ORIGINAL RESEARCH PAPER

Pathology

X-LINKED ADRENOLEUKODYSTROPHY: AN OVERLOOKED DIAGNOSIS IN ADDISON'S DISEASE

KEY WORDS: X-linked adrenoleukodystrophy; Addison's disease; tuberculosis; ABCD1

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal fatty acid beta-oxidation disorder. ABCD1 located at Xq28 is the causative gene. In males, X-ALD is considered to be a frequent cause of Addison's disease (AD). We report the case of an 11-year-old boy who presented with AD and cutaneous hyperpigmentation. He had been diagnosed with pulmonary tuberculosis at eight months. At the age of seven years, he was diagnosed with AD. MRI revealed megalencephaly and butterfly-shaped hyperintensities in the frontal region. This prompted us to consider the possibility of X-ALD. Sequencing of ABCD1 revealed a de novo missense mutation (c.1201C>T; p.Arg401Trp). One year later, after suffering two recurrent episodes of grand-mal seizures followed by loss of vision and speech, the patient became stuporous and remained in this state until death at the age of 13. Identification of X-ALD in children during early stages would give them an opportunity for better treatment/management options.

INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal fatty acid beta-oxidation disorder characterized by the accumulation of very long-chain fatty acids (VLCFA) in tissues throughout the body, with the highest levels in the white matter and axons of central nervous system, the adrenal cortex, and the Leydig cells of testis. The prevalence of this fatal progressive neurodegenerative disorder is estimated as 1:20,000 to 1:50,000.

The clinical manifestation of X-ALD initially consists of adrenal disorders, gait disturbances, behavior abnormalities, poor scholastic performance, poor memory, and difficulties in hearing, vision, speech and writing. Generalized hypertension, loss of cognitive and motor functions, convulsions and dysphagia has been observed in the advanced stages. In males, X-ALD is considered to be a frequent cause of Addison's disease (AD).1 An underlying X-ALD condition in patients presenting with symptoms of AD often goes undiagnosed or are diagnosed late, only when they develop behavioral abnormalities and show poor scholastic performance, which in turn compromises patient management.

X-ALD diagnosis is generally confirmed by examining the plasma levels of VLCFA and/or brain magnetic resonance imaging (MRI). ABCD1 located at Xq28 is the single causative gene for X-ALD which is inherited in an X-linked recessive pattern. The frequency of de novo mutations in the index case is estimated to be around 4%.2

CASE REPORT

Informed consent to publish this report was obtained from the patient's father. An 11-year-old boy born of non-consanguineous marriage presented with AD, cutaneous hyperpigmentation and sparse hair growth. During the past one year he had developed restlessness and hyperactivity. He exhibited poor scholastic performance, concentration and memory.

The boy was born at term and generalized cutaneous hyperpigmentation was noticed at birth. Early development was uneventful with normal development of motor, cognitive, linguistic and social skill milestones. He was diagnosed with pulmonary tuberculosis (TB) at the age of eight months and undergone treatment for six months. At the age of seven years, he was diagnosed with AD. He had been undergoing treatment [hisone (hydrocortisone), floricot (fludrocortisone), shelcal] for AD when he presented at our hospital at the age of 11 years. Non-contrast computed tomography (NCCT) showed symmetrical hypodense areas in the periventricular and subcortical white matter in bilateral frontal regions, with bilaterally symmetrical calcifications adjacent to frontal horns of lateral ventricles. Magnetic resonance imaging (MRI) revealed megalencephaly and butterfly-shaped hyperintensities in the frontal region. This prompted us to consider the possibility of X-ALD in this patient. Even though determination of plasma VLCFA is the first line of diagnosis for X-ALD, this could not be done due to lack of facility. The entire coding region (10 exons) of the causative gene ABCD1 was then screened for mutations by Sanger Sequencing. A missense mutation (c.1201C>T; p.Arg401Trp) was observed in exon 3. As per The ALD Mutation Database (https://adrenoleukodystrophy.info/mutations-and-variants-in-abcd1), this is classified as a pathogenic mutation. Based on the results of NCCT, MRI and ABCD1 sequencing, the patient was diagnosed with X-ALD. His mother's evaluation was not consistent with carrier status suggesting a de novo mutation. The patient was prescribed Lorenzo's oil, gamma linolenic acid, hydrocortisone, mineralocorticoids, anticonvulsants, atypical antipsychotics, nootropics and multivitamin tablets. One year later, after

suffering two recurrent episodes of grand-mal seizures followed by loss of vision and speech, the patient became stuporous and remained in this state until death at the age of 13.

DISCUSSION

This is a typical case of X-ALD. Brain structural abnormalities revealed by NCCT and MRI, and a de novo missense mutation (c.1201C>T; p.Arg401Trp) in ABCD1 gene confirmed the diagnosis. During the first presentation of this patient in our hospital, neurological symptoms associated with X-ALD had already set in.

AD in young males could be suggestive of X-ALD prior to neurologic manifestations. AD, with a prevalence rate of 1 in 100,000, is classically seen with cutaneous and mucosal hyperpigmentations.3 AD in young males could be suggestive of X-ALD prior to neurologic manifestations. In developed countries, about 75–80% of AD is caused by autoimmune destruction of the adrenal cortex. In the developing countries however, AD is widely associated with TB.4 Intriguingly, our patient had been diagnosed with pulmonary TB at the age of eight months. Therefore, the index of suspicion for X-ALD had been very low initially.

Early detection of X-ALD significantly improves the chances of treatment success. Hematopoietic stem cell transplant, if performed at an early stage, is a promising strategy to ameliorate the neurological sequelae associated with X-ALD.5

Declarations of interest

None

REFERENCES

1. Lauretti 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; 81:470-4.
2. Wang Y, Busin R, Reeves C, et al. X-linked adrenoleukodystrophy: ABCD1 de novo mutations and mosaicism. Mol Genet Metab. 2011; 104:160-6.
3. Lanza A, Heulfe I, Perillo L, et al. Oral manifestation as a sign of Addison's disease: a brief reappraisal. Open Dermatol J. 2009; 3:3-6.
4. Soedarso MA, Nugroho KH, Meira Dewi KA. A case report: Addison disease caused by adrenal tuberculosis. Urol Case Rep. 2018; 20:12-4.
5. Mahmood A, Raymond GV, Dubey P, et al. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: A comparison study. Lancet Neurol. 2007; 6:687-92.