Case Report

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A 16-year-old boy presented with triple-A syndrome associated with neuromuscular disorders: a case report

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Introduction and importance: Allgrove syndrome (AS) (AAA syndrome) is a rare autosomal recessive disease caused by mutations in the AAAS gene located on chromosome 12q13. The AAAS gene encodes for the ALADIN protein (alacrima, achalasia, adrenal insufficiency, neurologic disorder). AS can manifest with a plethora of symptoms. Early recognition of the syndrome remains challenging due to its rarity and progressive nature. This report presents an unusual case of triple-A syndrome (TAS) with concurrent neuromuscular manifestations. Understanding the atypical presentation of this syndrome is vital for early diagnosis and appropriate management.

Case presentation: We report a 16-year-old boy with severe malnutrition presented with painful swallowing, fatigue, and bilateral congenital ptosis. Barium swallow, upper gastrointestinal endoscopy, and Shimmer test were performed, which led to the diagnosis of TAS. Treatment included laparoscopic Heller's procedure, artificial tears, hydrocortisone.

Clinical discussion: TAS, also known as AS, is a rare multisystem disorder characterized by achalasia, Addison's disease, and alacrima. This syndrome is occasionally referred to as 4A syndrome due to the inclusion of autonomic dysfunction. There is no treatment for AS. Management includes artificial tears for alacrima, glucocorticoid replacement therapy to treat adrenal insufficiency, and treatment of achalasia.

Conclusion: This case emphasizes the importance of considering atypical presentations of TAS. Early diagnosis and treatment are paramount in addressing the varied components of this rare disorder. Understanding the clinical complexities of this syndrome aids in improved patient care and underscores the necessity for comprehensive evaluation and management in similar cases.

Keywords: achalasia, adrenal insufficiency, alacrima, Allgrove syndrome, case report, congenital ptosis, dental caries, triple-A syndrome, xerostomia

Background

Triple-A syndrome (TAS), also known as Allgrove syndrome (AS) has been rarely described worldwide and was first identified in 1978 by Jeremy Allgrove. It is a neglected disease, commonly manifesting with the triad of adrenal insufficiency, achalasia of the esophageal cardia, and alacrima (AAA (.The earliest and most frequent symptom in most cases is alacrima, and it is associated with achalasia in ~75% of cases[1]. The adrenal insufficiency may be a late finding or may not appear at all[2].

HIGHLIGHTS

- Allgrove syndrome (AS) is a rare multisystem syndrome that has a wide range of presenting manifestations.
- The main three components of AS are alacrimia, adrenal insufficiency, and achalasia.
- Additional features include dental, oral, neurological, and autonomic manifestations could be present.
- It is diagnosed clinically in most cases; the treatment focuses on managing individual conditions.

Adrenal insufficiency, also called Addison's disease, is a failure of the adrenal glands to produce adequate amounts of adrenocortical hormones, which leads to the deficiency in all three hormones produced by the adrenal cortex: androgen, cortisol, and aldosterone. Symptoms usually do not appear before more than 90% of the adrenal cortices have been destroyed.

Achalasia happens when the lower esophageal sphincter fails to relax as well as losing peristalsis in the distal esophagus leading to accumulation of food in that part, which can cause dysphagia. Alacrima is the absence or inadequacy of tear production.

After adrenal insufficiency and achalasia have been corrected, the worsening of neurologic impairment seems to be a major prognostic factor for the TAS[3]. This case report concerns a 16-year-old boy who was referred for evaluation of dysphagia and was a challenging diagnosis. A high degree of suspicion enables

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all the components of this syndrome to be searched for, as early diagnosis can reduce morbidity and mortality.

This work has been reported in line with the SCARE 2023 criteria[4].

Objective

To report a rare case of AS in a 16-year-old male with neuromuscular disorders.

Case report

A 16-year-old boy presented at our hospital with complaints of dysphagia to liquids and solids. His parents reported that he had difficulties eating solid food starting early when he was an infant. The patient gave a history of poor vision, generalized weakness, dysarthria, and fainting recently. He was born full-term with no complications from non-consanguineous parents. The other siblings are healthy and asymptomatic.

On examination, he was thin, with a body mass index of 10.7 kg/m^2. He had severe muscular atrophy and several light pigmentations of the skin on the child's trunk.

In the beginning, Myasthenia gravis was suspected due to the patient's abnormal gait, acetylcholine receptor (ACHR) antibody test was ordered, and it was normal at 0.28 mmol/l.

His baseline investigations revealed a hemoglobin of 14.4 g/dl, total leukocyte count of 9.700/cmm^3, platelet count of 439×10^9/l, his basal serum cortisol level was normal 13.87 µg/dl (normal range = 5–25 µg/dl). We performed a morning cortisol assay and plasma adrenocorticotropic hormone (ACTH) test, and both were normal, which excluded adrenal insufficiency. Aldosterone and plasma renin activity (PRA) were both normal. Electrolyte levels were normal sodium 136 mmol/l (normal 135–145) and potassium 4.1 mmol/l (normal 3.1–5.5).

The patient was hypoglycemic, which explains the fainting fits. Other tests like blood tests, thyroid-stimulating hormone (TSH), liver function tests (LFTs), and kidney function tests were all normal.

A thoracic contrast-enhanced computed tomography scan did not show anything significant.

A contrast esophagram series showed a 'bird's beak' appearance (Fig. 1) followed by upper gastrointestinal endoscopy (Fig. 2). Esophageal manometry is used to confirm the diagnosis of achalasia; it was not available at the time so we relied on the first two tests to diagnose it.

Ophthalmological consultation revealed keratopathy and corneal ulceration with congenital ptosis. A Schirmer's test was positive; wetting was 2 mm in the right eye and 1.5 mm in the left eye at 5 min, whereas normal wetting at 5 min is greater than 5 mm, which confirmed bilateral alacrima. Dental consultation reported a presence of xerostomia and dental caries without any pigmentations of the oral mucosa; a panoramic radiograph of the teeth was ordered, which showed generalized caries and multiple teeth deformities (Fig. 3).

Based on these findings, a clinical diagnosis of AS was made. We could not perform a genetic study to confirm the diagnosis because it was not available.

Treatment consisted of artificial tears for the alacrima. To treat the achalasia, a laparoscopic Heller procedure was performed.

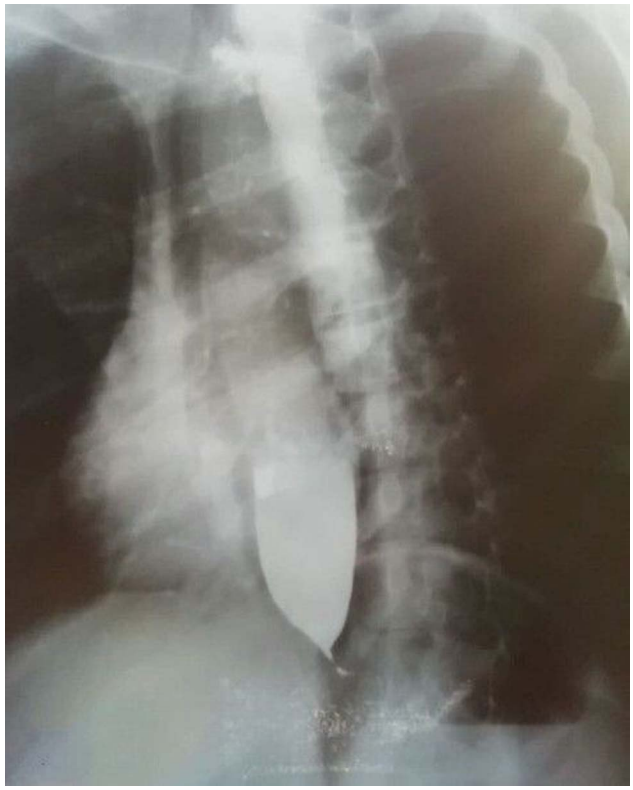

Figure 1. Barium swallow showing dilated esophagus with bird's beak deformity.

Upon subsequent assessments, the patient exhibited a marked enhancement in his overall well-being, and notably, the patient reported an improvement in his dysphagia and was able to gain 4 kg within a month. His vision improved with the application of artificial tear drops. However, during our evaluations, we identified hypoglycemia alongside a mild manifestation of adrenal insufficiency, leading us to initiate a therapeutic regimen involving the prescription of a low-dose hydrocortisone.

The patient will be followed up regularly to monitor the development of the case.

Discussion and conclusion

AS is a hereditary autosomal recessive syndrome, and its exact prevalence is unknown as case reports are a rarity. It usually manifests in the first decade of life.

The syndrome is characterized by three main components: alacrima, achalasia, and adrenocorticotropic insufficiency. In some cases, patients could present with only two[5,6], for example, achalasia and alacrima, without adrenocortical insufficiency, as in our case.

Rivera-Suazo *et al.*[6], discussed that AS could present early in life with two or more manifestations and develop the classical triad later in life, which points to the importance of early diagnoses and increasing awareness among healthcare professionals regarding this syndrome.

Alacrima is the earliest and most persistent finding; it occurs due to structural abnormalities in the lacrimal gland and autonomic dysregulation[7].

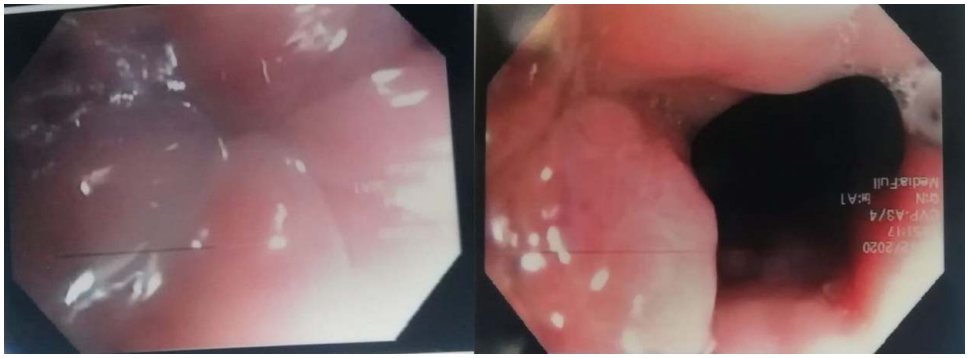

Figure 2. Puckering of the gastroesophageal junction necessitating more pressure than usual to traverse.

Adrenocortical insufficiency due to ACTH resistance occurs owing to progressive adrenal destruction at a variable time after birth; it usually presents as skin pigmentation and hypoglycemic attacks and is the leading cause of mortality in this syndrome[8].

Some studies indicate that adrenocortical insufficiency may develop later, even 5–10 years after other manifestations, like achalasia[9]. So, the patient should be monitored for a long time by the doctors and parents, as in our case, the patient showed some pigmentation on his trunk at presentation with fainting attacks due to hypoglycemia. The development of adrenal insufficiency was noted at later stages.

Luigetti *et al*.[1], revealed that achalasia is the first symptom of AS. On the other hand, Örnek *et al*.[10], considered the first manifestation is alacrima, but it is usually unnoticed.

AS could have other additional symptoms that differ from one patient to another. Miyazawa *et al*.[11], presents a case of suffering from muscle weakness and dysarthria as a neurological abnormality called 4A syndrome, as in our case, but our patient was also suffering from congenital ptosis. Melek *et al*.[12], mentioned the strong connection between alterations in the oral cavity and systemic health; in our case, the patient had xerostomia with generalized dental caries without any pigmentations of the oral mucosa, which points to the importance of early referral to dental specialists for these patients for adequate dental care and treatment.

There is no cure for TAS; treatment focuses on managing individual conditions. The prognosis depends on the identification and treatment of adrenal failure. Lifelong glucocorticoid replacement therapy is needed for adrenal insufficiency. Mineralocorticoid replacement is also needed whenever this deficiency is also present. Alacrima is managed by applying topical lubricants.

Achalasia can be treated with pneumatic balloon dilatation, endoscopic myotomy, or Heller's, which is used in our case because many specialists had recommended the Heller myotomy over other interventions[6,13]. By actively searching for the other elements of TAS, their effects may be minimized early.

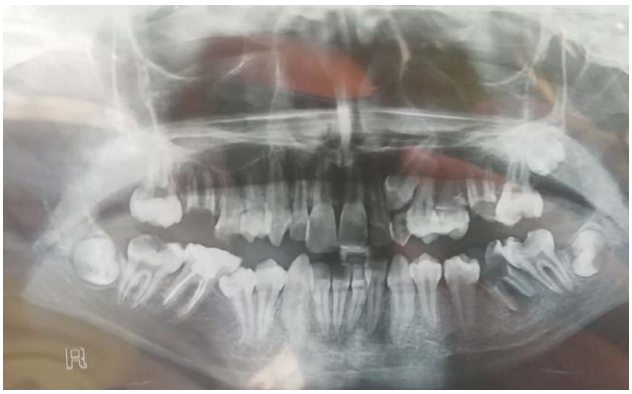

Figure 3. Panoramic radiograph of the teeth.

Conclusion

AS is a multisystem disease, and the main manifestations may appear at any time from infancy to adulthood. Although there are a few published cases of AS in the medical literature, we recommend that this syndrome should be suspected in patients with neurological disorders like muscle atrophy or dysarthria associated with any two of the main symptoms of the syndrome (alacrima, achalasia, and adrenal insufficiency).

Ethical approval

The study adhered to the tenets of the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient's parents/legal guardian and the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.N.S.: followed up with the patient, obtained the patient's consent, wrote in the original draft, reviewed the literature, prepared the figures, and reviewed and edited the manuscript; N.S., A.R., Y.A., and B.A.: wrote up part of the original draft, reviewed the literature, and reviewed the final manuscript; A.N.: made therapeutic regimen, examined and followed up the patient, and revised and edited the final manuscript. All authors have read and approved the manuscript.

Conflicts of interest disclosure

No conflicting relationship exists for any of the authors.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
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References

[1] Luigetti M, Pizzuti A, Bartoletti S, *et al*. Triple A syndrome: a novel compound heterozygous mutation in the AAAS gene in an Italian patient without adrenal insufficiency. J Neurol Sci 2010;290:150–2.
[2] Chu ML, Berlin D, Axelrod FB. Allgrove syndrome: documenting cholinergic dysfunction by autonomic tests. J Pediatr 1996;129:156–9.
[3] Dumic M, Barišic N, Kusec V, *et al*. Long-term clinical follow-up and molecular genetic findings in eight patients with triple A syndrome. Eur J Pediatr 2012;171:1453–9.
[4] Sohrabi C, Mathew G, Maria N, *et al*. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2023;109:1136–40.
[5] Alhussaini B, Gottrand F, Goutet JM, *et al*. Clinical and manometric characteristics of Allgrove syndrome. J Pediatr Gastroenterol Nutr 2011; 53:271–4.
[6] Rivera-Suazo Y, Espriu-Ramírez MX, Trauernicht-Mendieta SA, *et al*. Allgrove syndrome in a toddler: alacrima and achalasia, with no adrenal insufficiency. Rev Gastroenterol Mex 2020;86:441–3.
[7] Clark AJ, Weber A. Adrenocorticotropin insensitivity syndromes. Endocr Rev 1998;19:828–43.
[8] Kinjo S, Takemoto M, Miyako K, *et al*. Two cases of Allgrove syndrome with mutations in the AAAS gene. Endocr J 2004;51:473–7.
[9] Kurnaz E, Duminuco P, Aycan Z, *et al*. Clinical and genetic characterisation of a series of patients with triple A syndrome. Eur J Pediatr 2018; 177:363–9.
[10] Örnek K, Atilla H, Zilelioğlu G. Pediatric alacrima, achalasia, and mental retardation. J AAPOS 2002;6:261–3.
[11] Miyazawa H, Kimura M, Yonezawa H, *et al*. Sporadic triple A (Allgrove) syndrome with novel tandem mutations. Intern Med 2021;60: 799–802.
[12] Melek BD, Yacine R, Mehdi D, *et al*. Dental involvement in a child with triple A syndrome. Int J Dent Oral Sci 2017;4:498–502.
[13] van Lennep M, van Wijk MP, Omari TIM, *et al*. Clinical management of pediatric achalasia: a survey of current practice. J Pediatr Gastroenterol Nutr 2019;68:521–6.