X-LINKED ADRENOLEUKODYSTROPHY CHARACTERIZED BY ADRENOCORTICAL INSUFFICIENCY: A CASE REPORT WITH 16-YEAR FOLLOW-UP

Long-Jiang Zhang*, MD; Xiang-Lei Li, MM; Zhe Su, MD; Xia Liu, MM; Qin Zhang, MD; Hong-Tao Qi, MM
Department of Endocrinology, Shenzhen Children's Hospital, Shenzhen 518000, Guangdong, China

ABSTRACT

Introduction: *X-linked adrenoleukodystrophy (X-ALD) is the most common genetic peroxisomal disease. Its clinical manifestations are diverse, and its progression highly varies. In the present study, an X-ALD patient was followed-up for 16 years to investigate the clinical manifestations and disease progression.*

Case presentation: *One X-ALD patient was regularly followed-up and re-examined. The patient developed the disease at four years old, which mainly manifested as primary adrenocortical insufficiency with decreased level of serum cortisol and increased serum cortiocotropin, accompanied by hypothyroidism with increased serum thyrotropin level. Furthermore, the level of serum very-long-chain fatty acids were elevated (C26, 1.72 nmol/ml; C24/C22, 1.57 nmol/ml; C26/C22, 0.038 nmol/ml). The genetic test revealed that there was a mutation in exon 1 of the ABCD1 gene, c.565C>T(p.R189W). Follow-up observations were performed for 16 years. At present, the patient is 20 years old, without neurological abnormalities. Hydrocortisone and levothyroxine tablets are supplemented daily to maintain normal thyroid function. The auxiliary hair development was at stage A1, while pubic hair development was at stage PH4. The bilateral testes are 15 ml in size. The levels of androstenedione (<0.3 ng/ml) and dehydroepiandrosterone sulfate (24.50 μg/dl) were low.*

Conclusion: *X-ALD affects multiple systems in the human body, and may be mainly characterized by primary adrenocortical insufficiency. Furthermore, this may also affect the production of androgen in the adrenal cortex, together with the thyroid function.*

Keywords: *X-linked adrenoleukodystrophy, ABCD1 gene, adrenocortical insufficiency, hypothyroidism.*

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Introduction

X-linked adrenoleukodystrophy (X-ALD) is the most common genetic peroxisomal disease that belongs to X-linked recessive hereditary diseases. For this disease, the ALD protein is dysfunctional due to the mutation of its encoding gene Xq28 ATP-binding cassette subfamily D member 1 (ABCD1), leading to the disorder of peroxisome-mediated β-oxidation of very-long-chain fatty acid (VLCFA). This induces the VLCFA to be deposited in blood and tissues, especially in brain tissues, peripheral nerves, adrenal gland and testes, and induces the progressive demyelination of the central nervous system, which may be complicated by adrenal atrophy or dysplasia[1, 2]. Its clinical manifestations vary, which range from severe brain type in children or adults to asymptomatic types. Furthermore, approximately 20% of female patients may have relatively mild neurological manifestations. The proportion of patients characterized by merely primary adrenocortical insufficiency is the smallest, but most patients present with adrenocortical insufficiency. However, the disease only affects the function of adrenal glucocorticoids in the early stage, and in most patients, it eventually affects mineralocorticoid function of[3-5]. The present study presents a case report of a patient with X-ALD mainly characterized by adrenocortical dysfunction complicated by hypothyroidism and insufficient adrenal androgen secretion, which was caused by ABCD1 gene mutation, together with the results of the 16-year follow-up.

Case presentation

The male patient is presently 20 years old. The onset of the disease was at approximately four years old. The main manifestations were fatigue, poor appetite and gradual deepening of skin color. At six years old, the patient was diagnosed as "primary adrenocortical insufficiency and elevated serum thyroid stimulating hormone (TSH)" in a hospital. The patient orally took hydrocortisone and levothyroxine for four years, but irregularly. The patient continued to feel weak and had a poor appetite, and there was no significant improvement in skin color. At 11 years old (in May 2010), the patient visited our hospital for treatment, who was generally introverted and disliked speaking.

The results of the physical examination revealed the following:

• height (Ht), 143.7 cm (-0.7 sd); weight (Wt), 28.5 kg;

• body mass index (BMI), 13.8 kg/m2; P, 80 beats/min; blood pressure (Bp), 110/70 mmHg;

• lucid mental status;

• dark skin;

• obvious pigmentations with gingiva, areola, wrinkles on the finger joints and perineum;

• 15 ml in size of bilateral testes;

• penis with 4 × 1.5 cm in size; both pubic hair and auxiliary hair were at Tanner stage 1.

The test of thyroid function indicated the following:

• serum thyrotropin (thyroid stimulating hormone [TSH]) was 32.66 μTU/ml (normal range: 0.51-4.94 μTU/ml);

• cortisol at 8 am was 0.69 μg/dl (normal range: 4.3-22.4 μg/dl);

• serum cortiocotropin at 8 am (adrenocorticotropic hormone [ACTH]) was 1,980 pg/ml (normal range: 7.2-63.6 pg/ml).

The results of the serum VLCFA test revealed the following: hexacosanoic acid (C26) was 1.72 nmol/ml (normal range: <1.30 nmol/ml); C24/C22 was 1.57 (normal range: <1.39); and C26/C22 was 0.038 (normal range: <0.023). The genetic test revealed that there was a mutation in exon 1 of the ABCD1 gene, c.565C>T (p.R189W). It was verified by Sanger family testing that the patient's father was normal at this site, but the patient's mother has the same site mutation (Figure 1). By questioning the family history, no similar situation in the family was found. When the patient was a newborn, the screening revealed that the thyroid function at birth was normal.

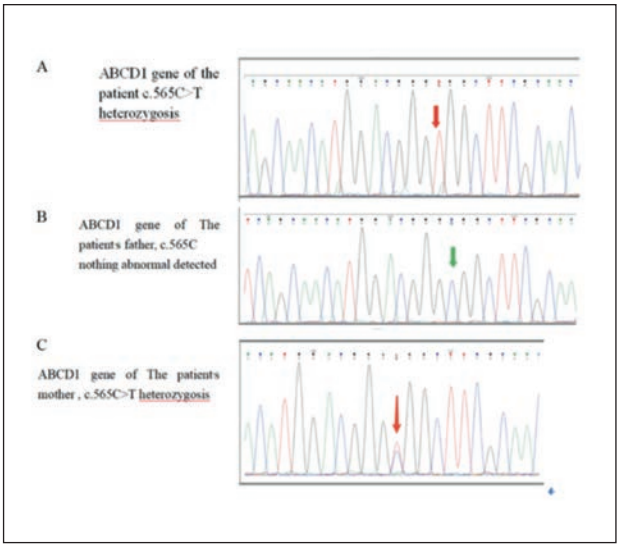

Figure 1: Gene sequencing of the patient and his parents using the Sanger method. The red arrow indicates the mutation site of Exon-1 in ABCD1, c.565C>T(p.R189W), revealing that the patient and his mother have the same mutation.

Treatment and follow-up

The patient orally took hydrocortisone (10-12 mg/m2.day) twice a day, and orally took levothyroxine tablets.

The patient and the patient's parents were instructed to undergo regular re-examinations. Since the patient failed to orally take hydrocortisone with regularity, according to the doctor's advice, and often missed or stopped taking hydrocortisone, adrenal crises occurred twice during the follow-up observations (the manifestations included abdominal pain, vomiting, fever, poor spirits and fatigue; the examination conducted in local hospitals revealed that the levels of serum sodium decreased, and the condition improved after providing an intravenous drip of hydrocortisone).

Except for introversion, poor speech and fatigue, no hearing and visual impairment, behavioral and neurological abnormalities were found. The patient could normally participate in school sports, and the academic performance was at the general level. Multiple detections revealed that the blood electrolyte, blood lipid, liver and kidney function were normal.

Thyroid function fluctuated due to the irregularity of oral use of levothyroxine. The thyroid-associated antibodies were negative, blood cortisol remained low, and ACTH remained elevated. The re-examination by head MRI was performed in September 2018, and no significant abnormal imaging changes were found (Figure 2).

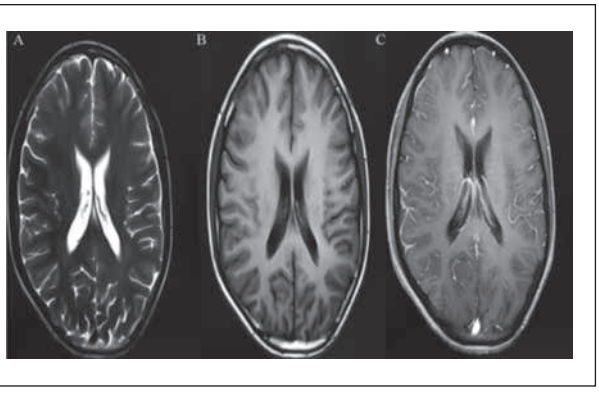

Figure 2: The MRI of the brain tissue of the patient revealed no abnormalities (September 16, 2018).

At present, the patient is 176 cm in height and 56 kg in body weight, with a blood pressure of 120/76 mmHg. However, the whole body skin remained dark, and the pigmentations at the gingiva and areola, and wrinkles of the finger joints and perineum were obvious. Furthermore, there was no swelling of the thyroid gland at palpation. The neurological examination results were normal, and muscle strength and muscle tension of the limbs are normal, together with normal visual acuity and hearing. The development of bilateral auxiliary hair was at stage A1, while the development of pubic hair was at stage PH4. The bilateral testes were 15 ml in size, and the penis was 8 × 2.5 cm in size (Figure 3).

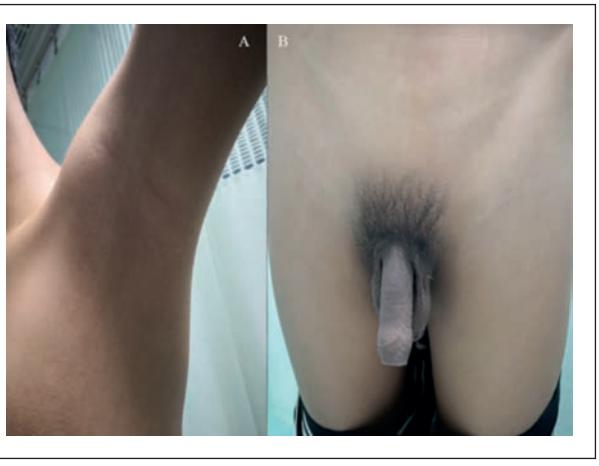

Figure 3: Secondary gender characteristics: hircus, stage A1; pubes, stage PH4.

Other related tests at present were as follows: serum LH level was 5.21 U/L (normal range: 1.24-8.62 U/L), serum FSH level was 3.03 U/L (normal range: 1.27-12.96 U/L), the testosterone level was 18.81 nmol/L (normal range: 6.06-27.06 nmol/L), estradiol level was 43.00 pg/ml (normal range: 20-75 pg/ml), serum androstendione level was <0.3 ng/ml (normal range: 3.2-6.8 ng/ml), dehydroepiandrosterone sulfate level was 24.50 μg/dl (normal range: 156-293 μg/dl), serum 17α-hydroxyprogesterone level was 0.95 ng/ml (normal range: <2.32 ng/ml, radioimmunoassay), and serum progesterone level was 0.12 ng/ml (normal range: 0.1-0.84 ng/ml). Results of the serum VLCFAs detection: C22 was 46.1 nmol/ml (normal range: <96.3 nmol/ml), C24 was 72.3 nmol/ml (normal range: <91.4 nmol/ml), C26 was 1.76 nmol/ml (normal range: <1.30 nmol/ml), C24/C22 was 1.56 (normal range: <1.39), and C26/C22 was 0.038 (normal range: <0.023). The patient controlled the fat intake only through diet, especially the intake of saturated fatty acids, without orally taking Lorenzos oil. The follow-up observation revealed that there were no significant changes in the content of serum VLCFAs.

Discussion and conclusion

The incidence of X-ALD ranges from 1/20,000 to 1/30,000, and the difference among countries in the world is not significant[6]. However, the clinical manifestations are quite diverse. Particularly in the male patients, it may manifest as the most severe cerebral type or asymptomatic type, while in the female patients, this may lead to mild neurological impairments. Mare Engelen et al.[7] divided X-ALD into four categories, according to these clinical manifestations: cerebral type: cerebral adrenoleukodystrophy (CALD, including pediatric cerebral type, adolescent cerebral type and adult cerebral type), adrenomyeloneuropathy (AMN, including AMN combined with brain injuries and AMN without brain injuries), simple Addison type, and female patients. Among these, AMN and pediatric cerebral type have the highest incidence, accounting for 40-46% and 31-35%, respectively. The proportion of simple Addison type is low.

A Japanese scholar[8] reported that one of 11 children with ALD had the simple Addison type. The onset age of patients is usually lower than two years old, and often develops before 7.5 years old[9]. The incidence of adrenocortical insufficiency gradually decreases with age. Patients often present with fatigue, unexplained vomiting, anorexia or high-salt intake, as well as extremely dark skin (the common sites including gingiva, palmprint, wrinkles of the joints, areola and perineum), hypoglycemia, hyponatremia and hyperkalemia by biochemical tests, decreased serum cortisol level, and significantly increased ACTH level. In addition, it would be years or decades before the presentations of neurological

symptoms. Laureti reported that[4] five of 14 patients with primary adrenocortical hypofunction were diagnosed as adrenal protein malnutrition.

The patient in the present study has been followed up for more than 16 years. At present, the function of corticosteroids has not been affected. Thus, regular follow-up is necessary. It remains unclear whether the secretion of adrenal male steroid hormones is affected in this type. The patient in the present study is 20 years old, without auxiliary hair, and the development of pubic hair is at stage PH4, and with low serum levels of dehydroepiandrosterone sulfate and androstenedione. However, it remains to be further confirmed whether these suggests that the production of adrenal androgen is affected. In addition, it remains unknown whether thyroid dysfunction is associated with the disease in the present patient. The investigators failed to confirm this, because the patient refused to undergo thyroid biopsy.

Although patients with X-ALD were divided into the above-mentioned categories according to the clinical manifestations, the clinical manifestations were not static. The time of progress from adrenocortical hypofunction to neurological dysfunction is highly diverse, which has been reported to range from half a year to up to 32 years[10]. Some studies had verified that the simple Addison type has a higher risk for neurological impairment, and most patients with simple Addison type would progress into the AMN type in their middle age. Therefore, for asymptomatic patients or patients with merely adrenocortical dysfunction and a family history, close observation and regular follow-ups should be carried out. The present patient developed the disease at four years old, and was characterized as simple adrenocortical hypofunction. To date, no neurological impairment was found in this patient. The head MRI revealed no abnormalities. However, the possibility of developing into the other types could not be excluded.

X-ALD is caused by the mutation of the ABCD1 gene. The ABCD1 gene is located on Xq28, consists of 10 exons, and encodes a messenger RNA with a length of 4.3 kb, and adrenoleukodystrophy protein (ALDP), which consists of 745 amino acids. At present, more than 1,300 different mutations have been detected in patients with X-ALD. In the present case, gene testing confirmed the haplozygotic variant c.565 C>T (p.R189W) at exon 1 of the ABCD1 gene. Sanger sequencing confirmed that the mutation at this site originated from the mother of the patient, while the site of the patient's father was found to be normal. Lachtermacher et al. reported that the same mutation in this site was characterized by simple adrenocortical hypofunction[11]. However, most studies revealed that there was no correlation between the genotypes and clinical manifestations in X-ALDs. Although the mutation of the ABCD1 gene was confirmed, patients may have significantly different neurological and neuropathological characteristics[12]. This suggests that the clinical manifestations of ALD patients may be affected by the modification of other genes or environmental factors. Asheuer M considered that[13] the expression of GB1 might be correlated with the severity of the disease. In addition, head trauma or stroke may be the triggering factors for the onset of cerebral ALD.

At present, there is no reliable method or experimental data to predict the progression of X-ALD. Asymptomatic patients and patients with simple adrenocortical dysfunction should be closely followed up, in order to detect the neurological impairments as early as possible, and provide timely interventions.

The limitation of the study was that the relationship between thyroid dysfunction and the X-ALD in the present case could not be determined due to the lack of thyroid biopsy. Furthermore, the patient did not regularly take the medicine and often missed taking the medicine. Hence, the ACTH remained high. In further treatments, patients should be reminded to regularly take their medication and pay close attention to the changes in thyroid function.

References

1) Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. Biochim Biophys Acta 2012;1822:1465-1474.
2) Douar AM, Mosser J, Sarde CO, Lopez J, Mandel JL, Aubourg P. X-linked adrenoleukodystrophy gene: identification of a candidate gene by positional cloning. Biomed Pharmacother 1994;48:215-218.
3) Moser HW, Moser AB, Naidu S, Bergin A. Clinical aspects of adrenoleukodystrophy and adrenomyeloneuropathy. Dev Neurosci 1991;13:254-261.
4) Laureti S, Casucci G, Santeusanio F, Angeletti G, Aubourg P, Brunetti P. X-linked adrenoleukodystrophy is a frequent cause of idiopathic Addison's disease in young adult male patients. J Clin Endocrinol Metab 1996;81:470-474.

5) Nascimento M, Rodrigues N, Espada F, Fonseca M. Adrenoleukodystrophy: a forgotten diagnosis in children with primary Addison's disease. BMJ Case Rep 2012;2012. pii: bcr2012006308.
6) Wiesinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. Appl Clin Genet 2015;8:109-121.
7) Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJ, Aubourg P, Poll-The BT. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis 2012;7:51.
8) Miyoshi Y, Sakai N, Hamada Y, Tachibana M, Hasegawa Y, Kiyohara Y, Yamada H, Murakami M, Kondou H, Kimura-Ohba S, Mine J, Sato T, Kamio N, Ueda H, Suzuki Y, Shiomi M, Ohta H, Shimozawa N, Ozono K. Clinical aspects and adrenal functions in eleven Japanese children with X-linked adrenoleukodystrophy. Endocr J 2010;57:965-972.
9) Jorge P, Quelhas D, Oliveira P, Pinto R, Nogueira A. X-linked adrenoleukodystrophy in patients with idiopathic Addison disease. Eur J Pediatr 1994;153(8):594-597.
10) Moser HW, Bergin A, Naidu S, Ladenson PW. Adrenoleukodystrophy. Endocrinol Metab Clin North Am 1991;20:297-318.
11) Lachtermacher MB, Seuánez HN, Moser AB, Moser HW, Smith KD. Determination of 30 X-linked adrenoleukodystrophy mutations, including 15 not previously described. Hum Mutat 2000;15:348-353.
12) Mehrpour M, Gohari F, Dizaji MZ, Ahani A, Malicdan MC, Behnam B. An ABCD1 Mutation (c.253dupC) Caused Diverse Phenotypes of Adrenoleukodystrophy in an Iranian Consanguineous Pedigree. J Mol Genet Med 2016;10. pii: 222.
13) Asheuer M, Bieche I, Laurendeau I, Moser A, Hainque B, Vidaud M, Aubourg P. Decreased expression of ABCD4 and BG1 genes early in the pathogenesis of X-linked adrenoleukodystrophy. Hum Mol Genet 2005;14:1293-1303.

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Corresponding Author:
Long-Jiang Zhang
Department of Endocrinology, Shenzhen Children's Hospital, No. 7019 Yitian Road, Futian District, Shenzhen 518000, Guangdong, China
Email: zhanglj_med2059@163.com
(China)