

Allgrove syndrome

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ABSTRACT Allgrove syndrome is a rare autosomal recessive disorder. It is also known as the 3A syndrome and characterised by the triad of achalasia, alacrima and adrenal insufficiency. The AAAS gene is encoded on chromosome 12q13. We report the case of a 23-year-old woman who presented at the hospital with adrenal crisis that was triggered by infection of the urinary system and gastrointestinal bleeding. She had a known diagnosis of achalasia for eight years, and ophthalmologic examination revealed alacrima. Based on our findings, the patient was diagnosed with Allgrove syndrome.

Keywords: adrenal insufficiency, achalasia, alacrima, Allgrove syndrome, Singapore Med J 2012; 53(5): e92–e94

INTRODUCTION

Allgrove syndrome (AS), also known as 3A syndrome (AAAS), was first identified in 1978.⁽¹⁾ The disease is characterised by adrenocorticotrophic hormone (ACTH)-resistant adrenal insufficiency, alacrima and achalasia. It is an autosomal recessive disorder and the AAAS gene is coded on chromosome 12q13. Mutation in the AAAS gene results in insufficiency in the protein function known as aladin or adracalin. This may possibly be responsible for AS.^(1,2) We report AS in a female patient who presented to our hospital with adrenal crisis triggered by infection of the urinary system and gastrointestinal bleeding.

CASE REPORT

A 23-year-old woman presented to our clinic with complaints of tachycardia, sweating, exhaustion, fainting and melaena. She had a past medical history of achalasia diagnosed eight years ago, and had undergone a surgical myotomy for the disorder. On examination, her blood pressure was 80/50 mmHg, pulse was 110 beats per minute and body temperature was 35°C. There was hyperpigmentation on the scar tissue located in the epigastric area and buccal mucosa. The basic laboratory findings were as follows: haemoglobin 9.7 mg/dL (normal range [NR] 12–16 mg/dL); fasting plasma glucose 51 mg/dL; blood urine nitrogen 51 mg/dL (NR 8–20 mg/dL); creatine 3.1 mg/dL (NR 0.4–1.0 mg/dL); sodium 132 mmol/L (NR 136–144 mmol/L); potassium 4.9 mmol/L (NR 3.6–5.1 mmol/L); cortisol 4.52 µg/dL (NR 6.2–19.4 µg/dL); C-reactive protein 213 mg/L (NR 0–8 mg/L). The ACTH level of the patient could not be measured at admission, as there was a technical malfunction in the laboratory. Her ACTH level, measured on Day 15 of treatment, was 800 pg/ml.

Pyuria and Gram-negative bacilli were detected by urine microscopy. No bacterial growth in the blood culture was detected at admission. The patient was assessed to have adrenal crisis, and glucocorticoid treatment was administered. For

supportive care, erythrocyte suspensions were transfused and cephtriaxone 2 g/day was administered for the urinary tract infection. Her oesophagus was found to be full of solid food during endoscopic examination. An oesophagography was performed three days after she was fed liquid food, and revealed narrowing in the cardio-oesophageal junction. Balloon dilatation was performed to relieve the obstruction. The dose of glucocorticoid was slowly tapered and then discontinued. ACTH stimulation test was performed three days after the discontinuation. Cortisol values at baseline, 30th, 60th, 90th and 120th minutes were as follows: 2.33 µg/dL, 2.14 µg/dL, 1.97 µg/dL and 2.54 µg/dL. The diagnosis of adrenal insufficiency was confirmed after the ACTH stimulation test, and prednisolone 5 mg/day was given for maintenance. The patient's past medical history revealed that she had not have tears when crying since childhood. Alacrima was detected after she was referred to the Department of Ophthalmology. She was diagnosed with AS in view of the existing clinical and laboratory findings. Electromyography (EMG) and brain magnetic resonance (MR) imaging, which were performed to rule out neurological involvement, were found to be normal. In addition, the patient's family history revealed that two siblings had died at a younger age without being diagnosed. On observing clinical improvement after the pneumatic dilatation for achalasia, she was discharged.

DISCUSSION

Allgrove syndrome was first defined by Allgrove et al in 1978, and is characterised by the triad of achalasia, alacrima and adrenal insufficiency.⁽¹⁾ Gazarian et al suggested that this syndrome should be named 4A syndrome, with the addition of autonomic dysfunction, motor neuropathy, sensory disorder, mental retardation and similar neurologic diseases as the fourth component.⁽³⁾ Our patient had the classic triad of achalasia, alacrima and adrenal insufficiency, and was thus diagnosed

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with AS. Her neurological examination, brain MR imaging and EMG, which were all performed to screen for neurological involvement, were found to be normal. Generally, AS displays a familial cluster.⁽⁴⁾ Although we could not do a genetic examination, the death of two siblings at a young age suggests that other members of the family could have had this syndrome. There is also a possibility that our patient was the first case in the family.

ACTH insensitivity is an important component of AS. Another genetic reason for ACTH insensitivity is familial glucocorticoid insufficiency (FGD). In both cases, primary adrenal insufficiency is present. Since ACTH insensitivity is present in both diseases, AS was thought to be a variant of FGD in the past. Recent studies, however, have shown that AS is a different entity, with different molecular and genetic aetiologies. The ACTH receptor gene, located on the short arm of chromosome 18 (18p11.2), is responsible for FGD, while the gene responsible for AS is located on the long arm of chromosome 12 (12q13).^(2,5,6)

Currently, the incidence of AS is still unknown, and the syndrome has only been published as case reports in the literature. Adrenal insufficiency generally starts at pre-puberty. However, since there exist cases reported in the third decade of life, the diagnosis of AS should not be excluded in the absence of adrenal insufficiency.^(7,8) Several cases have displayed classical symptoms of primary adrenal insufficiency such as hypoglycaemia symptoms and shock. During skin examination, hyperpigmentation may be seen, and pigmentation changes in the buccal mucosa, loop areas and scar tissues should be carefully examined.⁽⁵⁾ Our patient presented to the hospital with adrenal insufficiency, which was triggered by infection of the urinary system and gastrointestinal bleeding. She was also hypoglycaemic and hypotensive, and had hyperpigmentation in the abdominal scar tissue and buccal mucosa. Despite the presence of risk factors such as upper gastrointestinal bleeding and urinary tract infection, her cortisol level was 4.52 µg/dL.

Hyperpotassaemia, a likely finding in adrenal insufficiency, was not present in our case. In a recently published series, hyperpotassaemia (> 5 mEq/L) was observed in only nine out of 18 patients diagnosed with adrenal insufficiency.⁽⁹⁾ For this reason, it should be borne in mind that the absence of hyperpotassaemia does not necessarily exclude a diagnosis of adrenal insufficiency. It is very difficult to make a diagnosis of adrenal insufficiency in the presence of an infection. Hypotension can be observed both in infection-related sepsis and adrenal insufficiency. It is still debatable whether the cortisol level indicates adrenal insufficiency in critical patients. While some have claimed that a random cortisol measurement below 15 µg/dL is sufficient to diagnose adrenal insufficiency,⁽¹⁰⁾ others have asserted that the level should be below 25 µg/dL.⁽¹¹⁾ According to another opinion, a cortisol increment < 9 µg/dL after cosyntropin stimulation is adequate for making a diagnosis of adrenal insufficiency.^(10,12) However, others have opined that

adrenal insufficiency is likely with a baseline cortisol level < 10 µg/dL and a cosyntropin-stimulated cortisol level < 44 µg/dL.⁽¹³⁾ In our case, the baseline cortisol level was 4.52 µg/dL and the peak cortisol level after cosyntropin stimulation was 2.54 µg/dL; these values are consistent with adrenal insufficiency in the above studies.⁽¹⁰⁻¹³⁾ Based on our finding of adrenal insufficiency, we initiated steroid replacement therapy. Upon steroid treatment, our patient's serum glucose and arterial blood pressure returned to normal. Hence, the diagnosis of adrenal insufficiency was confirmed via ACTH stimulation test.

Alacrima is considered to be an early symptom of AS, and appears during early infancy.^(5,8) Our patient's past medical history suggests that her alacrima had begun during childhood. Oesophageal achalasia, however, is rare in children. The absence of peristalsis within the body of the oesophagus is characterised by a relaxation defect in the gastro-oesophageal sphincter and a dilatation in the proximal oesophagus. Achalasia may sometimes be a component of AS, and displays autosomal recessive inheritance.^(2,8,14) Oesophagography of the patient revealed a narrowing in the cardio-oesophageal junction and a dilatation of the oesophagus proximal to the junction. Histopathologic examination was not performed. In AS, adrenal insufficiency is typically diagnosed concurrently with or after achalasia detection.⁽⁴⁾ However, adrenal insufficiency in our patient was diagnosed eight years after the appearance of achalasia.

In conclusion, our patient was diagnosed with AS in view of the triad of achalasia, alacrima and adrenal insufficiency, although no genetic analysis was done. We report this case to highlight that adrenal insufficiency may appear at a later stage in AS and that there is a need to evaluate the adrenal functions of young patients with alacrima and achalasia.

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