

Case Report

Triple A syndrome: Non-sense c.884G>A mutation making sense through its clinical triad

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ABSTRACT

Triple A syndrome is a rare autosomal recessive disorder characterized by triad of achalasia, alacrimia, and adrenal insufficiency. Autonomic dysfunction, neurological, and dermatological manifestations widen phenotypic spectrum. It arises from mutations in *AAAS* gene. Symptoms typically manifest in childhood; delayed presentations into adulthood are exceedingly rare. We report a 25-year-old male with 17-year history of progressive dysphagia, alacrimia, generalized fatigue, and diffuse hyperpigmentation. Laboratory evaluation and imaging suggested primary adrenal insufficiency. Esophageal manometry demonstrated achalasia. Ophthalmological assessment confirmed severe dry eye disease. Genetic testing identified a pathogenic homozygous non-sense mutation in *AAAS* gene (c.884G>A). Treatment with glucocorticoid and mineralocorticoid replacement, artificial tears, and esophageal pneumatic dilation led to significant clinical improvement. This case underscores presentation with classical triad of the syndrome at 8-years of age, albeit delayed first physician contact and diagnosis. Early recognition of its cardinal features is critical to prevent life-threatening complications such as adrenal crises and esophageal perforation.

Keywords: Triple A syndrome, Alacrimia, Achalasia, Adrenal insufficiency, Non-sense mutation

INTRODUCTION

Triple A syndrome (Allgrove syndrome) is a rare autosomal recessive disorder first described by Allgrove *et al.*, characterized by the triad of achalasia, alacrimia, and adrenocorticotrophic hormone (ACTH) resistant-adrenal insufficiency.^[1] Global prevalence is estimated at 10 in 100,000, though it is more common in regions with high rates of consanguinity.^[2] The condition results from point, frame-shift, or splice-site mutations in *AAAS* gene, located on chromosome 12q13, leading to functional cellular derangements.^[2,3] This gene, highly expressed in brain, adrenals, and gastrointestinal tract mucosa, encodes alacrimia-achalasia-adrenal insufficiency neurologic disorder (ALADIN) protein. ALADIN is a 546 amino acid nuclear pore complex protein belonging to the tryptophan-aspartic acid (WD) repeat domain containing family of genes, essential for intracellular macromolecule transport.^[3] Genetic heterogeneity is not uncommon, as not all patients with this syndrome demonstrate mutations in *AAAS* gene.^[3] Typically, symptoms manifest during childhood, most consistently with alacrimia. Achalasia and adrenal insufficiency develop later in the disease course. Delayed

presentation into adulthood is rare.^[4] Approximately 70% of patients exhibit the complete triad, while about a third also show autonomic dysfunction, leading some authors to refer it as 4A syndrome; achalasia, alacrimia, adrenal insufficiency, and autonomic abnormalities.^[5] Other symptoms reported include neurological and dermatological manifestations, short stature, microcephaly, osteoporosis, and dysmorphic features, highlighting the wide array of phenotypes and lack of a clear genotype-phenotype correlation. Genetic testing is crucial for diagnosis but does not predict the phenotype or prognosis. The presence of two of the three cardinal clinical entities strongly suggests triple A syndrome. However, diagnosis can be challenging at onset, when patient typically presents with only one symptom. Differential diagnoses include other causes of adrenal insufficiency, such as familial glucocorticoid deficiency and adrenoleukodystrophy. The syndrome can also be confused with Sjögren's syndrome when alacrimia and xerostomia are presenting symptoms. Definitive treatment is lacking. Management focuses on addressing individual signs and symptoms. Early diagnosis is crucial to prevent life-threatening adrenal crises. This report highlights a case of non-sense mutation positive triple A syndrome with classical clinical triad at presentation, without additional abnormality.

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Received: 11 December 2024 Accepted: 10 January 2025 Epub ahead of print: 28 February 2025 Published: 17 March 2026 DOI: 10.25259/IJMS_293_2024

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CASE REPORT

Clinical history

A 25-year-old male with no prior comorbidities presented with 17-year history of insidious onset progressive symptoms of dysphagia, generalized fatigue, alacrimia, and diffuse hyperpigmentation. Dysphagia progressively worsened over time, particularly to solids. He described a sensation of food getting stuck in his throat, accompanied by difficulty swallowing and breathing during feeds. This led to significant weight loss over the years. Generalized weakness and fatigue initially manifested as early exhaustion during play, gradually affecting his daily activities. Family members noted that he produced minimal tears while crying. In addition, he experienced difficulty in chewing food, requiring water to aid swallowing due to dry mouth. Skin hyperpigmentation gradually involved entire body, including nails, knuckles, palms, soles, and moist areas such as tongue and oral mucosa. The patient otherwise healthy until 8-years of age, these symptoms affected his physical and functional abilities. There was no history of low-grade fever, night sweat, cough, dyspnea, facial puffiness, pedal edema, constipation, skin rash, petechiae, purpura, oral or genital ulcers, hematuria, frothuria, reddening of eyes, photosensitivity, arthralgia, alopecia, skin tightening, livedo reticularis or racemosa, and Raynaud's phenomenon. Significant toxin, drug and radiation exposure, and self and contact history of tuberculosis were absent.

Clinical examination

Weighing 35 kg with height of 165 cm, he looked cachectic. Built was average, generalized wasting was noted. He was afebrile to touch, blood pressure of 86/54 mmHg with no evidence of postural hypotension, pulse rate 74/min, respiratory rate 12/min, and room air SpO₂ 96%. General physical examination revealed mild pallor without pedal edema or raised jugular venous pressure. There was blackish pigmentation of lips, gums, buccal mucosa, and tongue, with diffuse darkening of skin color involving knuckles and palmar creases [Figure 1]. Systemic examination was within normal limits.

Laboratory details

Laboratory investigations demonstrated pancytopenia: hemoglobin 10.8 gm% with hematocrit 32%, total leucocyte count 3,500/mm³, and platelet count 72,000/mm³. Reticulocyte production index of 1.2% ruled out the possibility of hemolysis. In addition, there was hyponatremia (serum Na⁺ 107 mEq/L) and hypokalemia (serum K⁺ 3.38 mEq/L). Renal and liver function tests and inflammatory markers were unremarkable. Random blood glucose was 100 mg/dL. In view of chronic asthenic symptoms with leucopenia, thrombocytopenia, euvolemic hyponatremia, and generalized skin hyperpigmentation, we evaluated for laboratory evidence of hypocortisolism. Serum 8:00 am morning cortisol was low normal; 6.82 µg/dL



Figure 1: Skin color at (a) 7-years of age, compared to (b) 25-years of age at presentation, (c) diffuse blackish pigmentation of tongue, (d) skin over extensor surface of knees, (e) knuckles, bilateral (f) shin and (g) palms, all suggestive of Addisonian pigmentation.

(normal: 5–23 µg/dL). Serum ACTH level was significantly elevated; 763 pg/mL (normal: <46 pg/mL). Viral markers were non-reactive. Autoimmune work-up, including rheumatoid factor (RAF), anti-cyclic citrullinated peptide (anti-CCP), anti-nuclear antibody (ANA), extractable nuclear antigen (ENA) profile, and anti-Sjögren's syndrome A/B (SSA/SSB) [Ro/La] antibody, was negative. Serum angiotensin converting enzyme (ACE) and Immunoglobulin G4 (IgG4) levels were normal.

Further evaluation

Primary adrenocortical insufficiency was thus suggestive. This was further corroborated with contrast-enhanced computed tomography of abdomen, which showed bilateral atrophic adrenal glands [Figure 2]. However, ileo-caecal area appeared normal with no evidence of abdominal tuberculosis. Mantoux test was negative. As part of dysphagia evaluation, the patient underwent barium swallow and upper gastrointestinal endoscopy (UGIE). The former showed characteristic “bird-beak” appearance [Figure 3]. UGIE revealed dilated esophagus with food particles, associated

with uncoordinated non-propulsive contraction of proximal dilated segment. High-resolution esophageal manometry was suggestive of Chicago type II achalasia [Figure 4]. Ophthalmological examination was suggestive of severe dry eye disease. Schirmer's test was positive; wetting at end of 5 min in both eyes was 2 mm (normal: 10–15 mm). Tear film break-up time bilaterally was 5 seconds (normal: >10 seconds).

Diagnostic wrap-up

The presenting triad of achalasia, alacrimia and adrenocortical insufficiency, made us suspect triple A syndrome. Subsequently, whole exome sequencing was done on the Illumina Novaseq 6000 next genome sequencing

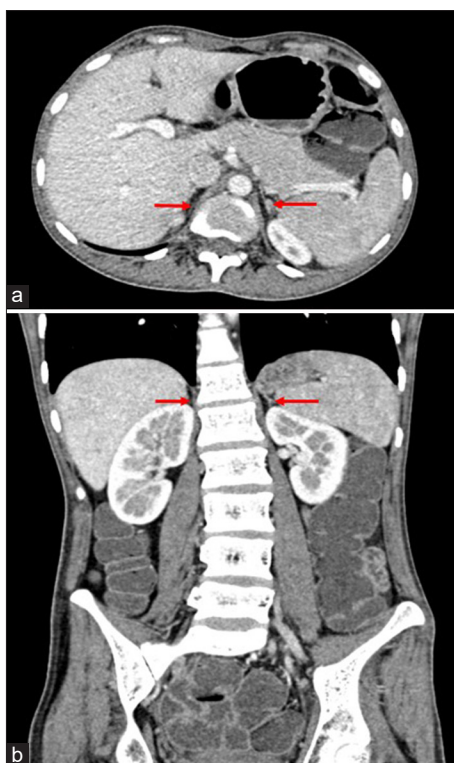


Figure 2: Contrast-enhanced computed tomography of abdomen showing bilateral diffusely atrophic adrenal glands (red arrows) in (a) axial and (b) coronal sections. Maximum width of body, medial limb, lateral limb of right and left adrenal gland are 2.1 mm, 1.4 mm, 1.3 mm and 1.7 mm, 2.2 mm, 1.5 mm, respectively.

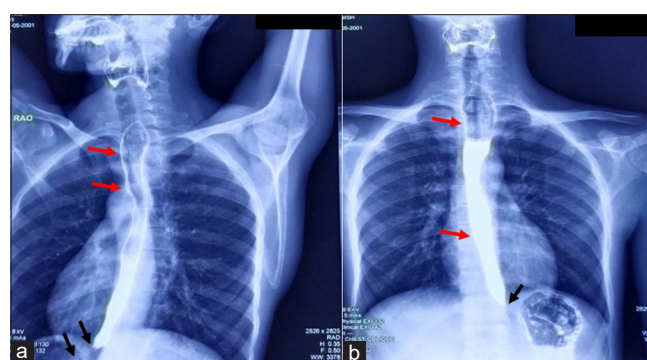


Figure 3: Barium swallow in (a) antero-posterior oblique and (b) postero-anterior views demonstrating smooth, short-segment tapering at the lower esophageal sphincter with narrowing at gastroesophageal junction, giving the “bird-beak” appearance of esophagus (black arrows); dilated proximal esophageal segment (red arrows).

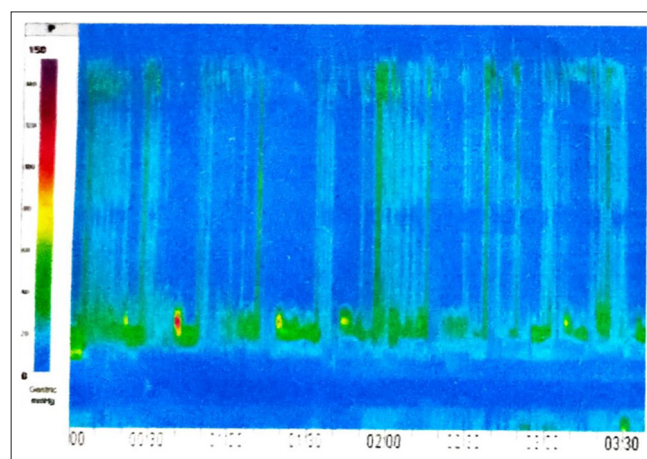


Figure 4: High-resolution esophageal manometry showing 100% failed peristalsis with pan-esophageal pressurization in 60% swallows (10 × 5 mL water swallows), suggestive of Chicago type II achalasia cardia. Distal contractile integral of esophagus is 314 mmHg.s.cm; integrated relaxation pressure at 4 s in the lower esophageal sphincter is 19 mmHg.

(NGS) platform. It was positive for a likely pathogenic variant; homozygous non-sense mutation, c.884G>A (p.Trp295Ter) in exon 9 of AAAS gene (transcript NM_015665.6). Hence, the definitive diagnosis of Allgrove syndrome was clinched.

Treatment and response

Treatment was initiated before genetic confirmation. He was started on hydrocortisone (subsequently prednisolone) and fludrocortisone as a part of glucocorticoid and mineralocorticoid replacement, respectively. There was substantial clinical improvement. Appetite and fatigue improved; the patient became more active. Blood pressure readings increased to an average of 114/70 mmHg. Hyponatremia resolved by 6th day (138 mEq/L). Leukopenia and thrombocytopenia improved (7,100/mm³ and 140,000/mm³, respectively, on day 6 of therapy). At present, the patient is maintaining on 13.5 mg prednisolone and 0.1 mg fludrocortisone. He gained weight of 2 kg over a period of 2 months from starting therapy and is now performing daily routine activities with complete energy and efficiency. Carboxy-methyl-cellulose artificial tear drop was prescribed for alacrimia. He underwent pneumatic dilation of the lower esophageal sphincter, leading to significant improvement in dysphagia.

DISCUSSION

Triple A syndrome is a quite rare disorder. Only 100 cases have been reported worldwide till now; very few from India. Our case was notable for its delayed diagnosis into adulthood despite the presence of early symptoms. Delayed recognition underscores the variability in onset and progression of this disorder. However, our patient had the classical clinical triad of alacrimia, achalasia, and adrenal insufficiency at presentation unlike cases reported previously. Vallet *et al.* documented a 19-year-old patient with predominant achalasia and alacrimia but without adrenal insufficiency at the time of diagnosis.^[6] An Indian report mentioned 2.5-year-old patient of Allgrove syndrome with alacrimia and adrenal insufficiency but without achalasia. Diagnosis was confirmed by demonstrating homozygous frameshift deletion c.762delC (p.Ser225Valfs*36) at exon 8 of AAAS gene.^[7] Sultan *et al.* reported a 16-year-old boy who developed dysphagia since early infancy,^[8] unlike our case whose swallowing difficulty started at 8-years of age. This highlights the potential for partial or evolving phenotypes. Goizet *et al.* reported a family with this syndrome exhibiting significant neurological manifestations such as peripheral neuropathy and ataxia, overshadowing the triad.^[9] Milenkovic *et al.* described a 12-year-old with autonomic dysfunction, recurrent infections, and intellectual disability in addition to the triad, indicating the breadth of phenotypic spectrum.^[10] Our patient lacked such neurological and systemic involvement. A review

by Handschug *et al.* emphasized the importance of genetic testing in diagnosing atypical presentations, particularly in older patients with incomplete or late-onset symptoms.^[2] In sync, we made the definitive diagnosis by whole exome sequencing, demonstrating homozygous non-sense mutation c.884G>A at exon 9 of AAAS gene.

Novelty of the case

This case is distinct for its delayed presentation and diagnosis despite long-standing nature of the symptoms. Presence of complete triad features, coupled with no significant neurological or autonomic involvement, contrasts with cases reported previously exhibiting atypical systemic features.

Clinical implications

Delayed recognition of triple A syndrome can lead to avoidable complications such as esophageal perforation in achalasia or adrenal crises in untreated adrenal insufficiency. Early identification of alacrimia in children with unexplained dry eyes should prompt further evaluation to prevent diagnostic delays.

CONCLUSION

Our case underscores the importance of recognizing cardinal features and phenotypic variability of triple A syndrome for timely diagnosis and management. The versatility in clinical presentation, as evidenced by this case and other reports, highlights the need for a high index of suspicion and role of genetic testing in confirming the diagnosis.

Acknowledgment: We want to thank residents and faculties of Department of General Medicine, Gastroenterology, Pediatrics, Ophthalmology, and Radiology for their constant help and support in evaluating the patient and completing the manuscript.

Authors' contributions: AR,VS,YP: Contributed to the evaluation, diagnostic work-up, and treatment of the case; AR,YP: Captured the patient and radiological images; AR,SD: Wrote the first draft of the manuscript. SD: The manuscript was critically reviewed and edited. All authors read and approved the final manuscript. The content and writing of this manuscript were exclusively contributed by the authors listed by name.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Roy A, Datta S, Sojitra VJ, Porwal YC. Triple A syndrome: Non-sense c.884G>A mutation making sense through its clinical triad. *Indian J Med Sci.* 2026;78:96-100. doi: 10.25259/IJMS_293_2024