Allgrove syndrome:acase report and review of the literature

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, fibroscopy, and manometry confirmed achalasia. In our case, there was no neurological involvement nor adrenal insufficiency. Treatment consisted of optimalmanagingof thesymptoms of the disease.

KEYWORDS: Achalasia, alacrymia, 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":

~~The triad of symptoms defines patients with this syndrome, Alacrimia, Achalasia, and Adrenal insufficiency~~.

In addition to this typical "AAA" presentation, there are severe neurological disturbances, sometimes highly incapacitating, affecting the autonomic, peripheral, and central nervous system~~s~~. These disorders do not coincide with the triple A triad; they develop later but ~~are disabling~~, altersignificantly r~~educing~~ 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). Oesogastroduodenalfibroscopydisclosed mycotic esophagitis, with a tight but penetrable cardiac orifice and oesophageal hypermotility. Oesophageal manometry revealed a defect in esogastric relaxation, hypertonicity of the lower esophageal sphincter, and apereistalsis, 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 natremia at 137mmol/l, potassium levelat 4.3mmol/l, and calcemia 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 ionogramsas well asadrenal 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.

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, ~~with no difference in race~~ (~~rational~~sex ratio = 1). ~~Age of onset is imprecise It affects both males and females, with no difference in race (rational sex = 1).~~ Age of onset is imprecise. [4]

~~Allgrove~~It 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, 6, 7].

The primary ophthalmological manifestations in triple A syndrome encompass alacrymia 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. Alacrymia emerges as the earliest and most specific symptom, with a prevalence exceeding 90% in affected subjects [4, 8, 9].

In our case, alacrymia was diagnosed using the Schirmer 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 oesogastroduodenalfibroscopy (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 alacrymia and achalasia, result from progressive neuronal degeneration [12]. The condition significantly impacts the patient's quality of life, especially ~~as~~ that no specific treatment is currently available. As of now, our patient's neurological examination remains normal.

The treatment of Allgrove's disease involves three components. ForAlacrymia: Regular application of lubricants and artificial tearsis suffiicent.

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 [13]. Regarding Adrenal insufficiency, ~~Management includes~~ 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 (9α-fludrocortisone 25 to 150 µg/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).

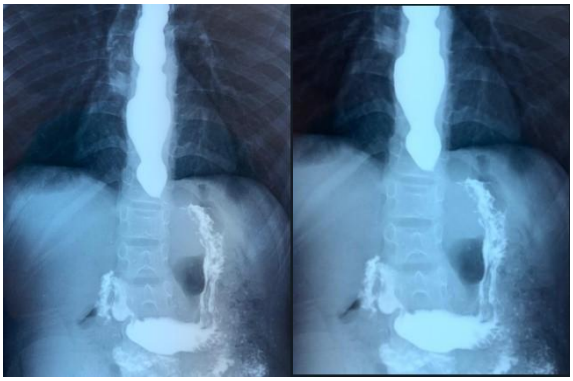

Fig 1: Oesogastroduodenal transit showing regular narrowing of the lower oesophagus.

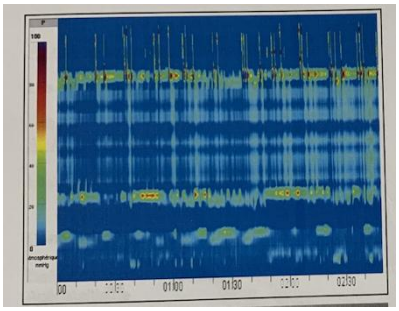

Fig 2: Esophageal manometry in favor of Chicago type I achalasia.

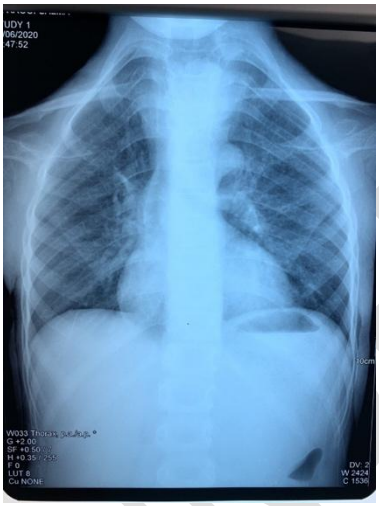

Fig 3: Front thoracic X-ray.

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