication of this case report.

3. Discussion

In the majority of reports of cerebral X-ALD, patients initially present with neurobehavioral disturbances that result in declining school performance.[1,3] Here, we present a case displaying both exhibitionism and neurobehavioral disturbances. The patient was observed exposing his penis and masturbating publicly, alongside his more usual symptoms of AdolCALD, which is a unique presentation. Such inappropriate sexual behavior is thought to derive from a lack of understanding of the feelings and changes associated with normal puberty, alongside the problems associated with social or intellectual impairment.[9] Therefore, we presume that the boy's exhibitionism may be attributed to the involvement of the frontal lobes, rather than the basal ganglia and thalamic lesion. Diagnosis is difficult when psychiatric symptoms are initially isolated without clinical somatic involvement or a family history. However, deterioration following treatment is an atypical feature that may suggest cerebral X-ALD.[10] Furthermore, brain MRI can be applied to distinguish as early as possible between psychiatric disorders and cerebral X-ALD.

The most common MRI pattern observed in cerebral X-ALD (66% of cases) reflects primary involvement of the deep white matter in the parieto-occipital lobes and in the splenium of the

corpus callosum. The second most common pattern (15%) involves the frontal lobe and genu of the corpus callosum, also known as anterior pattern disease. Other patterns may involve corticospinal or frontopontine projection fibers, primary cerebellar white matter, or a combination of parieto-occipital and frontal white matter.[5,11] The involvement of the internal capsule and basal ganglia were initially described in adrenomyeloneuropathy, which is seen mainly in adults presenting with distal axonopathy.[11] Basal ganglia involvement in cerebral X-ALD is extremely rare, and has occasionally been described in the predominantly frontal pattern of childhood cerebral X-ALD and combined frontal and occipital pattern of adult cerebral X-ALD.[6,7] To our knowledge, this is the first case reporting involvement of the thalamus in cerebral X-ALD.

Differential diagnoses identified by altered signal intensities of frontal white matter, the basal ganglia, or thalami include Alexander disease, X-ALD, and metachromatic leukodystrophy.[12] Due to neuronal involvement in the current patient, other inborn errors of metabolism and primary neuronal disorders that may cause early defects in myelination should not been disregarded.[13] However, cerebral X-ALD may be represented by a unique 3-layered pattern of predominantly white matter involvement on contrast-enhanced brain MRI. This would be characterized by an outermost zone of T2 hyperintensity corresponding to active demyelination, a middle layer with an enhanced rim corresponding to active inflammation, and a central zone with T2 hyperintensity where gliosis occurs, as seen in our case.[3,6] MR spectroscopy is another helpful technique that can provide evidence for X-ALD, with a lactate peak commonly observed in X-ALD, as seen in our case.[14] Next generation genetic sequencing can confirm the diagnosis and expedite the diagnostic process of X-ALD with atypical neuroimaging.

4. Conclusion

Our case shows that hypersexual behavior may be an initial presentation of AdolCALD. We recommend that physicians should not disregard cerebral X-ALD in patients with isolated psychiatric symptoms that show deterioration with treatment. Additionally, the basal ganglia and thalamus may be involved in the frontal variant of AdolCALD. A combination of detailed clinical evaluation, contrast-enhanced brain MRI, and next generation genetic sequencing can expedite the diagnostic process of this atypical variant of X-ALD.

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