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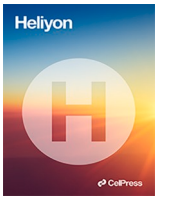

Case report

A female adult-onset X-ALD patient with pure cerebellar symptoms:a case report

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) caused by ATP-binding cassette subfamily D member 1 (*ABCD1*) gene defects is the most common inherited peroxisomal disorder.The female cerebello-brainstem dominant type in which cerebellum and brainstem are mainly involved is very rare. We report a 40-year-old female who was diagnosed as the rare disorder with magnetic resonance imaging (MRI) and genetic analysis mainly. Her initial symptoms were progressive slurred speech and writing disturbance. Her brain MRI showed obvious atrophy of brainstem and cerebellum. She did not have adrenal insufficiency. Genetic analysis showed a heterozygous missense mutation in exon 4 of the coding region of *ABCD1* (c.1252C > T, p.Arg418Trp).This is the first report of this particular mutation being associated with the cerebello-brainstem dominant phenotype of X-ALD, as well as the first description of this X-ALD variant in a (heterozygous) female patient.X-ALD should be considered in young and middle-aged patients with slow-progressing ataxia and dysarthria.

1. Introduction

X-linked adrenoleukodystrophy (X-ALD), the most common inherited peroxisomal disorder, is caused by ATP-binding cassette subfamily D member 1 (*ABCD1*) gene defects [1]. Peroxisomal dysfunction results in accumulation of saturated very long-chain fatty acids (VLCFA) mainly in adrenal cortex, testes and nervous system [1]. The most commom phenotypes of X-ALD include Childhood cerebral ALD and adrenomyeloneuropathy (AMN), which approximately account for 70–80 % of the patients [2,3].The rare phenotype of spinocerebellar or olivo-ponto-cerebellar form, which predominantly affect cerebellum and brainstem, only account for 1–2% X-ALD [4,5]. Mutation in exon1, 2, 8 or exon 9 of the *ABCD1* gene have been reported in these unusual phenotypic variants of X-ALD [3,5–9]. Here, we report an adult-onset X-ALD female patient presenting with pure cerebellar symptoms, derived from a heterozygous mutation at nucleotide position c.1252 of exon 4 in the *ABCD1* gene.

2. Case report

A 40-year-old female was hospitalized with progressive slurred speech and writing disturbance for 6 months. She was born in a non-

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consanguineous family, and her family members has no similar medical history. Her developmental milestones were normal in areas of motor, language and cognitive skills. During the course of the disease, she had no hearing loss, visual impairment, gait ataxia, weakness, seizure, mental disorder, urinary, bowel or sensory abnormality. In fact, her daily life had not been affected obviously.

On neurological examination, she was alert, cooperative and well nourished. Advanced cognitive function was normal. Her speech was dysarthric. There was no horizontal nystagmus and ophthalmoplegia. Muscle strength and tone of bilateral upper and lower limbs was normal. Deep tendon reflexes were normal. Her sensation to pinprick, light touch and proprioception were normal. There was dysmetria on bilateral finger-to-nose and heel-to-knee tests. Romberg's tests were negative. The pyramidal signs were not present.

The following laboratory tests including full blood count, liver function, renal function, electrolytes, humoral immune testing, antinuclear antibodies spectrum, anti-neutrophil cytoplasmic antibody, thyroid function, folic acid, vitaminB12, antistreptolysin O, rheumatoid factor, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), lactic acid, cytomegalovirus and herpes serologies, serum immunofixation electrophoresis, ceruloplasmin, sexual hormone, plasma renin, serum aldosterone, plasma cortisol, adrenocorticotropic hormone (ACTH), catecholamine and routine cytological and biochemical assessment of cerebrofluid, autoimmune encephalitis antibodies and pareneoplastic antibodies were unremarkable.

Brain magnetic resonance imaging (MRI) revealed hyperintensities on T2 weighted images and FLAIR sequences indicating demyelinating white matter lesions in bilateral cerebellar hemisphere, right middle cerebellar peduncles and pons (Fig. 1). No contrast enhancement was noted in these lesions after gadolinium injection. Obvious atrophy of brainstem and cerebellum was also observed. There was no lesions demonstrated by MRI in supratentorial cerebral white matter.

With informed consent, the patient received whole genome sequencing sampled from venous blood using next-generation sequencing technology. A heterozygous missense variant was identified at the nucleotide 1252 of the coding region in exon 4 of *ABCD1*(c.1252C > T/p.Arg418Trp/chrX:153001826) (Fig. 2A). The mutation led to a substitution of the amino acid 418 from arginine to tryptophan. This variant was classified as pathogenic according to The American college of Medical Genetics and Genomics (ACMG) [10]. Subsequently, genetic testing of the patient' son was conducted by Sanger sequencing method, and the same *ABCD1* gene mutation was detected (Fig. 2B), which is a hemizygousvariation. The patient's son is only 5 years old and has no symptoms currently. Unfortunately, he did not undergo an MRI examination.

Based on clinical manifestations and relevant examinations, the patient was finally diagnosed with X-ALD. The patient did not approve determination of the levels of the fatty acid C26:0 in the blood, which is also helpful for diagnosis of X-ALD. There is no specific therapeutic intervention available for this variant of X-ALD. The patient underwent speech and writing rehabilitation treatment during hospitalization, and the patient's symptoms did not significantly improve. After 1 year of follow-up, the patient's speech and writing symptoms did not worsen.

3. Discussion

The patient in this report presented with pure cerebellar symptoms including progressive dysarthria and writing disturbance. MRI

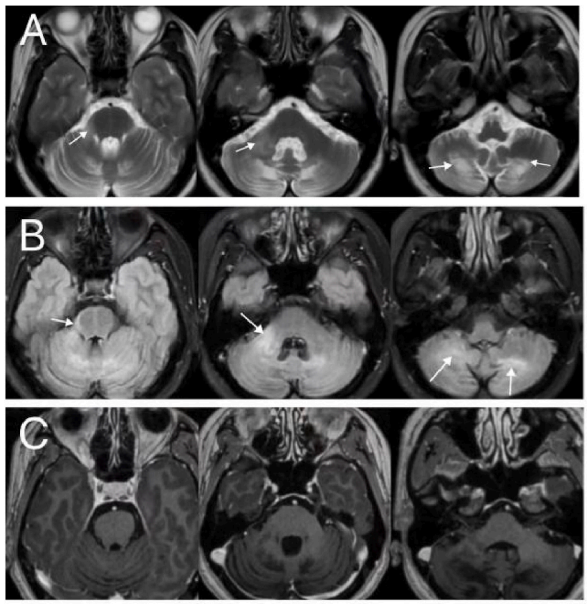

Fig. 1. MRI of 40-year-old female patient with cerebello-brainstem dominant X-ALD
(A) T2-weighted imaging (T2WI)and (B) Fluid attenuated inversion recovery (FLAIR) of the brain showed hyperintensities in pons, right middle cerebellar peduncles, and bilateral cerebellar hemispheres (white arrows). (C)No contrast enhancement was noted in these lesions after gadolinium injection.

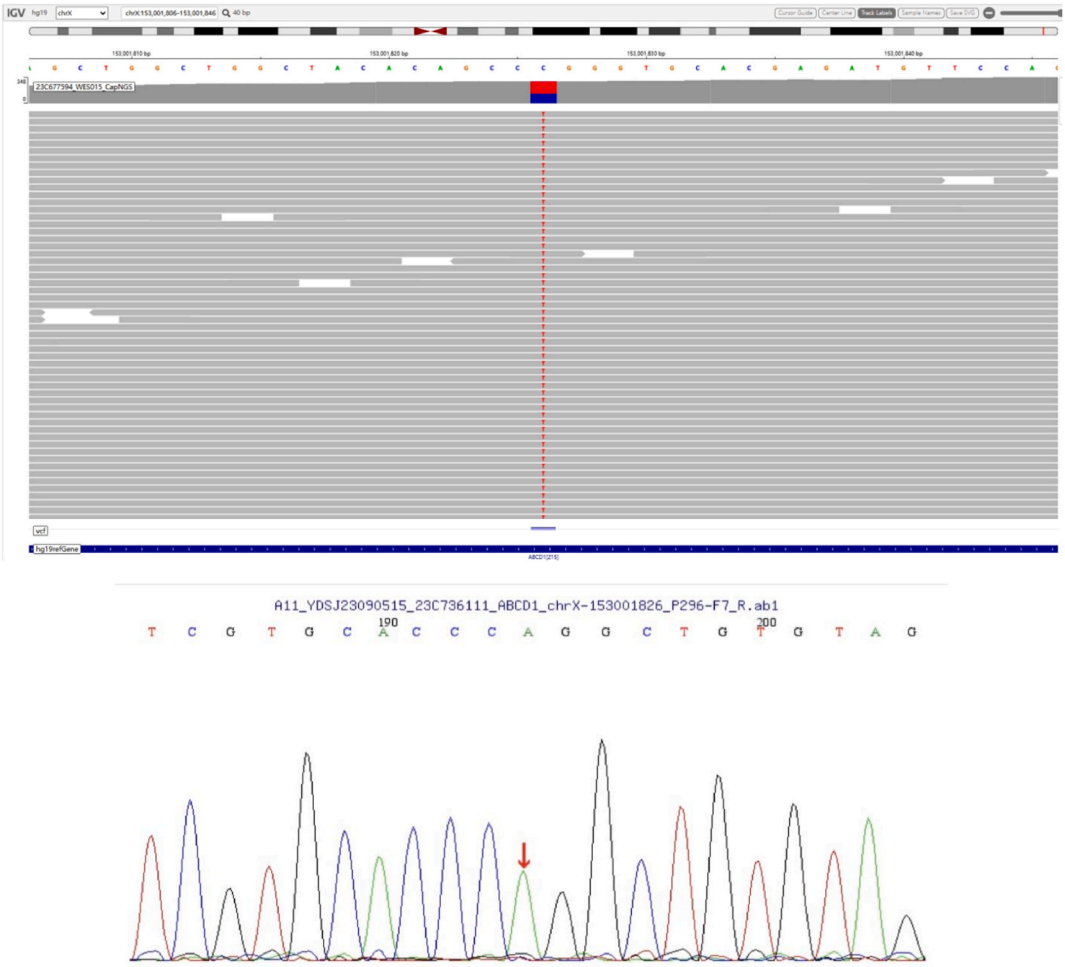

Fig. 2. Fig. 2A The *ABCD1* gene testing result of the patient. Whole genome sequencing indicated a heterozygous mutation of *ABCD1 gene* (c.1252C > T).Fig. 2B The *ABCD1* gene testing result of the patient's son. c.1252C > T mutation on exon4 of the *ABCD1* gene was identified in the patient' son by Sanger sequencing. Arrow indicates position of the novel mutation.

showed that only cerebellum and brainstem were selectively involved. Obvious atrophy of cerebellum and brainstem can be observed. Many potential causes for the lesions including metabolic, immune, infectious, neoplastic, endocrinous and toxic factors had been excluded according to the medical history and a series of laboratory tests. It was reasonable to focus on degenerative and hereditary diseases. Multiple system atrophy (MSA) was not considered due to the absence of symptoms and signs of pyramidal, extrapyramidal and autonomic nervous system in this patient. After whole genome sequencing, a mutation was found at the nucleotide 1252 of the coding region in exon 4 of *ABCD1*, which resulted in a substitution of the amino acid 418 from arginine to tryptophan. The patient was diagnosed ultimately as X-ALD. Regrettably, we did not obtain the concentration of VLCFA because the patient declined it.

X-ALD is caused by the defects of the *ABCD1* gene, which is located in Xq28. About 95 % of patients are males, while females are heterozygous carriers of the gene mutation. The total frenquency of X-ALD is estimated at approximately 1/17000 [11]. It was very rare that the X-ALD female patient presented with only cerebellum and brainstem involvement in adulthood, which was similar to clinical manifestation of spinocerebellar ataxia or olivopontocerebellar atrophy (OPCA). There was no reports previously regarding female patients with heterozygous mutation in the cerebello-brainstem form of ALD. Whereas cerebral ALD and adrenal insufficiency are extremely rare in female patients, 88 % of heterozygous X-ALD carriers were reported to show late-onset AMN-like symptoms and signs of myelopathy and neuropathy after 60 years of age [12]. Most reported patients either have suffered Addison's disease before occurrence of cerebellar symptoms or developed pyramidal, extrapyramidal and autonomic symptoms and cognitive or psychiatric dysfunction with the progress of the disease [6,9,13,14]. Considering that the duration of the symptomatic disease in this patient at diagnosis was only 6 months, it is possible that symptoms related to cerebrum, spinal cord and adrenal gland damage will occur in the future. However, the patient's symptoms had not worsened (or improved) at 1 year follow-up. So, apparently, 18 months after onset of symptoms other disease manifestations had not developed. Kotaro Ogaki et al. reported a patient presenting with cerebellar ataxia, weakness and autonomic dysfunction, who was diagnosed as possible multiple system atrophy (MSA) in later stage disease before death [5]. Retrospectively, cerebello-brainstem dominant form of X-ALD was considered in this patient demonstrated by

neuropathological studies and p.R163G mutation in *ABCD1* gene [5]. Similar clinical features of present variant of X-ALD remind us that X-ALD should be considered as important differential diagnosis of MSA or OPCA.

Brain MRI of most reported spinocerebellar or olivopontocerebellar variant of adult X-ALD showed white matter demyelinating lesions and/or atrophy in cerebrum, brainstem and cerebellum [3,6–8,15–17]. The frontopontine or corticospinal projection fibers from the medulla to internal capsule and cerebellar white matter were more easily be involved in these adult patients. Spinal cord can also be involved indicated by hyperintensity in posterior columns and lateral funiculi with the disease progress [14]. In very few reports, MRI abnormalities appearing predominantly in brainstem and cerebellum has been noted [3 7 8 16 17]. In the present case, white matter demyelinating lesions and atrophy was confined to brainstem and cerebellum. It cannot be excluded that the lesions extend to other cerebral areas during the whole disease. Notably, the brain MRI in one case showed no T2 hyperintensities or atrophy in the brainstem and cerebellum, although the patient was diagnosed as cerebello-brainstem dominant form of X-ALD [5]. There is some limitation in brain MRI helping diagnosis of atypical variants in adult X-ALD.

So far, 1227 unique ABCD1 variants have been registered in ALD mutation database (https://adrenoleukodystrophy.info), including some that are not pathogenic (955 listed as pathogenic or likely pathogenic). There were mutations in exon1, 2, 8 or exon 9 of the *ABCD1* gene that have been reported in the rare phenotype of spinocerebellar or olivo-ponto-cerebellar form of X-ALD [3 59]. These mutations usually are located in the transmembrane or ATP-binding cassette domain of *ABCD1* gene. In this study, a missense mutation in exon 4 was found in the adult-onset X-ALD female patient with pure cerebellar symptoms. The same mutation has also been reported in previous reports, but the patients presented with asymptomatic to AMN-like symptoms [18,19]. There is no definite correlation between genotype and phenotype. Although the frequencies is 1–2% globally, this rare phenotype has higher incidence in some Asia countries than in other parts of the world, especially in Japan (about 9 %) [20]. Maybe there are some other modulators including genetic, epigenetic or environmental factors contributing to this apparent geographic or ethnic bias. To unveil the relevance, abundant reports needs to be accumulated in fields of age at onset, initial symptom and symptom progression.

Currently, effective treatments for the X-ALD disease are limited. The available treatments of these X-ALD patients includes steroid replacement, Lorenzo's oil and stem cell therapy. Clinical efficacy of Lorenzo's oil has been found to be unsatisfactory. Haematopoietic stem cell transplantation has been demonstrated to arrest the inflammatory demyelination in the brain white matter also of cerebello-brainstem form of ALD, providing a novel therapy for the disease in future [21].

In conclusion, we described a female X-ALD patient only presenting with unusual cerebellar ataxia. This is the first report that the rare cerebello-brainstem dominant type of X-ALD was caused by heterozygous mutation in exon 4 of *ABCD1*(c.1252C > T, p. Arg418Trp). Although there is no effective treatment, early identification of the rare disease will be helpful in future therapy.

4. Ethics statement

We have obtained written informed consent from the patient for publication of the data. The study was approved by the Research Ethics Board of the First affiliated hospital of Chongqing medical university.

5. Data availability statement

Data included in article/supp. material/referenced in article.

Funding statement

None.

CRediT authorship contribution statement

Wenjing Qi: Writing – original draft, Software, Resources, Data curation. **Du Cao:** Writing – review & editing, Resources, Methodology. **Lei Hao:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Xiuming Guo:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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