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Research article

Central precocious puberty in a boy with X-linked adrenoleukodystrophy caused by a novel *ABCD1* mutation

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is a rare genetic disorder caused by pathogenic variants in the *ABCD1* gene. The symptoms include primary adrenal insufficiency (PAI), progressive spinal cord disease, inflammatory demyelinating cerebral disease, and primary hypogonadism. It is exceptionally rare that pediatric PAI is accompanied by central precocious puberty (CPP). The purpose of this study was to better understand the diversity of clinical manifestations of X-ALD and to identify the *ABCD1* gene mutation in a case of a boy with X-ALD accompanied by CPP. We collected clinical, laboratory and imaging data, and used whole-exome sequencing (WES) analysis to evaluate the pathogenicity of the variant. We also predicted the potential deleterious effects of the novel mutation using Mutation Taster and generated three-dimensional protein structures using Swiss-Model and PyMOL Viewer software. The patient presented with PAI accompanied by CPP. Adrenal gland CT revealed adrenal hypoplasia. Gonadotropin-releasing hormone stimulation tests revealed CPP. WES revealed a novel variant (c.1376dup) in the *ABCD1* gene, which resulted in a reading frameshift and a premature termination codon (p.Leu461ProfsTer95). Sanger sequencing confirmed that the variant was inherited from his heterozygous mother. Mutation Taster predicted that the variant could be harmful. The overall three-dimensional structures of the mutant wild-type proteins were visually distinct. Our results shed light on additional aspects of X-ALD. The premature activation of the hypothalamic-pituitary-gonadal axis may possibly be related to the pathogenic *ABCD1* gene mutation.

1. Introduction

X-Linked adrenoleukodystrophy (X-ALD) is an X-linked recessive hereditary peroxisome disease with incomplete penetrance. It predominantly affects males with an incidence of about 1:20,000 [1]. Newborn screening for X-ALD in US revealed higher incidence of 1:10,500 [2]. Unfortunately, there is a lack of epidemiological investigations of X-ALD in China [3]. The condition is caused by

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mutations in the adenosine triphosphate (ATP) binding cassette subfamily D member 1 (*ABCD1*) gene with complex clinical manifestations. It usually manifests as primary adrenal insufficiency (PAI) or myeloneuropathy often associated with cerebral ALD [4]. Boys between 0 and 10 years had the highest cumulative percentage of PAI (46.8%) [5]. The disease can occur at any age and can be classified into seven clinical subtypes: childhood cerebral ALD (CCALD), adolescent cerebral ALD, adult cerebral ALD (ACALD), adrenomyeloneuropathy (AMN), adrenal insufficiency-only (Addison's disease), and asymptomatic or presymptomatic types [6]. X-ALD patients typically present with hypogonadism [7,8]. Up to now, only one case of central precocious puberty (CPP) has been reported in patients with X-ALD [9].

In this study, we identified a novel frameshift mutation of *ABCD1* gene in a boy with X-ALD accompanied by CPP. This finding contributes to a more comprehensive understanding of the wide spectrum of clinical manifestations of X-ALD.

2. Subjects and methods

2.1. Subjects

The boy was 9 years old and 6 months old. He admitted to the hospital due to progressive skin pigmentation for more than 9 years. The child had skin pigmentation since birth, which was progressively aggravated, especially his lips. Dark fingernails, toes, and nail beds were found two years ago. Skin pigmentation became obvious after a skin rash on his back. In addition to the above symptoms, the child had no other symptoms of adrenal deficiency such as nausea, vomiting, fatigue after activity, etc. He was a school-age child with average academic performance. He was hospitalized for more than 20 days due to cyanosis of the lips after birth. He was the second child born by vaginal delivery after a full-term pregnancy, with a birth weight of 3000 g. He had no medical history of central nervous system infection, trauma, or surgery. His parents and sister were healthy. He came to our hospital for a definitive diagnosis.

2.2. Clinical evaluation

Serum levels of adrenocorticotropic hormone (ACTH), cortisol (COR), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T), prolactin (PRL), 17-hydroxyprogesterone (17-OHP), free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH) levels were measured by an automated chemiluminescent immunoassay system (Advia Centaur, Siemens, Healthcare Diagnostics, USA). Serum very long chain fatty acids (VLCFAs) levels as C22:0, C24:0, C26:0, C24:0/C22:0, and C26:0/C22:0 were analyzed by gas chromatography/mass spectrometry (GC/MS) method. Serum COR concentrations were measured at 0, 30, 60 min after ACTH stimulation test (cosyntropin, 0.25 mg/m^2, intravenous). The peak COR level$>$18 μg/dl was considered normal. Serum LH and FSH levels were determined at 0, 30, 60, 90min after the gonadotropin-releasing hormone (GnRH) stimulation test (gonarelin, 2.5 μg/kg, maximum 100 μg, intravenous).

Bone age was measured by radiograph of the left hand and wrist and determined according to Greulich and Pyle's method. Brain and Pituitary magnetic resonance imaging (MRI) were performed using a 3.0 T scanner (Siemens, Erlangen, Germany) in the sagittal and coronal planes on T1-and T2-weighted imaging. Adrenal gland was scanned with 64-slice spiral computed tomography (CT) (Siemens, Erlangen, Germany).

The diagnostic criteria for the CPP were as follows: 1) Testicular enlargement$\geq$4 ml before the age of 9 years. The median age at puberty onset in Chinese boys is 10.55 years [10]; 2) An abnormally high annual growth rate; 3) Bone age was at least one year greater than the chronological age; 4) A peak LH level$\geq$5 IU/l and peak LH/FSH$\geq$0.6 after GnRH stimulation indicated Hypothalamic-Pituitary-Gonadal (HPG) axis was activated [11].

2.3. Whole-exome and Sanger sequencing

Whole-exome sequencing (WES) was performed on DNA from peripheral blood using the Genomic DNA Extraction Kit (Sangon Biotech). After fragmenting the genomic DNA, ligating the pairedend adaptor, amplification and purification, the Roche NimbleGenSeqCap EZ MedExome Library was used to capture the human exons. The captured DNA was eluted, amplified, purified, and sequenced by a high-throughput sequencer on the Illumina HiSeq sequencing platform. Sequenced data was compared to the hg19 human reference genome sequence (NM_000033.4). NextGene V2.3.4 software was used to identify genetic variants and obtain the coverage range and average sequencing depth of the target regions. The mean coverage of the targeted area was 241.04-fold. 99.47% of the targeted regions had 20reads or more. In addition, variants were annotated by NextGene V2.3.4. Annotation includes the conservation of nucleotide base and amino acid, biological function prediction, frequency of normal population (1000 Genomes Project, ESP6500, ExAc, dbSNP database). Variants were compared with data from Online Mendelian Inheritance in Man (OMIM), The Human Gene Mutation Database (HGMD) and ClinVar. The identified mutation site was verified by Sanger sequencing in the patient and his parents (Fig. 2A). Interpretation of sequence variants followed standards and guidelines of the American College of Medical Genetics and Genomics (ACMG).

2.4. Bioinformatics analysis

Mutation Taster (http://www.mutationtaster.org/) was performed to predict the potential deleterious effects of the novel frameshift mutation. Swiss-Model software (https://swissmodel.expasy.org/interactive) was used to make three-dimensional protein structure models [12]. PyMOL 2.5 Viewer software was used to visualize and analyze the impact of variants on the protein structure.

3. Results

3.1. Clinical characterization

The boy presented with skin pigmentation and precocious puberty. His height was 149.5 cm (P90-97), weight was 42 kg (P90-97), and body mass index was 19.7 kg/m^2. On physical examination, skin pigmentation was apparent in his body skin, especially in lips, fingernails, toes, and nail beds (Fig. 1A). Hyperpigmented dark spots were present on his back and buttocks. It was worth noting that he presented with penis of 5 cm in length, bilateral testicular volume of 8 ml, and no pubic hair. Neurological examination revealed no abnormalities.

Baseline levels of adrenal hormones, sex hormones, thyroid function tests, and VLCFAs are shown in Table 1. GnRH stimulation tests reported that the peak level of LH was 20.58 U/l and the peak stimulated LH/FSH ratio was 2.89, suggesting CPP. At 8am, the COR level was 3.82 μg/dl and ACTH level was >1250 pg/ml. At 4pm, the COR level was 3.43 μg/dl and ACTH level was >1250 pg/ml. At 0am, the COR level was 3.39 μg/dl and ACTH level was 633 pg/ml. ACTH stimulation test showed that COR levels at 0, 30, and 60 min were 3.82, 3.13, and 3.61 μg/dl, respectively. The liver function, lipids, serum tumor markers, virus detection, and routine blood examination were normal.

His bone age was 11 years. An initial MRI of the brain and pituitary had no obvious abnormality. CT scan revealed bilateral slender adrenal (Fig. 1B). After 6 months, follow-up brain MRI showed that there were small slightly high signal intensities scattered on the left fronto-parietal white matter in FLAIR sequences. Following a multidisciplinary expert discussion, the result of the MRI was non-specific white matter changes that were not related to X-ALD disease.

3.2. Genomic analysis and protein structure prediction

WES revealed a novel frameshift variant (c.1376dup) in exon 4 of the *ABCD1* gene in the patient. The c.1376dup variant would cause the substitution of leucine (Leu) with Proline (Pro) in codon 461, which resulted in a reading frameshift and a premature termination at codon 95 (p.Leu461ProfsTer95). The frameshift mutation abolished the ATP binding domain of *ABCD1*, which certainly resulting in loss of function. Sanger sequencing confirmed that the variant was inherited from his heterozygous mother. His father and elder sister were negative for the variant (Fig. 2B). This mutation is likely pathogenic according to the ACMG: PVS1+PM2_Supporting. The *ABCD1* gene mutation is transmitted through X-linked inheritance. Therefore, for this type of inheritance, hemizygous mutations cause disease.

Mutation Taster predicted that the variant was possibly harmful (Fig. 3A). The overall three-dimensional structures of the wild-type and mutant proteins were visually distinct. Protein structures starting from amino acid position 461 (including α-helices, β-sheets, and loop region) were changed (Fig. 3B).

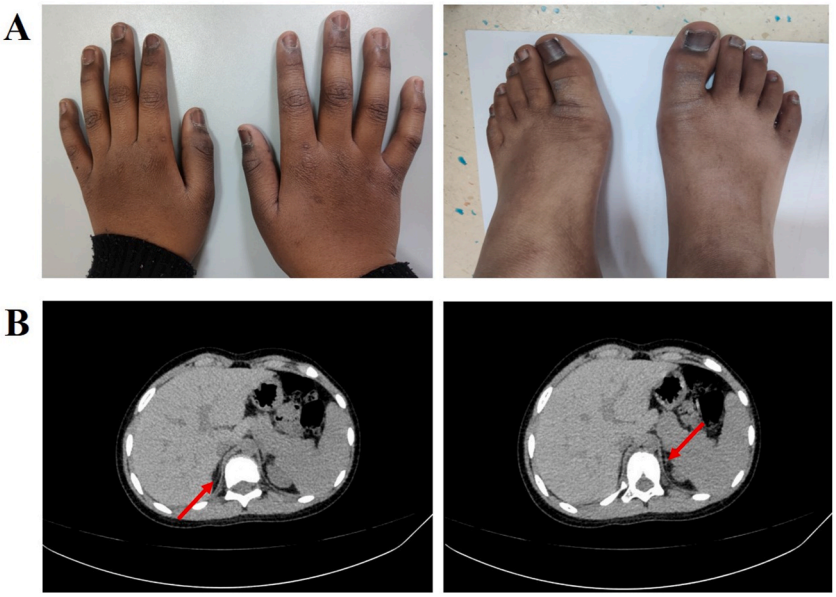

Fig. 1. Clinical manifestations and CT features of the proband. (A) Cutaneous hyperpigmentation was presented both on hands and feet. (B) Adrenal gland CT revealed adrenal hypoplasia. Red arrows showed slender adrenal gland on both sides. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

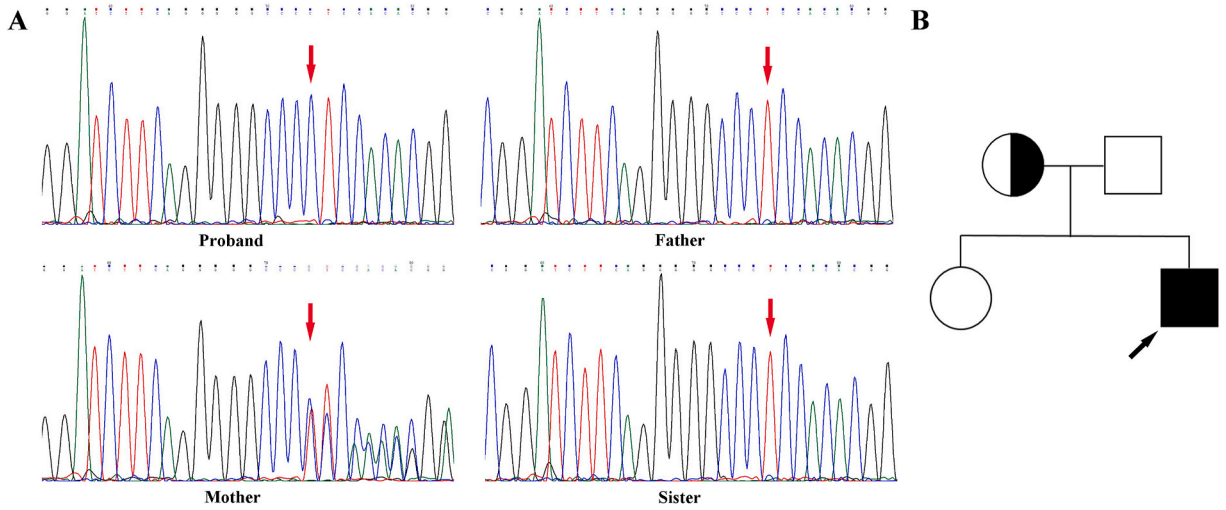

Fig. 2. *ABCD1* variants and pedigree of the proband. (A) *ABCD1* gene mutation analysis of family. (B) The pedigree of this family.

Table 1
Laboratory parameters in the proband.

Parameters	Value	Reference
COR 8:00 a.m. (μg/dl)	3.82	5–25
ACTH 8:00 a.m. (pg/ml)	>1250	0–46
FSH (IU/l)	1.92	0.20–4.52
LH (IU/l)	1.30	0.37–2.64
E2 (pg/ml)	<11.8	0–39.8
T (ng/dl)	48.42	3–301
PRL (ng/ml)	8.72	2.1–17.7
17-OHP (nmol/l)	0.91	0–5.0
FT3 (pmol/l)	6.78	3.5–6.5
FT4 (pmol/l)	14.86	11.5–22.7
TSH (mIU/l)	3.495	0.51–4.94
C22:0 (nmol/ml)	71.0	≤96.3
C24:0 (nmol/ml)	91.7	≤91.4
C26:0 (nmol/ml)	4.28	≤1.30
C24:0/C22:0	1.29	≤1.39
C26:0/C22:0	0.060	≤0.023

3.3. Literature review

To better understand the clinical manifestations of patients with X-ALD accompanied by CPP. The data from previously reported cases presenting the same clinical features were collected from the literature. Only two cases were reported, including the current case. The clinical and laboratory parameters are shown in Table 2.

4. Discussion

X-ALD has been identified as peroxisomal disease caused by mutations in the *ABCD1* gene. The *ABCD1* gene is located on Xq28, consists of 10 exons, contains 745 amino acids, and encodes the peroxisomal transmembrane ALD protein (ALDP) [1]. So far, more than 1,300 *ABCD1* pathogenic and likely pathogenic variants have been reported in the ALD Variant Database (https://adrenoleukodystrophy.info/mutations-and-variants-in-abcd1). Among them, the highest mutation rate was observed in exon 1, accounting for approximately 41.0% (563/1371), while the mutation rate in exon 4 was 5.4% (74/1371). There were various forms of *ABCD1* gene mutations. The missense mutations were the most common type (58%, 801/1371), followed by frameshift mutations (23%, 316/1371). Mutations in the *ABCD1* gene can lead to unstable expression of ALDP, causing defects in peroxisome β-oxidation, and resulting in VLCFAs metabolic disorders [13]. The disorders lead to abnormal accumulation of VLCFAs in cells and tissues, particularly in the white matter of the brain, spinal cord, adrenal gland, and testis. This accumulation results in the appearance of central nervous system disorders, peripheral nerve myelin disorders, adrenal insufficiency, and sexual dysfunction [4]. In this study, our patient exhibited high levels of VLCFAs. A novel frameshift mutation in exon 4 of *ABCD1* (c.1376dup) was found. The c.1376dup variant cause the substitution of Leu with Pro in codon 461, which results in a reading frameshift and a premature termination at codon

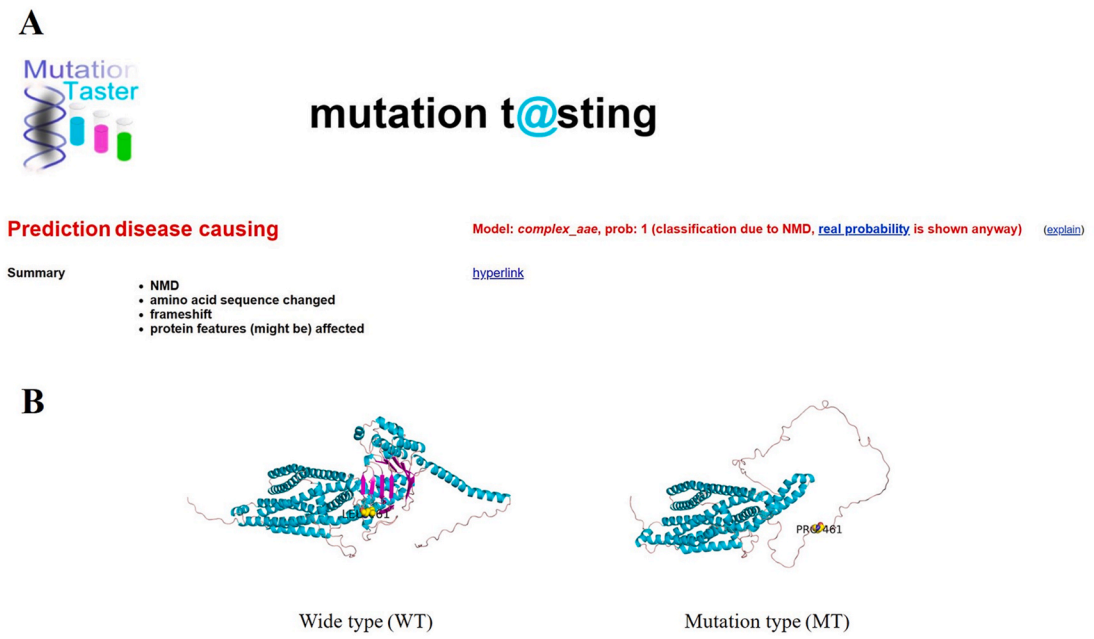

Fig. 3. *ABCD1* damaging mutation and protein prediction of three-dimensional structure. (A) Mutation Taster predicted that the variant was possibly harmful. NMD: nonsense-mediated mRNA decay. (B) The overall three-dimensional structures of the wild-type and mutant proteins were visually distinct. Purple lines indicated the region of amino acids altered by the frameshift mutation of *ABCD1* (c.1376dup). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Clinical and laboratory parameters in two cases of boys with *ABCD1* Mutation presenting with X-ALD accompanied by CPP.

Parameters	P 1	P 2
Sex	M	M
Family history	No	Yes
Age at diagnosis, years	9.5	6.6
Bone age, years	11	8
Height, cm (SDS)	145.9 (1.31)	124.5 (0.39)
Weight, kg (SDS)	42.0 (1.41)	23.5 (0.04)
Body mass index, kg/m2 (SDS)	19.7 (1.19)	15.16 (−0.21)
Testicular volume (ml)	8	5–6
Penile length, cm	5	6
ACTH (pg/ml)	>1250	>2000
C22:0	No change	No change
C24:0	↑	↑
C26:0	↑	↑
C24:0/C22:0	No change	↑
C26:0/C22:0	↑	↑
Mutation	c.1376dup	c.1826A > G
Exon	4	8

95. To the best of our knowledge, this mutation has not been previously reported. The sequence of ATP-binding cassette (ABC) domain contains Walker A (aa. 507–515) and B (aa. 626–630) motifs that are involved in the binding and hydrolysis of ATP to the translocation of solutes across cell membranes [14]. The amino acid sequence of Walker A motif is changed and the region of Walker B motif is truncated due to a frameshift mutation in the *ABCD1* gene. Therefore, the mutation of the *ABCD1* gene results in the loss of ALDP function.

The clinical manifestations of ALD vary greatly with high genetic heterogeneity. There is no correlation between *ABCD1* genotypes. The same phenotype may be caused by mutations of different gene location, different phenotypes may appear at the same locus in the same family [3], and the phenotypes are different at different stages of the disease [15]. There is no discernible relationship between the extent of ALDP function loss and the severity of the disease. The distribution of clinical phenotype in X-ALD patients varies between children and adults. Cerebral ALD mostly occurs in children and AMN in adults [15]. The phenotype of patients with X-ALD is significantly influenced by other genetic factors, the existence of modifier genes, and environmental factors [16]. In the present study,

the proband only showed skin pigmentation without any other symptoms of adrenal deficiency, such as nausea and vomiting. The proband's mother was a heterozygous carrier of the mutation without any symptoms.

Kemp et al. reported that approximately 75% of adult males with X-ALD experience clinical or subclinical gonadal dysfunction [15]. It is exceptionally rare that pediatric PAI is accompanied by CPP. Several reported gene mutations that lead to PAI complicated with CPP include DAX1 [17], CYP11B1 [18], and NNT [19]. The most common was DAX1 gene. Only one case of a boy from China with *ABCD1* gene mutation presenting with PAI accompanied by CPP has been reported [9]. Now we reported the 2nd case. The cause of precocious puberty in children with X-ALD is still unclear. It may be related to the following factors. Firstly, overproduction of ACTH secondary to adrenal insufficiency may cause precocious puberty. High ACTH levels act on testicular Leydig cells through melanocortin receptor 1 (MC1R), increasing testosterone secretion [17]. Secondly, it was reported that ALDP was also strongly expressed in a subpopulation of secretory cells in the anterior pituitary [20]. From this it can be inferred that deficiency of the ALDP in X-ALD patients resulted in disturbances of the HPG axis [9]. Thirdly, the hypothalamic-releasing thyrotropin-releasing hormone (TRH) may cause an overlap increase in the secretion of luteinizing hormone-releasing hormone (LHRH) or the pituitary gonadotropin due to a "drift" phenomenon [21]. Additionally, environmental factors and modifier genes may play a role [16]. Further basic research is needed to elucidate the exact pathogenesis.

The treatment for adrenal insufficiency involves selecting either glucocorticoid or mineralocorticoid supplementation based on the specific condition. Hematopoietic stem cell transplantation (HSCT) is currently the preferred treatment for cerebral ALD. When treated early, the 5-year survival rate can reach 94%. Gene therapy could be an option, but more safety data is needed. The main treatment for AMN is supportive, aimed at alleviating symptoms and relieving dysfunction [22]. In addition, Lorenzo oil and lovastatin have been proven to reduce plasma VLCFAs levels, but the former lacks data to prevent or slow down the disease's progress, while the latter has not shown significant results in subsequent studies [22]. Our patient was given hydrocortisone to make his cortisol levels normal. The predicted adult height according to the bone age was still acceptable. He did not receive Gonadotropin-Releasing Hormone Agonist (GnRHa) treatment for CPP. Early-onset Addison's disease may gradually develop into neuropsychiatric symptoms in a time-dependent way. The majority of male X-ALD patients diagnosed with adrenal insufficiency eventually develop cerebral ALD and/or myeloneuropathy, accompanied by a poor prognosis [4]. Therefore, early diagnosis plays a crucial role in managing this condition effectively.

5. Conclusion

In conclusion, the phenotype of X-ALD exhibits significant variability, with combined CPP being a rare occurrence. Genetic testing plays a crucial role in enhancing diagnostic accuracy and facilitating the early diagnosis and treatment of X-ALD patients. However, it is important to note that our study had a limited sample size. Therefore, a larger study would be required to validate our findings. Nonetheless, our report contributes to a better understanding of the diverse clinical manifestations observed in patients with X-ALD. Further research is needed to investigate the specific mechanism underlying the coexistence of PAI and CPP.

Ethics statement

The study was approved by the Ethics Committee of the Linyi People's Hospital (approval number: YX200087). Written informed consent was obtained from the patient's parents.

Data availability statement

The data of the presented case in our study has not been deposited into a publicly available repository. The data will be available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Chaoyue Zhao: Writing – original draft, Methodology, Investigation, Data curation. **Hanhong Zhu:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Jie Wang:** Visualization, Software, Methodology. **Wenlong Liu:** Resources, Investigation, Formal analysis. **Yongzhen Xue:** Supervision, Investigation. **Yanyan Hu:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

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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