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Case Report
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Esophageal Achalasia: The Missing Piece for the Diagnosis of Allgrove / Triple A Syndrome

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Abstract

Objectives and Study: Esophageal achalasia is a rare and underdiagnosed disorder in pediatrics (1). Triple A or Allgrove Syndrome (AS) is a clinical entity characterized by alacrimia, adrenal insufficiency and achalasia (2). We present the first case of AS in a Colombian teenager.

Methods: *A 13 year old presented with choking, dysphagia, and suspicion of Sjogren's syndrome. Medical history revealed a prior diagnosis of adrenal insufficiency, hypothyroidism, optic neuritis, and alacrimia. Barium swallow and High Resolution Manometry, confirmed type II achalasia, giving the start of the AS diagnostic journey. Despite an initial resolution of symptoms following endoscopic pneumatic dilatation, three months later symptoms reappeared and referral to surgical management was indicated.*

Results: *Achalasia, a motility disorder characterized by impaired peristaltism and inadequate lower esophageal sphincter relaxation (3), manifests as dysphagia, reflux, weight loss, and failure to thrive (4). AS is an autosomal recessive disease caused by a defect in the AAAS gene. The triad of symptoms—esophageal achalasia, alacrimia, and adrenal insufficiency—constitutes the diagnostic hallmark (2,4). The onset of symptoms follows a distinct pattern, with alacrimia typically presenting within the first year of life, adrenal insufficiency emerging in the first decade and achalasia developing in adolescence (1-5). AS diagnosis can be challenging, often leading to confusion with other conditions such as Sjogren's syndrome (2,4) Early recognition is crucial, given the syndrome's severe course and a notable rate of therapeutic failure associated with esophageal achalasia (5).*

Conclusions: *This case report not only highlights the underrecognized nature of AS but also emphasizes the importance of early diagnosis in guiding appropriate therapeutic strategies, improving the overall quality of life of patients (4,6,7). The presented case stands as the first reported triple A syndrome patient in Colombia, contributing to the global understanding of this rare entity.*

Keywords: : esophageal achalasia, Allgrove syndrome, Triple A syndrome, AAAS gene, Heller myotomy.

Introduction

Esophageal achalasia, a rare and often underdiagnosed disorder in pediatrics, is characterized by motility alterations along the esophagus (Flokas) [1]. The gold standard for its diagnosis is high-resolution manometry, which shows the absence of peristalsis, increased resting pressure on the lower esophageal sphincter (LES) and failure of the sphincter to relax [2]. Children with achalasia present with dysphagia, regurgitation, failure to thrive and thoracic pain. Its etiology is not completely understood but it is attributed to an imbalance between neurotransmitters due to the loss of the inhibitory myenteric plexus [1, 2]. Achalasia has been associated with trisomy 21, Chagas disease and familial cases due to Triple A syndrome (TAS) [2]. Allgrove Syndrome (AS), also known as TAS (OMIM 23550), is a rare autosomal recessive disorder characterized by the triad of alacrimia, adrenal insufficiency, and achalasia [3, 4]. It is caused by mutations in the AAAS gene, which encodes the ALADIN protein, involved in intracellular transduction pathways [5]. This case report outlines the diagnosis of AS in a 13-year-old Colombian teenager.

Clinical Case

A 13-year-old was referred to our institution with choking, dysphagia for both liquids and solids, and suspicion of Sjögren's syndrome. Her medical history revealed a prior diagnosis of adrenal insufficiency at the age of eight, for which she was receiving hydrocortisone. She was also diagnosed with hypothyroidism and was being evaluated for optic neuritis and dry eye. A salivary gland biopsy was negative for Sjögren's syndrome, and her Schirmer test was inconclusive. A barium swallow revealed decreased esophageal peristalsis, slow and incomplete emptying of the contrast medium and the bird-beak sign. High-resolution Manometry showed an elevated IRP of 61.9 and confirmed type II achalasia. When directly asked, the mother reported alacrimia since the patient was a toddler, which gave us the three cardinal symptoms for AS. Initial management included pneumatic balloon dilation; however, despite two sessions, three months later symptoms reappeared with an Eckard score of 5. Referral for surgical management was then indicated, and the patient underwent a Heller's myotomy without complications, resulting in an Eckard score of 1. Whole exome sequencing revealed a homozygous pathogenic variant (c.1331+1G>A) in the AAAS gene which confirmed AS diagnosis.

Discussion

Achalasia, meaning "failure to relax", is a motility disorder characterized by impaired peristalsis, inadequate LES relaxation, and increased sphincter pressure at rest [2, 6, 7]. It is a progressive, incurable disorder that significantly compromises the quality of life of patients and families [8].

The annual incidence of achalasia is estimated at 0.1 per 1000000 in the general population, with less than 5% of cases diagnosed in children under the age of 15 years [2, 8-10]. Achalasia has been associated with trisomy 21, AS, Chagas disease, familial dysautonomia, among others [11]. It has also been linked to autoimmune diseases, with up to one fourth of patients having thyroid disease, as seen in our patient [10].

The etiology of achalasia is not fully understood, but it is thought to be caused by degeneration of the myenteric plexus in the esophagus [12]. The main symptoms include progressive dysphagia, reflux, regurgitation, weight loss, and failure to thrive [7, 9]. Some patients also report nocturnal cough and frequent respiratory tract infections due to chronic aspiration [1, 2].These symptoms are part of the Eckardt score, which is used to grade severity and helps standardize response and outcomes [2].

The diagnosis can be made with an esophagram, which shows a dilated esophagus narrowing toward the LES, creating a characteristic "bird-beak" appearance, as seen in our patient [8]. The gold standard to diagnose achalasia is high-resolution manometry, which evaluates peristalsis, resting pressure in the esophagus and LES relaxation [2, 9]. The Chicago classification allows differentiation among the three types of achalasia: type I, characterized by minimal esophageal contractility; type II, with compartmentalized pressurization without peristalsis; and type III, marked by spastic distal contractions. The manometry performed in our patient showed type II achalasia, which has been associated with a better therapeutic response [2, 12].

Given the rarity of achalasia among children, there is no consensus regarding the first line therapy or follow-up protocols [7, 9, 10].The goal is to relieve dysphagia by reducing LES pressure [2, 8]. Successful treatment can be obtained with esophageal balloon dilation and surgery, which includes laparoscopic Hellers' myotomy and peroral endoscopic myotomy (POEM)(2,9). Both techniques have proven to be effective and safe in children, with no clear superiority of one over the other [2, 11, 13]. Due to their short-term effectiveness, calcium channel blockers and botulinum toxin are not commonly used in pediatrics [8]. A successful therapy is defined as an Eckardt score of less than 3 or reduction in IRP, though these criteria have not yet been validated in the pediatric population [14].

Allgrove syndrome (AS), also known as triple A syndrome (TAS), is a rare autosomal recessive disorder caused by a defect in the AAAS gene located on 12q13 [5]. This gene encodes the ALADIN protein, which plays an important role in the trafficking of proteins and/or RNA between the nucleus and the cytoplasm. Mutations in this protein interfere with redox homeostasis and inhibit steroidogenesis [4, 15].

AS exhibits phenotypic variability in terms of symptom onset, frequency and severity [16]. It also has multisystemic compromise due to the ubiquitous nature of the ALADIN protein [4, 17, 18]. This protein has a greater expression in the adrenal gland, gastrointestinal structures, pituitary gland and cerebellum [19].

Its prevalence is not well established; however, it is estimated to occur in 1 in 1 million individuals. This estimate may underestimate the true prevalence due to diagnostic difficulties [15, 16]. Some authors reported that up to 1% of cases of primary adrenal insufficiency may be due to AS [17].

The name "Triple A" refers to the triad of symptoms: alacrimia, esophageal achalasia and adrenal insufficiency. The onset of symptoms follows a variable pattern, as they can develop from childhood through adolescence [1, 4, 6, 20]. Up to two-thirds of

patients exhibit all three cardinal symptoms, one-third manifest only two of them and fewer than 10% present with just one [4, 5]. Alacrimia is often described as the first symptom to appear, but its recognition is typically retrospective since parents may not inquire about this abnormality, as seen in our patient [16]. Alacrimia as a single entity is extremely rare, and its presence should prompt consideration of congenital disorders [4, 5]. Adrenal insufficiency usually emerges in the first decade and can present with skin pigmentation, seizures or hypoglycemia [3, 9]. When asked, our patient was diagnosed due to syncope secondary to hypoglycemia. AS can be lethal, manifesting as severe hypoglycemia or autonomic dysregulation [4, 5, 16]. It is important to educate families about the risks of acute adrenal crisis, and to conduct a preoperative evaluation with an appropriate steroid protocol, as well as taking precautions to prevent aspiration and ocular injury [18, 21]. Regarding achalasia, it typically develops during adolescence. In addition to the classic triad of symptoms, some patients can present with autonomic dysfunction and neurological compromise, which is referred to as 4 A syndrome, Management is symptomatic. For alacrima, the treatment involves artificial tears or eye drops, with follow-up being important due to the risk of corneal abrasion. Adrenal insufficiency is managed with corticosteroid supplementation [4, 5]. Finally, for achalasia,as previously mentioned, there are different management options; the evidence particularly supports esophageal balloon dilation or Heller myotomy, as there is insufficient data on POEM for this pathology. Some authors describe children with AS as being refractory to achalasia treatment and requiring more critical measures [5, 16, 22]. Due to the broad spectrum of AS symptoms, a multidisciplinary approach for diagnosis, management, and follow-up is recommended [16].

This case report not only highlights the underrecognized nature of AS but also emphasizes the importance of early diagnosis in guiding appropriate therapeutic strategies, improving the overall quality of life of patients [4 ,6, 7]. The presented case stands as the first confirmed triple A syndrome patient in Colombia, contributing to the global understanding of this rare entity.

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