Case Report

CLINICAL COURSE OF A UNIQUE CASE OF ALLGROVE SYNDROME AND CHALLENGES OF HYPOGLYCEMIA MANAGEMENT

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ABSTRACT

Objective: Allgrove syndrome (AS), also known as triple-A syndrome, is a rare disorder characterized by alacrima, achalasia, adrenal insufficiency, and other manifestations such as problems related to growth, puberty, and neuropsychological development. Although the genetics of this disorder have been studied extensively in recent decades, clinical information is still lacking.

Methods: We present a unique case of AS from which we have gained significant insight into its clinical course, especially the management of hypoglycemia.

Results: The patient initially presented with altered mental status at age 3 which was found to be due to hypoglycemia. Laboratory values confirmed primary adrenal insufficiency with isolated glucocorticoid deficiency. With additional history of alacrima, a genetic test was obtained which confirmed the diagnosis of AS. For over 10 years, we have been following her growth, puberty, and development. We experienced some challenges in managing her hypoglycemia initially. Certain metabolic effects of steroid overdose were noted. To resolve this problem, we found dextrose supplementation quite effective.

Conclusion: The rarity and isolated glucocorticoid deficiency of AS pose clinical challenges for initial diagnosis. Hypoglycemia associated with alacrima should alert the suspicion of AS. Management of hypoglycemia in AS is complicated by achalasia and may benefit from incorporation of both glucocorticoid and dextrose supplementation to prevent side effects of steroid overdose. (AACE Clinical Case Rep. 2019;5:e357-e361)

Abbreviations:

AS = Allgrove syndrome; ACTH = adrenocorticotropic hormone

INTRODUCTION

Allgrove syndrome (AS), also known as triple-A syndrome, is a rare autosomal recessive disorder first described in 1978 (1). The classic triad in AS includes alacrima, achalasia, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. In addition, AS can be associated with neurologic abnormalities, skin changes, developmental delay, poor growth, and delayed puberty (2).

Presentation and progression of symptoms in AS vary greatly. Alacrima presents in infancy as the first sign of the triad but is often dismissed by parents and clinicians (3). Achalasia occurs in 75% of all cases and can present at any age (2,4). Mild symptoms of dysphagia and vomiting may present years before the diagnosis of achalasia (5).

Adrenal insufficiency usually manifests within the first decade of life (2,3). It can manifest as recurrent mild hypoglycemia, hypoglycemic seizures, or even sudden death. It is commonly the presenting symptom and the one that leads to the diagnosis of AS (3,4). The majority of AS patients with adrenal insufficiency have glucocorticoid deficiency, although cases of mineralocorticoid deficiency...
have also been reported in about 15% of cases (2,4). A subset of patients with AS do not develop adrenal insufficiency (6). Hyperpigmentation due to elevated ACTH levels is commonly present.

Additionally, as many as 85% of patients with AS exhibit various neurological dysfunctions which tend to present later in adolescence or adulthood. The central, peripheral, and autonomic nervous systems can all be involved. Motor and speech delay as well as impaired intellect are common in patients with AS (2).

Although the genetics of AS have been studied extensively, clinical information, especially of long-term course, is still lacking. Here we present a case of AS with some unique features, valuable information of its clinical course, and the knowledge we learned in long-term management of hypoglycemia over more than 10 years.

CASE REPORT

A previously healthy, 3-year-old female was brought to the emergency department after she was found unresponsive. Her fingerstick glucose level was low, at 28 mg/dL (normal range is 70 to 115 mg/dL), but with normal vitals and initial laboratory evaluation including comprehensive biochemical profile, electroencephalogram, electrocardiogram, and sepsis workup. After treatment with intravenous dextrose, she regained consciousness and was admitted for further evaluation.

Her blood sugar remained normal after a 12-hour fast. Upon discharge, her cortisol level was found to be extremely low (<1 g/dL), which prompted a high-dose cortrosyn stimulation test. Her low stimulated cortisol plus elevated baseline ACTH level of 965 pg/mL (normal range is 5 to 27 pg/mL) confirmed primary adrenal insufficiency (Table 1). Adrenal 21-hydroxylase antibody was negative. An abdominal computed tomography scan revealed bilateral adrenal gland atrophy and a hyperdense liver.

Her physical exam was normal with no hyperpigmentation, hypopigmentation, goiter, organomegaly, or clitoromegaly. She was Tanner stage 1. The patient’s parents are both of white-Hispanic descent. Family history was unremarkable with no reported adrenal insufficiency or sudden death.

Further history revealed that the child fatigued easily and required long naps daily. She had been noted to cry without much tears since infancy. Adrenal insufficiency with alacrima prompted genetic testing for AS, which resulted positive for a homozygous IVS14+1 G>A (or c.1331+1 G>A) mutation in the AAAS gene.

The patient was started on maintenance hydrocortisone therapy (12.5 mg/m²/day). The patient improved and regained her energy level. Her lab results showed normalized ACTH levels, which is unusual in AS, but indicates adequate hydrocortisone dosage. Her adrenal hormone levels are presented in Table 1. However, she experienced several hypoglycemic episodes down to 30 mg/dL, 2 of which developed into seizures around age 6 during viral illness. Stress-dose hydrocortisone levels of 25 to 75 mg/m²/day were often administered for 2 to 3 consecutive days during mild illness.

Although no more severe hypoglycemia (<50 mg/dL) occurred after age 7, her glucose levels were low (50 to 60 mg/dL) during acute illness. To maintain normal blood sugar, we noticed that a stress-dose level of hydrocortisone alone was inadequate; she also required dextrose supplementation. The patient gained notable weight at age 8, going from the 25th percentile at age 5 to the 65th percentile at age 8 (Fig. 1). Her hemoglobin A1c level also increased from 5.1 to 6.1% between ages of 7.5 and 8.5.

Due to concerns for development of metabolic syndrome, we kept her maintenance hydrocortisone at a lower dose, close to 10 mg/m²/day, and limited her stress-dose levels to no more than double or triple the daily dose during mild illness. We incorporated glucose gel supple-

<table>
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<th>Hormone Levels Before and After Hydrocortisone Treatment</th>
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<td>Age (years)</td>
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<tr>
<td>Cortisol, baseline (g/dL)</td>
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<td>Cortisol, stimulated (g/dL)</td>
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<td>4-115</td>
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<tr>
<td>Dehydroepiandrosterone sulfate (µg/dL)</td>
<td>35-430</td>
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<tr>
<td>Androstenedione (ng/dL)</td>
<td>8-50</td>
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mentation as part of the stress plan. During an acute illness, we recommended her to check her blood glucose level before meals. She was instructed to take 15 mg of glucose gel every 15 to 30 minutes as needed to maintain blood glucose levels >60 mg/dL. Glucose gel was usually required no more than 3 times a day. No more episodes of hypoglycemia were recorded after age 9 after implementing this new stress plan. Her hemoglobin A1c level improved from 6.2 to 5.4% (Table 2).

For her achalasia, routine upper gastrointestinal tract studies with esophagram were normal from ages 4 to 7. At age 9, she developed severe dysmotility which was confirmed by esophagram and manometry study. She required balloon dilation at age 10 then again at age 14. Now she is able to tolerate a soft diet. For her alacrima, she used artificial tears regularly for dry eyes. Her symptoms have been stable with no report of corneal ulcerations.

Our patient has mild learning difficulty but is able to maintain average grades in an integrated co-teaching class. She was diagnosed with attention-deficit/hyperactivity disorder at age 4 but never required medication. Around age 9, she developed migraines. Headaches have been under control with MigreLief, a dietary supplement containing magnesium, riboflavin, and puracol (feverfew). She has not developed any other neurological symptoms. The patient is now 14 years old. She had normal puberty development at age 10 and menarche occurred at age 12. Her menstrual cycles have been regular. Currently she is at Tanner stage IV. She has been growing along the 10th percentile for height and 50 to 75th percentile for weight. Her current height is almost 5 feet and her mid-parental height is 5 feet 2 inches. Unexpectedly, an extremely elevated anti-thyroglobulin antibody level was found at the time of diagnosis at 2,370.8 IU/mL, but it gradually decreased to 10.1 IU/mL recently. Thyroid function tests have remained in normal ranges (Table 2). She had a normal thyroid ultrasound.

**DISCUSSION**

AS has been linked to the AAAS gene (achalasia-addisonian-alacrima syndrome gene) located at chromosome...
12q13, which has marked expression in neuroendocrine and gastrointestinal structures (7,8). More than 30 mutations in the AAAS gene have been observed and a wide spectrum of phenotypes can exist even within the same mutation (9). The mutation seen in our patient (c.1331+1 G>A) is one of the most commonly described ones associated with AS (10).

In regards to management, we would like to highlight the challenges in treating adrenal insufficiency in patients with AS. In our case, high doses of maintenance and stress steroids contributed to central obesity, weight gain, and elevated hemoglobin A1c levels. We found that using supplemental oral glucose gel was effective in treating hypoglycemia and enabled us to avoid excessively high doses of hydrocortisone, preventing development of metabolic syndrome.

We also believe hypoglycemia management in patients with AS is complicated by achalasia. Achalasia in children with AS was found to have a more severe progression than normal achalasia (11). Dysphagia may also exacerbate hypoglycemia if the patient is unable to eat or drink when ill. Before balloon dilation, our patient’s hypoglycemia was difficult to control possibly due to delayed transit and absorption of hydrocortisone and food. Glucose gel can be absorbed by the oral mucosa, bypassing any swallowing difficulties, and is thus a better route for glucose supplementation in patients with dysmotility. Treatment of achalasia is critical not only for management of hypoglycemia but also growth and nutrition.

Our patient’s ACTH level has been monitored routinely. When she missed doses of hydrocortisone, we noticed a subsequent rise in ACTH level. After onset of puberty, her 17-hydroxyprogesterone increased to a normal level of 92 ng/dL and her dehydroepiandrosterone sulfate level remained low. There was no evidence of mineralocorticoid deficiency (Table 1).

Poor growth and short stature are often described as a part of AS (12). Our patient is in the normal range for height although on the lower end of her genetic potential. Based on scarce clinical information from human and animal studies, puberty and fertility could also be affected (12,13). Our case showed normal puberty development and regular menstrual cycles.

Our case also showed some unique features, which have not been reported per our knowledge. These include hyperdense liver and positive anti-thyroglobulin antibody, although their clinical implications are unclear.

### CONCLUSION

The rarity and isolated glucocorticoid deficiency of AS pose clinical challenges for initial diagnosis. Hypoglycemia associated with alacrima should alert the suspicion of AS. Management of hypoglycemia in AS is complicated by achalasia and may benefit from incorporation of both glucocorticoid and dextrose supplementation to prevent side effects of steroid overdose.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES