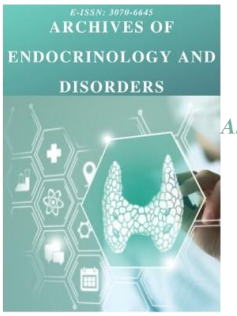

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Case Report

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Adrenal Insufficiency as the First Manifestation of Triple A Syndrome: A Case Report

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Abstract

Background: Triple A syndrome is a rare, underdiagnosed autosomal recessive disorder presenting as alacrima, achalasia and adrenal insufficiency, typically in that order; however, in our case, it presented in a different sequence.

Case presentation: A 5-year-old Caucasian Colombian girl presented with weakness, asthenia, fatigue, anorexia and progressive hyperpigmentation of skin for 6 months without sun exposure. Basal serum cortisol was very low (0.61 µg/dL) and Adrenocorticotropic Hormone (ACTH) was elevated (> 1,250 pg/mL), confirming the diagnosis of primary adrenal insufficiency. Hydrocortisone therapy was started with progressive depigmentation of the skin. Six months later she presented with dysphagia and Allgrove syndrome was suspected. The analysis of the AAAS gene revealed a homozygous missense mutation in exon 12.

Conclusion: Triple A syndrome should be suspected in children who presented with primary adrenal failure without a known cause.

Keywords: Adrenal Insufficiency; Triple A Syndrome; Hyperpigmentation; Missense Mutation

Introduction

Triple A Syndrome (TAS), also known as Allgrove syndrome (OMIM#231550), is a rare autosomal recessive disorder first described by Allgrove in 1978 [1]. Triple A syndrome is frequently difficult to diagnose, leading to delayed diagnosis [1]. It is characterized by the classic triad of adrenal insufficiency resistant to ACTH, achalasia and alacrima, which is present in nearly two-thirds of patients [1-4]. Alacrima commonly manifests as the first symptom in Triple A syndrome, succeeded by achalasia, with adrenal insufficiency emerging later [1]. Adrenal insufficiency, reported in approximately 85% of patients, is often triggered by infectious processes and can pose a life-threatening risk if not identified early [1]. Additionally, TAS may be variably associated with dysfunction of the autonomic nervous system, followed by central and peripheral nervous system abnormalities, which some authors refer to as the "4A syndrome." If spinal amyotrophy is present, it is referred to as the "5A syndrome [1]."

Triple A syndrome is caused by homozygous or compound heterozygous mutations in the AAAS gene (12q13.13), which encodes a protein of the Nuclear Pore Complex (NPC) commonly known as ALADIN [1,2]. This protein is involved in the nucleocytoplasmic transport of proteins and RNA and, therefore, plays a crucial role in cellular processes such as growth, cell differentiation, gene expression and DNA repair [5,6]. Most mutations cause mislocalization of ALADIN protein in the cytoplasm or mutations produce a truncated protein, as a result expression of this protein is seen reduced in the adrenal gland, brain and

gastrointestinal tract, the organs in which the main pathologic manifestations of disease occur [7]. Nonsense, missense, frameshift and splice-site mutations in the AAAS gene have been reported [7]. The AAAS gene is ubiquitously expressed in human tissues, which may explain the diversity of symptoms [1,2].

We present the case of a 5-year-old girl presented with clinical and paraclinical features suggestive of primary adrenal insufficiency, followed by the development of dysphagia and alacrima. Genetic analysis revealed findings consistent with Triple A syndrome.

Case Report

A 5-year-old Caucasian Colombian girl was referred to our endocrine center for the evaluation of weakness, asthenia, fatigue, anorexia and progressive hyperpigmentation of skin for 6 months without sun exposure. She was born full-term, from non-consanguineous parents. Basal serum cortisol was very low (0.61 μg/dL) and Adrenocorticotropic Hormone (ACTH) was elevated (> 1,250 pg/mL), confirming the diagnosis of primary adrenal insufficiency, Hydrocortisone therapy was started with progressive depigmentation of the skin. Six months later she presented with dysphagia and Allgrove syndrome was suspected. The analysis of the AAAS gene revealed a homozygous missense mutation in exon 12. She did not present clinical or paraclinical features of mineralocorticoid insufficiency, without neurological involvement.

Discussion

Triple A syndrome or Allgrove syndrome (OMIM #231550), is a rare disorder with an autosomal recessive inheritance pattern and its exact prevalence remains unknown, as it is believed to be underdiagnosed [1]. Early diagnosis is challenging due to its rarity and high phenotypic heterogeneity, even within families. The classic triad, typically described in the order of alacrima, achalasia and adrenal insufficiency, is observed in only 2/3 of patients [8,9]. In our case, we observed a distinct sequence not commonly seen in the majority of cases in the literature, as the first manifestation in our patient was adrenal insufficiency, followed by the development of achalasia and alacrima.

Alacrima is often described as the initial manifestation, even in neonates and can be associated with both congenital and/or acquired conditions such as familial dysautonomia, lacrimoauriculodentodigital syndrome, ectodermal dysplasia (anhidrotic type), Sjögren's syndrome, congenital deglycosylation disorder, achalasia-related mental retardation syndrome and Triple A syndrome. Therefore, a thorough evaluation of patients presenting with alacrima is essential, as isolated alacrima is rare in pediatrics. The gold standard for diagnosis is the Schirmer test and pharmacological treatment focuses on symptom relief (artificial tears) [1,10].

Adrenal insufficiency is typically precipitated by viral infections and carries a high risk of sudden death from acute adrenal crisis if diagnosis is delayed [1]. Mineralocorticoid function is usually preserved. Clinical manifestations include fatigue, weakness, anorexia, vomiting, abdominal pain, hypotension, hypoglycemia and tachycardia, many of which were observed in our patient [1]. Progressive skin hyperpigmentation is a rare presentation in previously reported cases [11-14]; however, it was a prominent finding in our patient, leading to further investigations that confirmed adrenal insufficiency. It typically presents in the first decade of life and rarely in adulthood [1]. Diagnosis is confirmed by low morning cortisol levels and a low cortisol response during the Synacthen (ACTH) test, although if baseline ACTH levels are extremely high with low cortisol levels, dynamic testing is not essential for establishing the diagnosis of adrenal insufficiency, as was the case with our patient. Treatment involves hormonal replacement therapy with glucocorticoids to alleviate symptoms, including skin hyperpigmentation.

Achalasia is a primary esophageal motility disorder characterized by impaired relaxation of the lower esophageal sphincter and loss of esophageal peristalsis [1]. This results from an imbalance between excitatory and inhibitory neurons, often due to inflammatory, fibrotic or degenerative processes affecting the inhibitory myenteric plexus [1]. Clinical manifestations are diverse, ranging from immediate post-ingestion regurgitation and progressive dysphagia for both liquids and solids, to growth impairment and/or recurrent aspiration pneumonia. Barium swallow studies and esophageal manometry are crucial for diagnosing achalasia. Diagnostic findings include esophageal dilation, a "bird-beak" appearance of the narrowed esophagus, absence of esophageal peristalsis and delayed contrast medium emptying [1]. Management requires a multifaceted approach, typically involving repeated endoscopic dilations and pharmacological therapy with calcium channel blockers (nifedipine) [1].

Heller myotomy is indicated in cases refractory to initial management, where persistent lower esophageal sphincter stenosis is present. While neurological manifestations are frequently reported in the literature, they were not observed in our patient.

Conclusion

This case underscores the importance of considering Triple A syndrome in children with unexplained primary adrenal insufficiency. The notable phenotypic variability highlights the need for early diagnosis to prevent life-threatening adrenal crises.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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None.

Data Availability Statement

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Authors' Contributions

SA made the diagnosis, managed the pharmacological treatment. WM wrote the introduction and discussion; VL participated in the writing of the case report and verification of the list; VL and WM helped write the introduction as well.

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