



Allgrove Syndrome: A Case Report and Review of the Literature

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPR/2024/v14i5347

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/115994>

Case Report

Received: 12/02/2024

Accepted: 16/04/2024

Published: 23/04/2024

ABSTRACT

Allgrove syndrome, or Triple A syndrome, is a very rare autosomal recessive disorder with three key clinical features: achalasia, alacrima, and adrenal insufficiency. Around a third of patients present with additional features, such as neurological and autonomic manifestations (making it syndrome 4A). Alacrima usually appears in early childhood, while achalasia and adrenal insufficiency manifest later. In adulthood, the presentation is predominantly neurological, with autonomic impairment and polyneuropathy.

We report the case of a 7-year-old female patient who consulted us with delayed weight gain and nutritional issues, alacrimia, and chronic vomiting since the age of 6 months. Clinical examination revealed malnutrition, with weight and BMI less than 3 standard deviations. Alacrima was confirmed by a positive Schirmer's test. Oesogastroduodenal transit, gastric fibroscopy, and manometry confirmed achalasia. In our case, there was no neurological involvement nor adrenal insufficiency. Treatment consisted of optimal managing of the manifestations of the disease.

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Keywords: Achalasia; alacrimia; adrenal insufficiency; triple-A syndrome.

1. INTRODUCTION

Triple-A syndrome is a rare, complex, multi-system genetic disorder caused by one or more autosomal recessive mutations, resulting in a characteristic presentation of alacrimia, achalasia, and adrenal insufficiency, encapsulated in the acronym "AAA":

In addition to this typical "AAA" presentation, there are severe neurological disturbances, sometimes highly incapacitating, affecting the autonomic, peripheral, and central nervous system. These disorders do not coincide with the triple A triad; they develop later but alter significantly patients' quality of life. Hence, the syndrome is sometimes referred to as quadruple A (Alacrimia, Achalasia, Adrenal insufficiency, and Autonomic dysfunction).

In essence, Triple A syndrome appears to be a neuroendocrine syndrome with atypical, complex, and varied symptomatology. Early diagnosis is crucial for specialized management tailored to each patient's symptomatic profile [1,2].

We present a case from our department with this condition.

2. CASE PRESENTATION

S.E, a 7-year-old girl, the eldest of two siblings, born to parents in a 1st-degree consanguineous marriage, presented with a history of underweight and nutritional deficiency. Notably, she lacked tears even during crying spells and experienced chronic vomiting since the age of 6 months, leading to her admission to our clinic.

Upon initial clinical examination, a malnourished child was observed, underweight by less than 3 standard deviations, with a height of 119cm (+2SD) and a BMI of 9.88 (-3SD). Ophthalmological examination revealed severe tear production insufficiency, confirmed by Schirmer's test (<4mm), while neurological, mucocutaneous, and other examinations were normal. Oesogastroduodenal transit indicated esophageal achalasia (Fig. 1). Oesogastroduodenal fibroscopy disclosed mycotic esophagitis, with a tight but penetrable cardiac orifice and esophageal hypermotility. Oesophageal manometry revealed a defect in esogastric relaxation, hypertonicity of the lower esophageal sphincter, and aperistalsis, consistent with Chicago type I achalasia (Fig. 2). Biological examination showed normal cortisol (478.8 nmol/L) and ACTH (9.5 pg/ml) levels. The blood ionogram revealed no abnormalities, with sodium levels at 137mmol/l, potassium level at 4.3mmol/l, and calcium levels at 100mg/l. Blood glucose monitoring was normal. Genetic testing for the AAAS gene is currently underway.

The patient received treatment with artificial tears, a nasogastric tube for parenteral nutrition for two weeks, and antifungal treatment for her esophagitis. Progress was marked by the regression of vomiting and weight gain. Follow-up blood ionograms as well as adrenal function tests showed no abnormalities.

Six months later, the child was readmitted to the department with dehydration and malnutrition. A nasogastric tube was inserted for enteral feeding, and she was subsequently transferred to the pediatric surgery department for surgical treatment.

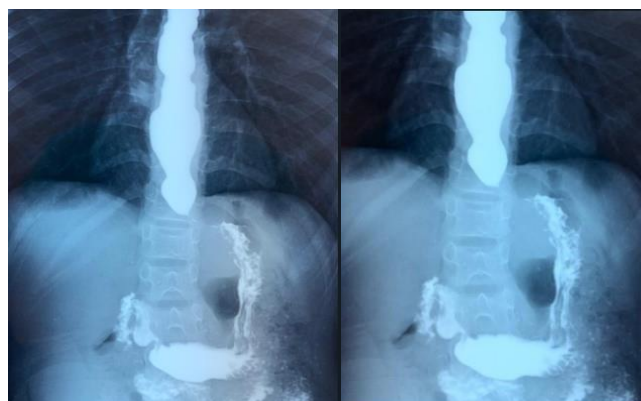


Fig. 1. Oesogastroduodenal transit showing regular narrowing of the lower oesophagus

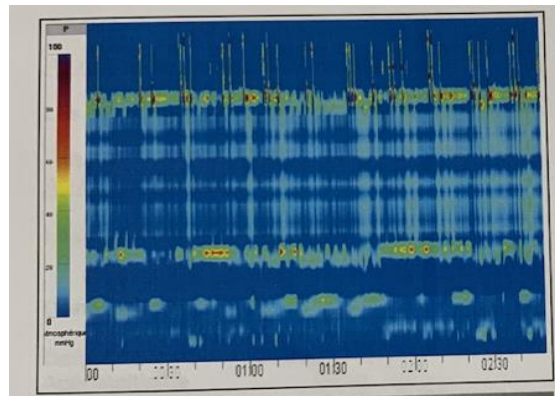


Fig. 2. Esophageal manometry in favor of Chicago type I achalasia



Fig. 3. Front thoracic X-ray, showing no abnormalities

3. DISCUSSION

Allgrove syndrome is a rare autosomal recessive inherited disorder. Its incidence is unknown, but around 200 cases have been reported worldwide since the syndrome was first described in 1978 [3]. It affects both males and females, sex ratio = 1 [4].

Is the consequence of a genetic mutation in the AAAS (Achalasia - Addisonianism- Alacrima Syndrome) gene, located on chromosome 12(12q13), coding for the nucleoporin ALADIN (Alacrima-Achalasia-Adrenal Insufficiency Neurologic Disorder) [2,4]. The hypothesis explaining the pathogenic mechanism of this syndrome suggests that mutation of the AAAS gene results in a defect in the localization of the ALADIN protein within the nuclear pore complex, inducing a defect in the import of intranuclear molecules, mainly antioxidant and DNA damage repair molecules [5-7].

The primary ophthalmological manifestations in triple A syndrome encompass alacrimia with atrophy of the lacrimal glands and the absence of lacrimation, kerato-conjunctivitis, pupillary anomalies (including slow pupillary clearance), accommodation disorders, amblyopia, and optic atrophy. Alacrimia emerges as the earliest and most specific symptom, with a prevalence exceeding 90% in affected subjects [4,8-9].

In our case, alacrimia was diagnosed using the Schirmer's test and managed with artificial tears to prevent ocular dryness.

Achalasia cardia is characterized by incomplete relaxation of the lower esophageal sphincter (LES), associated with a defect in peristalsis of the esophageal body, also known as megaesophagus. This condition leads to low-grade dysphagia (in around 75% of patients), regurgitation, vomiting, weight loss, and

sometimes nocturnal coughing. In our patient, achalasia was responsible for chronic vomiting, resulting in significant weight loss and undernutrition. Diagnosis is based on three examinations: barium oesogastroduodenal transit (TOGD), esophageal manometry, and oesogastroduodenal fibroscopy (FOGD) [7].

Adrenal insufficiency is observed in 70% of patients, developing gradually with a highly variable age of onset ranging from the first to the third decade. Typically, in their first decade, Triple A children experience several episodes of hypoglycemia or severe hypotension. Occasionally, extremely low cortisol levels can lead to a comatose state, a consequence of significant hypoglycemia that may result in sudden death [6]. Dermatologically, melanoderma is present in three-quarters of cases, progressing with long-standing glucocorticoid deficiency and sufficiently elevated ACTH levels [10]. In our case, the hormonal balance was normal, with no episodes of hypoglycemia.

Neurological manifestations in Allgrove syndrome can affect the autonomic, peripheral, and central nervous systems, often leading to mixed sensory and motor neuropathies later on [11]. This implies that neurons are the primary cells affected by AAAS mutations. Neurological symptoms, along with alacrimia and achalasia, result from progressive neuronal degeneration [12]. The condition significantly impacts the patient's quality of life, especially that no specific treatment is currently available. As of now, our patient's neurological examination remains normal.

Oral Health: Xerostomia has been noted in case reports among individuals with 3A syndrome, with confirmatory sialometry demonstrating reduced salivary secretion. Hyposalivation has also been identified as a cause of dysphagia following achalasia correction. [13]

A small, spastic, fissured tongue is a typical feature of the syndrome. Premature tooth loss has been reported, sometimes attributed to reduced saliva production and subsequent dental decay [14].

There is also significant symptom overlap between 3A syndrome and Sjögren syndrome, especially in patients potentially diagnosed with "achalasia sicca." [14]

Artificial saliva has proven effective for those with reduced salivary function, while oral candidiasis should be treated with antifungals. [14]

Our patient presents with a satisfactory oral health status.

The treatment of Allgrove's disease involves three components. For Alacrimia: Regular application of lubricants and artificial tears is sufficient.

Management options of achalasia includes myorelaxant drugs, pneumatic dilatation, botulinum toxin injection, and surgery (Heller myotomy). Myotomy proves effective in 92% of cases, providing the best long-term results [15], with an increased risk of gastroparesis and aspiration related to incisions on the lower esophageal sphincter [16-17]. Expert recommendations advocate for the use of antiemetics, antacids, and head elevation in managing these patients [16]. Regarding adrenal insufficiency, exogenous glucocorticoids (hydrocortisone at a replacement dose of between 15 and 20 mg/m²/d, divided into at least two doses in small children), mineralocorticoids (9 α -fludrocortisone 25 to 150 μ g/d per os in two daily doses adapted according to plasma renin levels), and, if required, DHEA (25 to 50 mg synthetic DHEA in capsule form, in one daily dose) are the required treatment.

4. CONCLUSION

Allgrove syndrome is a rare and multi-systemic disease characterized by significant clinical heterogeneity. Early and multidisciplinary management is essential. Upon diagnosis confirmation, a genetic study to identify the AAAS gene mutation becomes crucial.

CONSENT

As per international standard or university standard, parental(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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