Primary Adrenal Insufficiency in a Newborn With Adrenal Hypoplasia Congenita Caused by a Mutation of the DAX1 Gene

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ABSTRACT
Adrenal hypoplasia congenita (AHC) is a rare inherited disorder of the adrenal gland caused by deletion or mutation of the dosage-sensitive sex-reversal AHC critical region on the X chromosome, gene 1 (DAX1) gene. The DAX1 gene is expressed in the adrenal cortex, the pituitary gland, the hypothalamus, the testis, and the ovary. Most affected infants present with failure to thrive, salt wasting, and hypoglycemic seizure in early life. Immediate mineralocorticoid and glucocorticoid replacement is essential. Most boys with AHC present with hypogonadotropic hypogonadism, resulting in failure to enter puberty and the need for testosterone treatment. However, a recent study revealed that the onset of puberty in boys with AHC can be variable, ranging from arrested or absent to precocious. We describe a case involving a newborn who presented with primary adrenal insufficiency due to a mutation of the DAX1 gene and was finally diagnosed with AHC.

Key Words: Adrenal hyperplasia congenita, Adrenal insufficiency, Infant newborn

INTRODUCTION
A clinical diagnosis of adrenal hypoplasia congenita (AHC) caused by a mutation in the dosage-sensitive sex-reversal AHC critical region on the X chromosome, gene 1 (DAX1) gene is not always easy to make. The clinical presentation of AHC is subtle in some cases. If a male newborn presents with adrenal insufficiency, he may be misdiagnosed as having 21-hydroxylase deficiency (congenital adrenal hyperplasia [CAH]), although the adrenal steroid profiles of these conditions are quite different. In AHC, 17 hydroxyprogesterone (17-OHP) levels are low, whereas they are elevated in CAH except in cases with a StAR gene defect (congenital lipoid adrenal hyperplasia) and 3β-hydroxysteroid dehydrogenase deficiency.

Because AHC results from a mutation in the DAX1 gene, a definitive diagnosis can be made by molecular genetic analysis of the DAX1 gene. Distinguishing between CAH and AHC is crucial because they are dissimilar in their clinical course and prognosis, as well as...
as in steroid management and genetic counseling approaches 1). Although only the adrenal gland of a patient with AHC may seem to be affected, pituitary and gonadal functions also need careful evaluation in follow-up visits. We report a case of AHC and emphasize the importance of a genetic analysis of the DAX1 gene in patients with adrenal insufficiency in the newborn period.

**CASE REPORT**

An 18-day-old male baby who presented with poor oral intake and failure to thrive was readmitted to the neonatal intensive care unit (NICU). He was a third child, with two older sisters and no family history of genetic or metabolic disease. His mother had not been treated with any drugs, including antenatal corticosteroids. He was born at 38 weeks gestation weighing 3,160 g (25-50th percentile) and had previously been admitted with neonatal respiratory distress syndrome (RDS) and treated with exogenous pulmonary surfactant replacement and ventilator care for 9 days from the day after birth. At the first admission, all electrolyte levels, including sodium, potassium, and chloride, were normal, and his serum glucose level was within the normal range. The results of newborn screening tests, including 17-OHP levels (0.8 ng/mL, reference 0-6.6 ng/mL), were also normal. He was discharged at 11 days after birth in good condition.

On physical examination, he showed poor weight gain, severely dehydrated skin, and normal male genitalia with average testicular volume (1 mL bilaterally). He had generalized dark skin, especially on the nipples, nail beds, and scrotum (Figure 1). Laboratory tests showed severe hyponatremia (Na: 121 mmol/L, reference 135-153 mmol/L), hypochloremia (Cl: 84 mmol/L, reference 99-115 mmol/L), hyperkalemia (K: 7.4 mmol/L, reference 3.5-5.3 mmol/L), elevated blood urea nitrogen (BUN) level (30.5 mg/dL, reference 3-12 mg/dL), and normal creatine (0.7 mg/dL, reference 0.3-1.0 mg/dL) with low serum osmolarity (264 mOsm/kg, reference 270-310 mOsm/kg), indicating hypo-osmotic dehydration caused by salt wasting. An endocrinological investigation revealed low levels of serum cortisol (12.1 mg/dL, reference 80-1,500 mg/dL) and aldosterone (22.6 ng/dL, reference 50-90 ng/dL) and high adrenocorticotropic hormone (ACTH) levels (734.4 pg/mL, reference 10-60 pg/mL).

We carried out an ACTH stimulation test to confirm a diagnosis of adrenal insufficiency. We measured serum cortisol and 17-OHP levels before and after intravenous administration of

![Figure 1](https://example.com/figure1.jpg)

**Figure 1.** Gross physical appearance. (A) He had generalized dark skin, especially on the nipples. (B) He showed hyperpigmentation in his nail beds. (C) He showed hyperpigmentation of his scrotum.
synthetic ACTH (Tetracosactrin). Baseline and stimulated levels of cortisol and 17-OHP are presented in Table 1. If baseline or stimulated levels of cortisol are higher than 18 mg/dL, the adrenal cortex is considered to be responding physiologically. None of the patient’s cortisol levels was over 18 mg/dL, before or after ACTH stimulation, indicating that he had primary adrenal insufficiency. The baseline level of 17-OHP was low, and ACTH stimulation did not cause a significant increase in his 17-OHP level. In a CAH patient, 17-OHP is increased at the basal level and markedly elevated after ACTH stimulation. In our patient, serum levels of cortisol and 17-OHP were both low, whereas the ACTH level rose, suggesting cortisol deficiency unrelated to 21-hydroxylase deficiency (CAH) or other adrenal enzyme deficiencies. His dehydroepiandrosterone sulfate (DHEAS) level was normal (6.3 μg/dL, reference 5-111 μg/dL), but near the lower limit. Tandem mass spectrometry showed no abnormality with amino acid, organic acid, or lipid metabolism. All of the saturated very long chain fatty acids (VLCFAs) were normal, so we excluded adrenoleukodystrophy as a cause of his primary adrenal insufficiency.

Abdominal ultrasonography showed that his adrenal glands had no corticomедullary differentiation (Figure 2). A molecular genetic study detected a hemizygous frame shift mutation (c.543delA) in the DAX1 gene, so we diagnosed AHC (Figure 3). He was treated with hydrocortisone at a dose of 20 mg/m²/day and fludrocortisone (Florinef®) 0.2 mg/day. After 3 weeks of treatment, he responded well with good appetite and weight gain, much-improved skin hyperpigmentation, and normalized blood sodium and potassium levels. He is now 9 months old and shows no other symptoms, such as nausea, vomiting, failure to thrive, or hypotension. He has experienced normal growth with a height of 68.5 cm (50-75th percentile) and a weight of 7.6 kg (50-75th percentile), and his development was quite normal up to that time. He has been checked regularly with monitoring of

Table 1. Results of the Adrenocorticotropic Hormone Stimulation Test

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<th>0 min</th>
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<tr>
<td>Cortisol (µg/dL)</td>
<td>12.1</td>
<td>15.3</td>
<td>13.7</td>
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<tr>
<td>17-OHP (ng/mL)</td>
<td>1.4</td>
<td>1.6</td>
<td>1.9</td>
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Abbreviation: 17-OHP, 17-hydroxyprogesterone.

Figure 2. Abdominal ultrasonography findings. (A) Both adrenal glands are slightly enlarged; the size of the left adrenal gland (arrow) is 1.2×0.4 cm. (B) The size of the right adrenal gland (arrow) is 0.6×0.5 cm. Neither adrenal gland showed corticomедullary differentiation.

Figure 3. Identification of a hemizygous missense mutation in the DAX1 gene, located at Xq21. The sequencing chromatogram shows a point mutation of c.543delA, leading to early termination. Abbreviation: DAX1, dosage-sensitive sex reversal adrenal hypoplasia critical region on chromosome X, gene 1.
his serum electrolyte and hormone levels. After treatment with hydrocortisone and fludrocortisone (Florinef®), all electrolyte levels, including sodium and potassium, have normalized. He is too young to be evaluated for hypogonadotropic hypogonadism and must be followed until puberty. We recommended that his mother be tested for DAX1 gene carrier status, but she refused.

DISCUSSION

X-linked AHC is a rare disease with a prevalence of approximately 1:12,500 in the USA. AHC results from mutations in the DAX1 gene on the short arm of the X chromosome (Xp21). The DAX1 gene is expressed in the adrenal cortex, the pituitary gland, the hypothalamus, the testis, and the ovary, and plays a central role in the maturation of the hypothalamic-pituitary-gonadal axis and the growth and development of the adrenal gland. In AHC, both cortisol and aldosterone secretion are reduced because of impaired development of the definitive zone of the adrenal gland in the first trimester of gestation. Approximately 60% of boys affected with AHC have early-onset salt-wasting primary adrenal insufficiency, usually within the first 2 months of life. Because adrenal crisis includes dehydration, hypovolemia, hypoglycemia, hyponatremia, and hyperkalemia, it is regarded as an endocrine emergency. Rapid recognition and prompt treatment are important for survival even before a diagnosis can be made. Initial therapy should consist of intravenous normal saline and dextrose. When stabilization is achieved with replacement doses of mineralocorticoids and glucocorticoids, therapy must be initiated, and appropriate counseling and education for steroid replacement during stress and sickness must be provided.

Some children with AHC who do not present symptoms early in life may undergo a period of relatively good health, and these children tend to present with more insidious signs and symptoms of the disease throughout childhood or, rarely, in adulthood. This apparently bimodal pattern of presentation may reflect age-related changes in mineralocorticoid secretion and sensitivity, sodium and fluid intake, and a counter-regulatory response.

In this case, our patient was born at 38 weeks gestation weighing 3,160 g (25-50th percentile), and he was admitted on the day after birth with neonatal RDS. We cannot find the patients who have AHC with RDS simultaneously. However, there was a report that a baby who presented respiratory distress diagnosed with transient tachypnea of the newborn (TTN) had AHC at the same time. His respiratory distress was resolved on postnatal day 2, but he showed persistent vomiting starting on day 7 and was finally diagnosed with AHC.

After the first admission, our patient had been treated with exogenous pulmonary surfactant replacement and ventilator care and discharged at 11 days after birth in good condition. All electrolyte levels and newborn screening tests were within normal range at that time. However, 7 days after discharge on postnatal day 18, he was readmitted to the NICU presenting with adrenal insufficiency, with symptoms of poor oral intake and failure to thrive. We excluded nonorganic causes of failure to thrive of neonates, such as poverty, parenting problems (e.g., history of depression or other mental disorders), or an inconsistent feeding schedule. We hypothesized that the organic causes of failure to thrive include infection, milk allergy, cerebral palsy, Down syndrome, or congenital heart disease, but he did not have any of them. We conducted a blood test to investigate metabolic and endocrinological causes of failure to thrive. It was revealed that he had primary adrenal insufficiency, but he did not have CAH.

Direct sequencing of the DAX1 gene revealed a hemizygous frame shift mutation (c.543delA), so he was diagnosed with AHC. There has been another report of an AHC patient who had exactly the same mutation as our patient. His prenatal history was unremarkable, and he was delivered in Turkey at term, with a birth weight of 3,000 g. He was admitted to the NICU at the age of 33 days, presenting with vomiting and failure to thrive. Both of these patients showed hyperpigmentation of the nipples and scrotum and had normal male genitalia. The laboratory results of these 2 patients revealed primary adrenal insufficiency, and both were diagnosed with AHC and the same mutation (c.543delA) of the DAX1 gene.

There is no obvious correlation between the types of mutations and the age of presentation or severity of adrenal insufficiency. There is a report of 3 boys of the same pedigree presenting with adrenal manifestations at 4 and 6 years of age and at a very early age (9 days), although they were all diagnosed as having AHC with the same mutation (c.622C>T) in the DAX1 gene. These features indicate phenotypic heterogeneity, probably caused by other genetic factors, such as modifier genes, which can influence the time of onset and severity of adrenal failure, or by environmental and personal factors such as infec-
tions, access to medical care, and a positive family history that can facilitate the diagnosis.10

Although details of AHC patients and mutations in the DAX1 gene have been reported worldwide, there have only been a few case reports from Korea.2,11,12 Considering the many reports of AHC patients in the Japanese population,13 the incidence of AHC might be underestimated in Korea.11 In 2005, 3 cases of AHC patients were reported in Korea for the first time.2 All 3 patients presented with adrenal insufficiency in the neonatal period, with symptoms of poor oral intake, lethargy, and hyperpigmentation. One patient who had a complete deletion of the DAX1 gene with Xp21 contiguous gene deletion syndrome, also presented with glycerol kinase deficiency and Duchenne muscular dystrophy in addition to AHC. The other 2 patients were diagnosed with AHC and novel mutations in the DAX1 gene and were treated with hydrocortisone and fludrocortisone (Florinef). In a follow-up report on these 2 AHC patients in 2011,10 they were then 12 and 9 years old, had developed normally, and their hyperpigmentation had resolved.

Other patients diagnosed with AHC, not in the neonatal period but in childhood or adulthood, have been reported in Korea. One patient was a 6-year-old boy who was brought to the hospital because of skin hyperpigmentation and fatigue and was finally diagnosed with AHC.2 He, too, was treated with hydrocortisone and fludrocortisone (Florinef). The patient’s age was 19 years at the time of the report,12 and testosterone enanthate was added because of hypogonadotropic hypogonadism. Another patient11 who had experienced multiple adrenal crises during mild respiratory and gastrointestinal infections since he was 13 years old, was finally diagnosed with AHC at the age of 23 years. Physical examination showed only scant pubic hair (Tanner stage 3) and low testicular volume (4 mL bilaterally). An endocrinological investigation showed that he had hypogonadotropic hypogonadism.

Hypogonadotropic hypogonadism has been identified as a component of AHC in affected individuals who survive into childhood. The most frequent pubertal disorder due to AHC related to DAX1 gene mutation is the absence of or a delay in puberty due to disorders of gonadotropin secretion. A typical example of an unfortunate outcome is the report of a male patient with CAH who had been followed and was therefore not treated with testosterone replacement until 24 years of age, when he was admitted with gonadal failure and was found to have a mutation in the DAX1 gene.14

The classically observed puberty disorder of AHC patients is hypogonadotropic hypogonadism, but rare cases of precocious puberty were reported recently.10 Three boys of the same pedigree were diagnosed with AHC, having the same mutation of the DAX1 gene (c.622C>T). Unlike the 2 patients with hypogonadotropic hypogonadism, the third patient surprisingly developed precocious puberty at the age of 10 months, presenting with testes that were 3/4 mL bilaterally, a penis length of 7 cm, and pubic hair. The mechanism of the mutation’s effect on puberty was unknown.

The clinical presentation of AHC is sometimes subtle, and the disease is not always recognized. A clinical diagnosis of AHC due to a DAX1 mutation is not always made. When a boy presents with salt wasting in the neonatal period, it is often misdiagnosed as CAH because of the higher prevalence of that disorder. The salt-wasting form of CAH is most common (59.4%) and does cause adrenal insufficiency in infancy; AHC accounts for only 1.6% of the incidence.15,16 Although the clinical symptoms of adrenal insufficiency are similar in the 2 diseases, the adrenal steroid profiles are quite different. In AHC, 17-OHP levels are low whereas they are increased in CAH.13 Distinguishing between these 2 disorders is important because they differ in their clinical course and prognosis, as well as in steroid management and genetic counseling approaches.13 A genetic analysis of the DAX1 gene is required for a definitive diagnosis of X-linked AHC as well as for genetic consultation in families.5 Although at present, only the adrenal gland of this patient seems to be affected, his pituitary and gonadal functions will be evaluated carefully in follow-up visits.

We are reporting a male newborn with AHC caused by a mutation in the DAX1 gene, and we emphasize the importance of genetic analysis of the DAX1 gene in patients with adrenal insufficiency in the neonatal period.

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