

## ACHALASIA-ALACRIMA-ACTH INSENSITIVITY SYNDROME (TRIPLE A SYNDROME) IN A SAUDI FAMILY

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The adrenocorticotrophic hormone (ACTH) insensitivity syndromes<sup>1</sup> consist of several rare disorders with absent or markedly impaired adrenal response to ACTH. In most affected patients the disorder is inherited, but in a small minority, an acquired abnormality induces the formation of antibodies that block the ACTH receptor.<sup>2</sup> The two known inherited causes of the ACTH-resistant syndrome are familial glucocorticoid deficiency (FGD), which has disordered adrenal function as the sole manifestation,<sup>3-5</sup> and the Allgrove (or triple A) syndrome,<sup>6</sup> in which ACTH insensitivity is associated with alacrima and achalasia. Patients with ACTH insensitivity characteristically have a low or undetectable plasma cortisol concentration, a high plasma ACTH concentration, and an absent adrenal response to ACTH stimulation, features that are typical of primary adrenal failure. However, contrary to what is found in the more common varieties of Addison's disease, the renin-angiotensin-aldosterone axis functions normally, suggesting that the cells of the zona glomerulosa retain appropriate response to physiologic stimuli. An awareness of these disorders is important because, as illustrated by one of our cases in this report, adrenal insufficiency may not be suspected in these patients, possibly because the fluid and electrolyte disturbances typically found in primary adrenal failure are absent. Besides this, the disorder can be fatal if proper treatment is not provided. Two cases involving a male and a female from a single Saudi family are reported to call attention to this rare disorder.

### Case Report

#### Case 1

A six-year-old Saudi male was referred to our hospital for the evaluation of recurrent hypoglycemic attacks. He was born at 39 weeks of gestation to a 32-year-old mother and a 47-year-old father who were first cousins. Developmental landmarks and growth were reported to be normal, although he was often listless, had a poor appetite, and could not keep up with mates at play. From the age of

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one month until he was about 3½ years old, he was brought to the emergency department on many occasions, and was admitted to the hospital two times, for the treatment of febrile illnesses that were usually associated with mucopurulent conjunctivitis, upper and lower respiratory tract infections, sometimes with bronchospasm, or vomiting and diarrhea. During some of these illnesses, he received brief courses of hydrocortisone.

At the age of 4½ years the patient had an episode of hypoglycemic coma (plasma glucose concentration of 1.7 mmol/L) that responded to intravenous glucose. When he was five years old, he was referred for a dermatological evaluation of diffuse hyperpigmentation. The change in skin color was attributed to an unspecified post-inflammatory process. Later, at the age of 5½ years, he was hospitalized again for hypoglycemic coma (plasma glucose concentration was 1.8 mmol/L). Serum concentrations of sodium, potassium, chloride, urea, creatinine and calcium were normal at that time, and on several occasions subsequently. At the end of a supervised 18-hour fast which did not result in any symptom of hypoglycemia, the plasma glucose and insulin were 3.8 mmol/L and 10 µIU/mL, respectively. He was then referred for endocrine evaluation.

On physical examination, the patient was a normal male with slight pallor. His blood pressure was 100/60 mm Hg. His height and weight were at the 50th and 75th percentiles, respectively. There was no goiter. He had moderate hyperpigmentation of the skin, gum, buccal mucosa, palmar creases, knuckles, and elbows. General physical examination was normal, except for an absent left testis; the right testis was of normal size and consistency. The penile length was appropriate for age and the urethra was in the normal position. Neurological examination was normal except for bilateral hyperreflexia without clonus. His performance at school was reported to be satisfactory. Blood hemoglobin was 10.3 g/dL, and hematocrit was 33%. Serum concentrations of sodium, potassium, chloride, urea, and creatinine were 138 mmol/L, 3.7 mmol/L, 107 mmol/L, 1.9 mmol/L, and 28 µmol/L, respectively. Serum calcium concentration was 2.3 mmol/L, phosphate was 1.2 mmol/L, and albumin was 38

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g/L. Table 1 shows the concentrations of some adrenal cortical hormones, ACTH, free thyroxine and thyrotropin in serum. The patient had a very low concentration of serum cortisol in association with a high plasma concentration of ACTH. In response to an injection of synacthen (ACTH<sub>1-24</sub>), serum cortisol rose to a peak value of only 11 nmol/L. Scrotal ultrasound showed a 1.3 cm scrotal right testis, while the left testis was absent from the scrotum and the inguinal canal. Plain abdominal x-ray and a CT scan of the adrenal glands were normal. Autoantibodies against adrenal cortex cytoplasm, thyroid peroxidase, and thyroglobulin were not detected in his serum.

Barium meal revealed a smooth tapering of the lower end of the esophagus, as well as considerable delay in the clearance of barium from the esophagus, features consistent with achalasia. Ophthalmologic examination that included the Schirmer's test revealed dry eyes and alacrima. Pre- and post-contrast CT scan of the brain, as well as an electroencephalogram (EEG) were normal. The patient had substantial clinical improvement after he was started on prednisolone. His appetite improved, he gained weight, and he became more active and playful. He is doing well on 2.5 mg prednisolone daily as well as artificial tears and is currently being evaluated for correction of the achalasia.

#### Case 2

The patient, a full sister of case 1, was brought to the endocrine clinic at the age of 4¼ years because of darkening of the lips, elbows and knuckles of the hands. Her brother had been started on therapy for adrenocortical failure about four months previously. The patient was in good health but had developed repeated episodes of vomiting in the weeks prior to presentation. She was the product of an uneventful pregnancy, but delivery was by emergency cesarian section because of breech presentation. Her developmental milestones occurred at normal times. On examination, the child looked well. Her blood pressure was 80/40 mm Hg. Her stature and weight were at the 20th and the 30th percentiles, respectively. There was mild, diffuse hyperpigmentation of the skin, with more severe involvement of the lip, gums, creases of the palms, buccal mucosa, and elbows. General physical examination, including an assessment of the external genitalia, was normal. Also, neurological examination was normal, except for bilateral hyperreflexia. Laboratory investigation revealed blood hemoglobin of 12.4 g/dL, packed cell volume of 36.8%, and total leukocyte count of 9130x10<sup>9</sup> per liter. Platelet count was normal. Fasting serum glucose was 5.1 mmol/L, urea was 3.1 mmol/L, creatinine was 32 µmol/L, sodium was 143 mmol/L, potassium was 4.0 mmol/L, chloride was 104 mmol/L, total protein was 65 g/dL, and albumin was 37 g/dL. Serum electrolytes, urea and creatinine were normal on two subsequent occasions. Table 1 shows the results of some endocrine tests. Peak

serum cortisol after synacthen injection was 122 nmol/L. A plain abdominal x-ray and CT scan of the adrenals were normal. Barium meal revealed smooth tapering of the lower esophagus, as well as a delay of esophageal emptying. Ophthalmological examination documented the presence of alacrima and dry eyes. She is presently well on 1.25 mg prednisolone daily (and artificial tears) but has recently had difficulty with solid foods. She has been referred for evaluation and surgical correction of the achalasia.

TABLE 1. Concentrations of serum adrenal cortical hormones, adrenocorticotropin, thyrotropin and free thyroxine in both patients.

Hormone	Case 1	Case 2	Normal Range
Cortisol (8 a.m.) (nmol/L)	3.3	83 and 41	138-690
Aldosterone (supine) (pmol/L)	170	155	80-260
Dehydroepiandrosterone sulfate (µmol/L)	<0.3	ND	0.3-0.7
Dehydroepiandrosterone (nmol/L)	<0.69	ND	0.7-9.5
17-hydroxyprogesterone (nmol/L)	<0.1	ND	<3.0
Adrenocorticotropin (8 a.m.) (pmol/L)	342	265	2-11
Thyrotropin (TSH) (mIU/L)	6.24	2.479	0.490-4.670
Free thyroxine (FT <sub>4</sub> ) (pmol/L)	12.26	16.74	9.14-23.81

ND=test not done.

#### Discussion

These two siblings had clinical and biochemical features of the ACTH insensitivity syndrome.<sup>1</sup> Each had hyperpigmentation, low concentration of serum cortisol, high plasma ACTH level, absent or markedly impaired cortisol secretion in response to synacthen stimulation, and a normal supine morning serum concentration of aldosterone.<sup>1,5</sup> Although no dynamic test of the renin-angiotensin-aldosterone axis was performed, the system probably functioned normally since none of the patients developed any electrolyte abnormality, despite several episodes of dehydration that were caused by vomiting and diarrhea. Case 1 additionally had concentrations of serum dehydroepiandrosterone sulfate, dehydroepiandrosterone, and 17-hydroxyprogesterone that were inappropriately low for his age. These results suggest that, in these patients, the production of cortisol and adrenal androgens was deficient but aldosterone was produced normally. Both patients also had achalasia and alacrima in addition to the disordered adrenocortical function, a combination known as the Allgrove or triple A syndrome.<sup>6</sup>

Familial glucocorticoid deficiency (FGD), a rare, recessive, autosomal disorder, was the first of the inherited ACTH insensitivity syndromes to be described.<sup>3</sup> Affected patients typically present in infancy or early childhood with hyperpigmentation, recurrent hypoglycemia, convulsions, or coma. Frequent severe infections as well as failure to thrive may also be initial manifestations. Unfortunately, the diagnosis of FGD is commonly delayed, possibly because adrenocortical hypofunction is rarely considered as a possible cause of the observed signs and symptoms. Perhaps the absence of the typical fluid and electrolyte abnormalities of adrenal insufficiency in these

patients accounts for the oversight. Familial glucocorticoid deficiency is characterized by the lack of response of the adrenal-to-exogenous ACTH, as well as the degeneration of the zona fasciculata/reticularis. Mutations of the ACTH receptor gene appear to be responsible for the disorder.

Several missense and nonsense mutations in this gene have been identified in affected individuals, and in all cases the mutation cosegregates with the disease in the family.<sup>1,7-10</sup> Though not yet conclusively proven, it is likely that these mutations disrupt receptor structure and thereby impair

ACTH binding and/or signal transduction. This would make the ACTH-receptor complex nonfunctional. Most of the mutations occur within the transmembrane domain of the receptor, although defects in the cytoplasmic and extracellular segments have also been identified.<sup>1,9-11</sup> Homozygous and compound heterozygous inheritance of the mutations appear to be most frequently responsible for FGD. However, in some patients with the typical clinical phenotype, no mutation in the coding region of the ACTH receptor gene has been detected,<sup>10,11</sup> suggesting that FGD may result from one or more other genetic defects.

The triple A syndrome, the second of the inherited corticotropin resistance syndromes, was initially considered to be a variant of FGD because ACTH insensitivity was common to both disorders.<sup>6</sup> However, data from recent studies suggest that the triple A syndrome is in fact a distinct entity with a different genetic and molecular etiology. For example, the gene for the ACTH receptor, which is responsible for FGD, has been found to be on the short arm of chromosome 18 (18p11.2),<sup>12</sup> but the gene for the triple A syndrome maps to the long arm of chromosome 12 (12q13).<sup>13,14</sup> Also, whereas mutations in the ACTH receptor gene have been found in a large proportion of patients with FGD, none has been identified in patients with the triple A syndrome.<sup>1</sup> These results support the conclusion that the triple A syndrome and FGD, the two recognized inherited disorders of corticotropin resistance, have different genetic etiologies.

At present no explanation for the association of achalasia, alacrima, and adrenal unresponsiveness to ACTH in the triple A syndrome is available. It was initially suggested that the ACTH receptor gene would provide the link to explain the association of the three main features of the syndrome because of evidence that ACTH has some neurotropic effects,<sup>16</sup> as well as the demonstration that ACTH binds to rat lacrimal glands.<sup>17</sup> However, in the absence of any documented mutation in the ACTH receptor in the triple A syndrome,<sup>1,15</sup> and the current evidence that the ACTH receptor gene is not expressed outside the adrenal cortex,<sup>18</sup> it is unlikely that mutations in the ACTH receptor gene would account for any of the three main features of the disorder. Ongoing studies designed to identify the defective gene and its product will probably provide the explanation. Whatever

may be responsible, it is essential that ACTH insensitivity, with or without achalasia and alacrima, should always be suspected in any child with hyperpigmentation, especially when complicated by hypoglycemia, convulsion, coma, or failure to thrive. A diagnosis can be established by documenting the presence of a combination of low cortisol, high ACTH, and normal renin and aldosterone concentrations in an 0800 to 0900 h plasma sample, as well as a lack of adrenal response to ACTH<sub>1-24</sub> stimulation. Treatment with a replacement dose of a glucocorticoid may be life saving. In a few patients, it may also be essential to exclude adrenoleukodystrophy (ADL),<sup>19,20</sup> an X-linked, recessively inherited neurological disease that can also cause impaired glucocorticoid production with minimal or no disturbance of mineralocorticoid production. Although adrenal failure may precede neurological dysfunction in ADL,<sup>21</sup> it is most unlikely that the disorder is responsible for the abnormalities in the patients reported here because case 2 was female, both patients had achalasia and alacrima, which are not features of ADL, and both lacked the typical changes seen in CT scan of the brain. Measurement of plasma concentration of very-long-chain fatty acids would exclude ADL.

Several recent publications have reported that some patients with the triple A syndrome have a variety of abnormalities in addition to the three cardinal features of the disorder.<sup>1</sup> The most common and serious of these abnormalities are a number of progressive, sometimes disabling, neurological defects involving the central, peripheral or autonomic nervous system.<sup>21,22</sup> Our patients had signs of pyramidal tract dysfunction, although they had normal CT scan of the brain and EEG. Case 1 also had subclinical hypothyroidism without serological evidence of chronic thyroiditis, and his left testis was absent. The relationship of these abnormalities to the main features of the disorder is unknown.

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