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The triad of shadows: Unraveling AAA syndrome

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Abstract
AAA syndrome, also known as Allgrove syndrome, is a rare autosomal recessive disorder characterized by the triad of adrenal insufficiency, achalasia, and alacrima. It results from mutations in the AAAS gene, leading to defective ALADIN protein function, which disrupts nuclear transport and increases cellular vulnerability to oxidative stress. This report presents the case of an 8-year-old girl with a history of dysphagia, absence of tears, and hyperpigmentation, ultimately diagnosed with AAA syndrome despite financial constraints preventing genetic confirmation. The diagnosis was established based on clinical features and relevant investigations, including ophthalmological and gastrointestinal assessments. The case highlights the challenges of diagnosing and managing AAA syndrome, emphasizing the importance of early recognition, multidisciplinary care, and long-term follow-up to address potential neurological and systemic complications. Prompt initiation of hormone replacement therapy and supportive management can significantly improve patient outcomes.

Keywords: AAA syndrome, achalasia, alacrima, adrenal insufficiency, genetic testing

Introduction
AAA syndrome, also known as Allgrove syndrome, is a rare autosomal recessive disorder and was first described by Allgrove *et al*. in 1978. This syndrome is typically identified by the presence of three key features: esophageal achalasia, the absence of tears (alacrima), and adrenal insufficiency that is resistant to stimulation by ACTH [1]. It is caused by mutations in the AAAS gene located on chromosome 12q13. Mutations in this gene lead to the production of a faulty ALADIN protein (alacrima–achalasia–adrenal insufficiency neurologic disorder), a WD-repeat protein of 546 amino acids that is responsible for nuclear pore function and oxidative stress response [2]. Mutations lead to defective nuclear transport and increased cellular vulnerability to oxidative damage, which subsequently affects various organ systems, particularly the adrenal glands, nervous system, and esophagus, leading to different clinical manifestations. We report a case of an 8-year-old girl who presented with swallowing difficulties and reduced tear production. Based on these clinical findings, a diagnosis of triple-A syndrome was established, however, her parents reported financial constraints preventing genetic testing.

Case report
An 8-year-old girl, born to parents with history of consanguineous marriage and with a history of NICU admission at birth, presented with a three-year history of dysphagia for liquids and no tears while crying, alongside a two-month history of intermittent low-grade fever with chills and rigors, dark pigmentation along the knuckles and fatigue, with a prior history of a single episode of seizure at age of four years. Initial evaluation at a local hospital led to a diagnosis of primary adrenal insufficiency, for which she was started on hydrocortisone and fludrocortisone, but she continued to experience repeated hospitalizations. She was referred to a tertiary care centre for further evaluation. The initial assessment revealed low blood pressure of 90/70 mmHg in the supine position, relevant investigations were sent that showed bicarbonate levels of 20.3 mmol/L. The human growth hormone was 8.91 ng/mL. Subsequent ophthalmological assessment confirmed severe alacrima, and a pediatric surgeon's consultation was done and barium swallow and endoscopy were advised, which revealed achalasia cardia. Integrating these findings, alongside relevant investigations and the established primary adrenal insufficiency, the patient was diagnosed with Allgrove Syndrome (AAA syndrome), explaining her multifaceted clinical presentation.

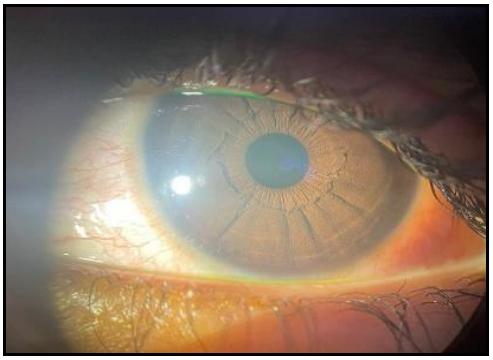

Fig 1: Anterior segment of right eye showing conjunctival congestion

Fig 2: Anterior segment of left eye showing conjunctival congestion and photophobia

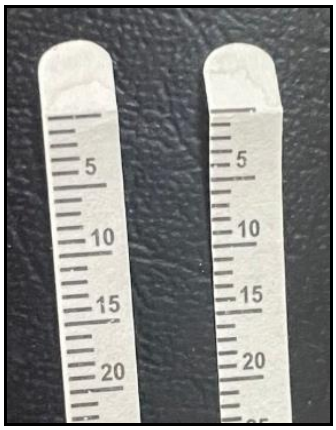

Fig 3: Schirmer's 1 test showing severe alacrimia

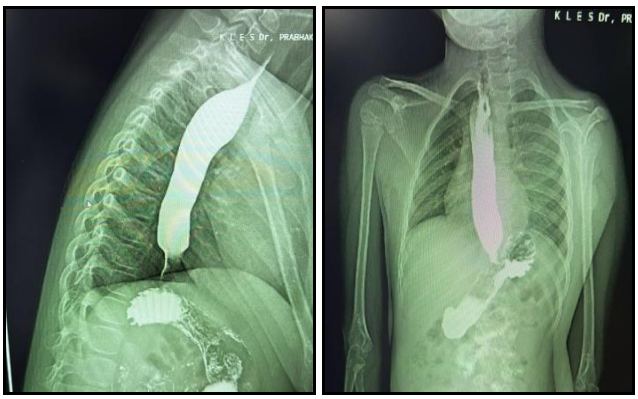

Fig 4: X ray with barium swallow showing presence of bird beak appearance classical of Achlasia cardia

Discussion

Allgrove syndrome, an autosomal recessive disorder with a 25% recurrence risk, has an unknown incidence due to its wide range of possible symptoms [1]. The defining characteristics of Allgrove syndrome include ACTH-resistant adrenal insufficiency, achalasia, and alacrimia. [3] The hallmark triad of Allgrove Syndrome can manifest incompletely, but the presence of at least two features is essential for clinical diagnosis, a scenario commonly known as "double-A syndrome" [4]. Another variation of triple A syndrome is "4A syndrome," which is diagnosed based on the sequential development of autonomic nervous system dysfunction and then central and peripheral nervous system involvement, characterized by features like muscular atrophy, fasciculation, hypoesthesia, nasal speech, ataxia, optic atrophy, and intellectual impairment [5]. The emergence of spinal amyotrophy as an additional feature allows for the classification as "5A syndrome" [6]. In this case, the 8-years-old girl presented with a spectrum of symptoms, including dysphagia for liquids, absence of tears while crying, intermittent low-grade fever, dark pigmentation of the knuckles, fatigue, and a history of a single seizure episode. The presence of primary adrenal insufficiency, along with severe alacrima and confirmed achalasia cardia, led to the diagnosis of Allgrove syndrome. The patient's history of NICU admission and parental consanguinity further support the genetic basis of this disorder.

Alacrima is often the earliest and most consistent manifestation of Allgrove syndrome, present in 90-100% of the patients, though it is frequently overlooked or misattributed to other causes [7]. In this case, the delayed recognition of alacrima underscores the need for heightened clinical suspicion, especially in children with unexplained ocular dryness [8]. Achalasia, characterized by impaired esophageal motility and lower esophageal sphincter dysfunction, contributed to the patient's dysphagia and required pediatric surgical evaluation for definitive diagnosis. The pathophysiology involves an imbalance between excitatory and inhibitory neurons within the myenteric plexus, driven by inflammatory processes, fibrosis, and neuronal degeneration. Clinically, patients may present with regurgitation of undigested food, progressive dysphagia to both solids and liquids, failure to thrive or weight loss, and recurrent aspiration pneumonia [9]. The diagnosis relies on the results of a barium swallow and esophageal manometry. The barium swallow may show esophageal dilation, a "bird beak" narrowing, lack of peristalsis, and poor emptying, while manometry provides further objective evidence of the esophageal motor dysfunction [10]. Acute adrenal insufficiency represents an abrupt and critical deficit in glucocorticoid activity, frequently precipitated by viral etiologies. The clinical presentation is characterized by fatigue, anorexia, emesis, abdominalgia, cyanosis, peripheral hypothermia, hypotension, tachycardia, and a thready pulse. Due to the potential for rapid decompensation and mortality, prompt and accurate diagnosis is paramount [11]. The presence of adrenal insufficiency, confirmed by recurrent hospitalizations and the need for steroid replacement therapy, is a hallmark of the syndrome and necessitates lifelong glucocorticoid and mineralocorticoid management. Beyond the classical triad, patients with Allgrove syndrome may develop neurological manifestations such as dysautonomia, cognitive impairment, and episodic seizures, as seen in this case [12]. The progressive nature of the disorder necessitates long-term follow-up to monitor for

additional complications, including autonomic dysfunction and neurodegenerative features.

This case highlights the importance of a multidisciplinary approach involving pediatric endocrinologists, gastroenterologists, ophthalmologists, and geneticists to ensure comprehensive care. The diagnosis of Allgrove syndrome should be considered in children with a combination of adrenal insufficiency, alacrima, and unexplained gastrointestinal dysmotility. Genetic testing for AAAS mutations may aid in confirmation, particularly in consanguineous families with a suspected hereditary pattern. Clinicians should maintain a high index of suspicion in pediatric patients presenting with components of the classic triad. Early diagnosis and appropriate management, including hormonal replacement therapy and supportive gastrointestinal and ophthalmologic interventions, are crucial to improving patient outcomes and quality of life. Further investigation may enable targeted therapies to address the root genetic and cellular issues of this condition

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