Case Report
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An Incidentally Identified Sporadic Case with Adrenoleukodystrophy with the *ABCD1* Mutation

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Adrenoleukodystrophy (ALD) is an X-linked disorder which has diverse constellation of clinical pictures, ranging from the severe childhood cerebral form to adrenocortical insufficiency without neurological manifestations. This disorder is caused by the mutations in the *ABCD1* gene encoding the adrenoleukodystrophy protein (ALDP), a transporter in the peroxisome membrane. ALD in most cases is inherited from one parent. Here, we report an incidentally identified sporadic case with ALD after traffic accident. He had adrenocortical insufficiency as well as abnormal findings in brain image. Genetic testing of *ABCD1* gene revealed a previously reported mutation. With the description of clinical features of ALD in this patient, we discussed the difficulty in determining an appropriate therapeutic option for ALD patients with minimal neurological manifestation.

Key words: Adrenoleukodystrophy, *ABCD1*

Introduction

Adrenoleukodystrophy (ALD, OMIM 300100) is an X-linked (XL) disorder that characterized by degenerative changes of white matter of central nervous system (CNS) and adrenal cortical insufficiency. The genetic defect responsible for ALD has been located on Xq28, the terminal segment of the long arm of X chromosome, the *ABCD1* gene.[1)] This gene encodes the peroxisome membrane bound adrenoleukodystrophy protein (ALDP), and the deficiency of ALDP leads to the accumulation of saturated very long chain fatty acids (VLCFA) with number of carbon atoms more than 22 in peroxisome which subsequently causes demyelination in CNS white matter, adrenocortical insufficiency and hypogonadism.[1-3)] XL-ALD is one of the very rare inborn metabolic disorder with the estimated incidence of 1 per 40,000 births. The clinical phenotypes of XL-ALD are variable, including childhood cerebral ALD, adolescent and adult cerebral ALD, adrenomyeloneuropathy (AMN), and Addison's disease only. In addition, some patients are identified even in their presymptomatic periods.[1-3)] In this report, we described a Korean boy with XL-ALD who was incidentally found after a car accident at his pubertal age, but manifested characteristic brain finding as well as adrenal insufficiency.

Case Report

The case is the second baby of non-consanguineous Korean parents. He was born after 40 weeks of gestation with birth weight of 2.9 kg without perinatal problems. His developmental mile stones had been normal. He experienced a car accident with loss of cons-

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ciousness at 12 years of age. Emergent brain magnetic resonance imaging (MRI) was done, which revealed bilateral symmetric high signal intensity on the white matter of both parieto-occipital lobes, including corpus callosum splenium in T2 weighted image (Fig. 1A). He recovered his consciousness immediately after the accident. He was transferred to our hospital for further evaluation. His weight was 36.8kg (10^{th}-25^{th} percentile), height 149.7cm (50 th percentile), and BMI 16.4 kg/m^2 (10^{th} percentile). His blood pressure was 104/53 mmHg and heart rate 88 rpm, respiratory rate 20/min, and body temperature 36.5℃. Hyperpigmentation was noted on his whole body area. He had not presented vomiting, fatigue, dehydration symptom. His mental status was alert. His pupils were isocoric with prompt light reflexes. Response to pain, position, vibration, and temperature were intact on both upper and lower extremities. However, left knee jerk and ankle jerk were increased with positive Banbinski sign on the same side. Other neurologic symptoms such as dysarthria or hand tremor were not noted. Serum sodium and potassium levels were 140 mmol/L (135-145 mmol/L) and 3.9 mmol/L (3.5-5.1 mmol/L), respectively. His blood cortisol level 5.7 ug/dL (normal range, 2.3-11.9 ug/dL) but adrenocorticotropic hormone level (ACTH) was remarkably high at 2,250 pg/mL (7.2-63 pg/mL). The plasma levels of VLCFA were also increased; C26 was 2.54 μmol/L (0-1.3 μmol/L), C24/C22 ratio was 1.40 (0-1.39 μmol/L), and C26/C22 ratio was 0.070 (0-0.023 μmol/L). Korean Education Research Institute-Wechsler Intelligence Scale for Children (KEDI-WISC) was done to evaluate his intelligence. His Full Scale IQ (FSIQ) was 86 (low average), Verbal IQ was 96 (average), Performance IQ was 78 (borderline), and Social intelligence was 106 (average). The results of electroencephalogram and brain auditory evoked potential test were normal. For a genetic diagnosis of XL-ALD, a total of ten exons and their exon-intron boundaries of the *ABCD1* gene were analyzed using genomic DNA from his peripheral leukocytes. He carries a splicing mutation, c.1780+1G>A (IVS7^{+1}G>A), which is previously reported in a patient with childhood cerebral type of ALD.[2] None of his family or relatives had suffered from ALD. Family member screening was done for his mother and older sister, both of whom do not carry the mutation in their peripheral leukocytes. Steroid replacement therapy was started with hydrocortisone (10 mg/m^2/day) and after 2 months, his ACTH level was decreased to 32.2 pg/mL. For hematopoietic stem cell transplantation (HSCT), human leukocyte antigen (HLA) was typed between him and his sister, which were not matched. Instead, an unrelated donor with matched HLA types was found. However, his parents refused to give HSCT to their son due to bone marrow transplantation risks and complications, despite our strong recommendation. At the follow-up evaluation at 13 year of age, brain MRI showed no interval change (Fig. 1B) and his cognitive function was still borderline of normal range (FSIQ=76, Verbal IQ=96, Performance IQ=73, Social intelligence = 95).

Discussion

The first XL-ALD case was described by Haberfeld and Spieler in 1910.[3] There are at least six distinct types ranging in decreasing order of severity from childhood cerebral ALD, adolescent and adult cerebral ALD, AMN, Addison's disease only, presymptomatic patients.[3] Our patient was childhood ALD. The most common clinical picture is a degenerative neurologic disorder appearing in childhood or adolescence and progressing to dementia and behavioral changes, intellectual deterioration, impaired vision,

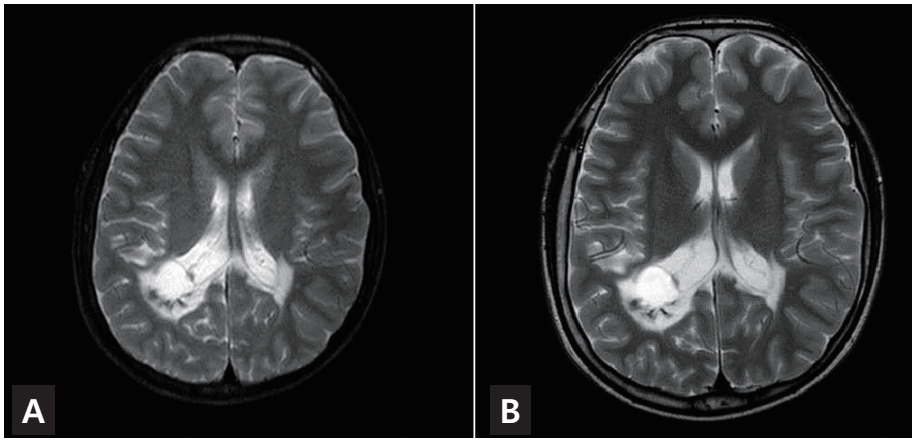

Fig. 1. T2-weighted magnetic image (MRI). (A) It shows bilateral symmetrical high signal intensities on the white matter of both parieto-occipital lobes, including corpus callosum splenium at 12 years of age. (B) No interval change was noted on white matter abnormality at 13 years of age compared with that of past MRI (A) at 12 years of age.

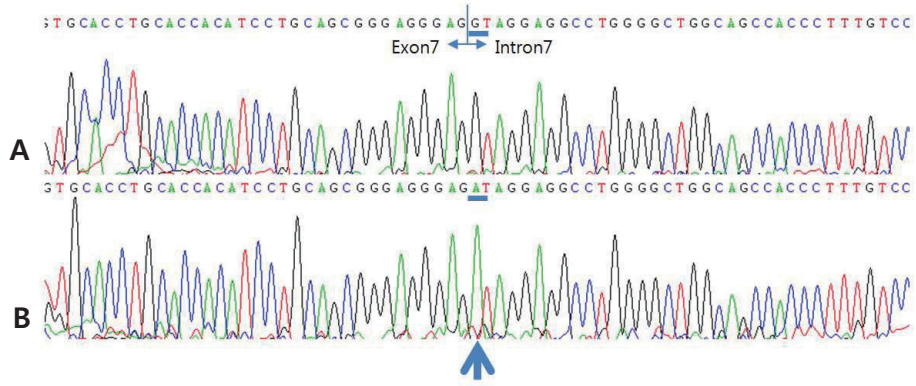

Fig. 2. The partial sequences of the *ABCD1* gene. (A) The electrogram is for normal control. c.1780+1G is located on the exon 7- intron 7 boundary. (B) The electrogram for the patient indicates the mutation, c.1780+1G>A (IVS7+1 G>A). The patient is a hemizygote for the mutation.

impaired hearing, gait abnormality, seizure and limb weakness.[4] Many patients have evidence of adrenal insufficiency at the time of neurologic presentation, but it may present without neurologic symptoms or can precede them by many years as in our patient. Recurrent vomiting, weakness, coma and skin hyperpigmentation resulting from excessive ACTH secretion are the signs of adrenal insufficiency. MRI scans of the brain are obtained as a part of evaluation in clinically suggestive patients with neurological signs. It usually demonstrates typical white matter lesions, showing symmetric and involving the corpus callosum and the periventricular parieto-occipital white matter.[5]

The *ABCD1* gene covers approximately 19-kb, contains 10 exons and 9 introns. To date, more than 400 different mutants *ABCD1* alleles have been reported in XL-ALD mutation database.[6-8] In Korea, 19 cases with ALD have been reported. In only 8 cases, mutations have been documented; 6 cases were childhood ALD and 2 cases were AMN.[4, 9-15] Our patient carries a *de novo* mutation, c.1780+1G>A (IVS7^{+1}G>A). This previously reported mutation is predicted to produce an aberrant splicing site of exon 7. When a patient with XL-ALD is identified, family member screening is recommended for genetic counseling because 95% of cases are maternally inherited.[16] In this case, his mother and sister were tested. However, both of them turned out to be non-carriers of the mutation. Therefore, the case is sporadic case, but the possibility of germline mosaicism in his mother still remains.

For treatment of ALD, corticosteroid replacement therapy is necessitated in case of adrenal insufficiency. However, steroid therapy does not prevent the development of CNS pathology. Although the use of Lorenzo's oil was reported to be effective in some presymptomatic patient with normal brain MRI findings, it also does not alter progression of CNS pathology. Currently, only HSCT at early stage of ALD is recommended as the treatment of choice.[17,18] Bone marrow transplantation can prevent the progression of the disease when done at an early stage before the clinical sign develops. After the transplantation procedure, demyelinating lesions usually continue to extend to for 12 months to 18 months and then their progression arrests. This delay seems to be due to the slow replacement of brain microglia from bone marrow-derived cells.[19] HSCT is mostly recommended to childhood cerebral form of ALD patients with minimal or mild neurological deficit with evidences of brain involvement and their performance IQ should be over 80.[18] Therefore, we strongly recommended HSCT to parents of our patient. However, his parents refused HSCT due to risks of complication of HSCT and absence of reports in Korea demonstrating the efficacy of HSCT in ALD.[20] Although his neurological deficit has not progressed over the one year of follow-up period, we repetitively have explained the necessity of HSCT in our patient.

In conclusion, despite its rarity, the entire clinical features of ALD have been described with therapeutic strategies according to their severities. However, the clinical and genetic characteristics of ALD in the Korean population are elusive. Patient cohort study is necessary to understand the natural clinical outcome of ALD in the Korean population.

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