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# ALLGROVE SYNDROME(TRIPLE-A SYNDROME):A CASE REPORT

Internal Medicine

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## ABSTRACT

Triple-A syndrome, also known as Allgrove syndrome, is an uncommon disorder which is inherited as an autosomal recessive pattern of inheritance, associated with mutations in the AAAS (achalasia–addisonianism–alacrima-syndrome) gene About 100 cases have been described in literature. The three AAA comprises Adrenal insufficiency secondary to Adrenocorticotropic hormone (ACTH) resistance, Achalasia cardia, and Alacrimia as well as central and peripheral nervous system involvement. We are reporting a case of a 24 year old diagnosed as triple-A syndrome with ACTH resistant Adrenal insufficiency, achalasia cardia, and alacrimia. She had Alicrimia since birth, and at the age of 15, she was diagnosed to have achalasia cardia.She developed signs and of symptoms of Adrenal insufficiency at the age of 7 years. Assessment of ACTH, cortisol, ACTH stimulation test confirmed she had adrenal insufficiency and physical examination showed she had foot deformity due to muscular atrophy caused by neuropathy.The diagnosis of Allgrove syndrome should be considered in every patient presenting with alacrimia or achalasia cardia.Her condition improved with steroids and artificial teardrops. Allgrove's syndrome may be an under diagnosed disorder. High index of suspicion is needed when patients present with such complex symptoms. Diagnosing and timely intervention helps in reducing the morbidity and mortality.

## KEYWORDS

**INTRODUCTION:**

Triple-Asyndrome, or Allgrove syndrome (AS), first described by Allgrove in 1978, is a rare disease with an estimated prevalence of 1per 1,000,000 individual, characterized by adrenal insufficiency, achalasia, and alacrimia, and it can be variably associated with ANS dysfunction and neurodegeneration. AS is an autosomal recessive disorder due to a mutation in the achalasia, addisonianism,alacrimia syndrome (AAAS) gene localized on chromosome 12q13 and codifying a protein called alacrimia, achalasia, adrenal insufficiency, neurologic disorder (commonly referred to as ALADIN), which is involved in transductional intracellular pathways.

The characteristic triad of AS may manifest incompletely, but at least 2 features are necessary to make the clinical diagnosis, then being the so-called "double-A syndrome".When autonomic nervous system dysfunctions are present, followed by a central and peripheral nervous system involvement (muscular atrophy, fasciculation, hypoesthesia, nasal speech, ataxia, optic atrophy, and intellectual impairment), the so-called "4A syndrome" is diagnosed.

The classic history and reasons for consultation include frequent complaints of the Absence of tears while crying/dry eyes at birth due to Alacrima, feeding difficulties, repeated vomiting, weight loss due to underlying Achalasia or seizure secondary to hypoglycemia resulting from the adrenal crisis, and delayed growth/milestones.

In AS, the onset of clinical features may not be simultaneous. Alacrimia represents the earliest and the most constant symptom, and it usually presents at birth. The symptoms of achalasia and adrenal insufficiency, due to glucocorticoid secretion deficiency appear later during childhood or adulthood. Adrenal insufficiency is reported in 85% of patients, whereas mineralocorticoid impairment affects only about 15% of the patients. According to the overall literature data, the full triad is found in almost two-thirds of patients, 2 symptoms in one-third, and 1 symptom alone in less than 10%.

The main aim of our work is to report a case of AAA syndrome that presents with multiple episodes of fever,vomitings ,difficulty in swallowing weight loss,general fatigue, generalized pigmentation and peripheral Neuropathy.

**Case Report:**

A 26 year old female Came to the Emergency department with the chief complaints of Giddiness and fall in home and had an Episode of GTCS. Upon checking the Glucose level, it was found to be as 30mg/dl. She also had hyperpigmentation over the skin, tongue, oral mucosa and all over the body for the past 5 years.

By taking the clinical history, her parents noticed lack of tears during crying since childhood. Ophthalmological examination is done. Schirmer's test was positive, wetting was 3 mm in right eye and 2.5 mm in left eye at 5 min, whereas, normal wetting at 5 min is > 5mm.

She was born full term from a consanguineous marriage.There is also a history of the patient's cousin brother dying at an early age for an unknown reason but he was suffering from failure to thrive.

At age of 15,she had multiple episodes of fever, vomitings, fatigue, reduced appetite and failure to thrive. she also developed gradual onset difficulty in swallowing,especially for solids, for which she was evaluated. Barium swallow test was done which showed tapering of Esophageal lumen near gastro-esophageal junction(Fig. 3) and thus a daignosis of Achalasia Cardia was made.

She performed below average in school and sports. MRI brain was done which showed no abnormality.

She had not attained menarche but all secondary characters were well developed. Ultrasound abdomen revealed Bilateral Atrophic ovaries(Fig.4) and Hypoplastic uterus(Fig.5).

On examination, she is dark skinned from head to toe(Fig.1). Hyperpigmentation is also seen over the tongue and oral mucosa which raised the suspicion of adrenal insufficiency. So,we performed a morning 8am cortisol assay which came to be 2.3ug/dl (Normal->5ug/dl) and Plasma ACTH levels were 220pg/dl.Plasma aldosterone concentration and Plasma renin activity were not measured as the patient was normotensive without any postural drop and her electrolytes are normal. To confirm the diagnosis, we performed a synacthen induction test, and the result was positive.

This confirmed the presence of Primary adrenal insufficiency (Addison's disease). Non contrast computed tomography of the adrenal glands was normal with no visible calcifications and tumors.

Following the examination , she in thin built, we found a deformity at the level of the foots such as Pes planus and Bilateral foot muscles wasting(Fig.2).This suggests either the presence of a bony deformity or atrophy at the level of nerves or muscles associated with Triple A syndrome. But by requesting an X-ray of the foots, we did not find any bony deformity, and to confirm the diagnosis, we performed an electrocardiogram of the nerves feeding the muscles of the both foot, and it was found that there was a peripheral neuropathy that led to atrophy of the muscles of the both foot. From the above, we conclude that the patient suffers from Triple A syndrome (Allgrove syndrome) with neuropathies.

Complete blood picture, Renal function test, Liver function test, Thyroid function test, Serum electrolytes, complete urine analysis were within the normal limits.Her calcium levels were on the lower side of the normal limits 7.0mg/dl(normal 8.6-10).

**Figure 1: Clinical Photograph showing Hyperpigmentation of the skin.**

**Figure 2: Clinical Photograph showing Atrophy of the Foot muscles.**

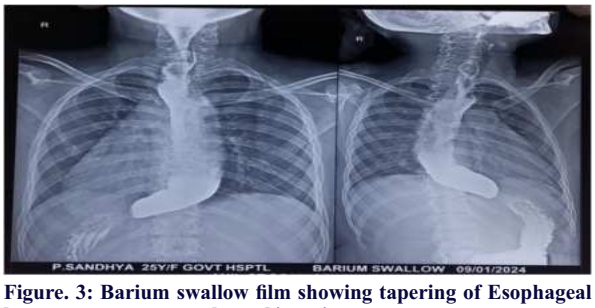


**Figure. 3: Barium swallow film showing tapering of Esophageal lumen near gastro-esophageal junction**

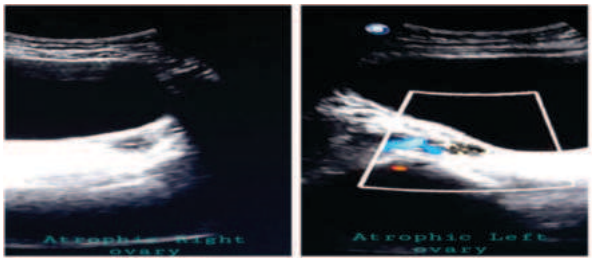


**Figure. 4:Ultrasound abdomen showing Bilatral Atrophic Ovaries.**

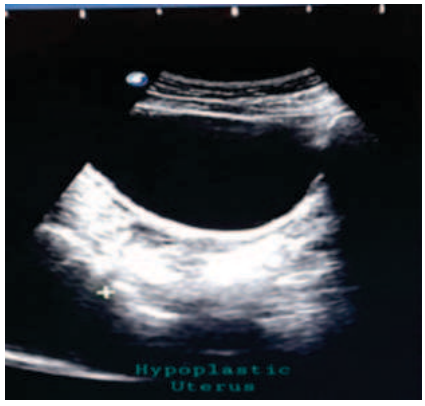


**Figure .5: Ultrasound abdomen showing Hypoplastic Uterus.**

On the basis of ACTH-resistant Adrenal insufficiency,Achalasia Cardia and Alicrimia and peripheral neuropathy,a Diagnosis of ALLGROVE SYNDROME or TRIPLE-A SYNDROME was made. Patient is started on Prednisolone 5mg once a day and is prescribed artificial tears.

**DISCUSSION:**

Allgrove syndrome is a rare disease where description is mostly limited to case reports. Allgrove syndrome is transmitted in autosomal recessive fashion; the genetic locus is AAAS gene located on chromosome 12q13 that encodes for ALADIN protein. These mutations lead to a truncated protein leading to basic pathophysiology of Allgrove syndrome. There is a marked variability in phenotype of genetically confirmed triple-A syndrome.Patients of Allgrove syndrome do not have any structural abnormality in their cells, suggesting that mutations in AAAS lead to functional impairment.

The clinical features of Allgrove syndrome are ACTHresistant adrenal insufficiency, alacrimia, and variable neurological involvement. The earliest clinical feature in literature is alacrimia which is present since birth in our patient. The usual presentation of Allgrove syndrome is during the latter half of the first decade of life. Achalasia cardia occurs in up to 75% of cases; patients usually present with dysphagia, weight loss, and heartburn. Age of occurrence of adrenal insufficiency is variable, it can present early in life with severe hypoglycemia, or it can present later with hyperpigmentation, failure to thrive, nausea, and recurrent vomiting.

Several papers have reported on hypoglycemic seizures as the first clinically relevant event,while other patients come to the attention of clinicians due to the onset of various neurologic disorders, such as optic neuropathy, amyotrophy, gait impairment or ataxia. The primary cause of mortality in AS is unrecognized adrenal crisis.The peculiar feature of adrenal insufficiency in Allgrove syndrome is primary adrenal insufficiency with normal mineralocorticoid function. The presence of normal electrolyte and absence of postural hypotension in our patient point toward the preservation of mineralocorticoid function. An involvement of neurological system including central, peripheral, and autonomic nervous system has been described in a significant number of patients. Neurological involvement is a late phenomenon as compared to other core manifestations of Allgrove syndrome. Polyneuropathy with distal distribution is a common presentation of nervous system involvement.Other neurological manifestations include involvement of autonomic system, mental retardation, amyotrophy, parkinsonism, ataxia, dementia, dystonia, and chorea. The cause of neuropathy in Allgrove syndrome is not clear. At present, there is no connecting pathological link between achalasia, alacrima, and adrenal unresponsiveness to ACTH in the Allgrove syndrome. ACTH has been found to have some neurotropic effect, and its receptor gene may provide some clues to elucidate the association of the three central features of this syndrome.

Our case is an 26-year-old patient diagnosed with alacrimia since birth by doing Schremer test and artificial tears were prescribed to avoid dry eyes constantly and at the age of 15 years, the patient complained of dysphagia and vomiting of undigested food. The presence of achalasia was diagnosed by barium swallow which showed tapering at Gastro-esophageal junction. The patient also complained of weight loss, general fatigue and generalized pigmentation,so we assested

Adrenocorticotropic hormone(ACTH), cortisol, ACTH stimulation test and we confirmed the presence of adrenal insufficiency and we had to constantly replace with hydrocortisone. Based on above, we have a rare case of Allgrove A syndrome, in addition to the patient's latest complaints, muscular atrophy in the foots is present as a result of peripheral neuropathy.There is no cure for triple A syndrome at this time.Treatment typically focuses on managing individual signs and symptoms of the condition(replacement of Glucocorticoids, surgical correction of achalasia if needed,artificial tears).We emphasize that Allgrove syndrome is a multisystem disease and the cardinal manifestations may appear at any time from infancy to adulthood.

## CONCLUSION:

In summary, this case report highlights the presentation and diagnosis of Algrove syndrome in an 26 year female. Her clinical features, including giddiness and fall in home, an episode of GTCS,lack of tears during crying, fever, vomitings, fatigue, reduced appetite, difficulty in swallowing, failure to thrive, hyperpigmentation of skin,tongue and oral mucosa and muscle wasting, align with the classic characteristics of this rare genetic disorder. Timely diagnosis and a multidisciplinary approach to management, including neurology, gastroenterology, endocrinology consultations and environmental modifications are essential for enhancing the patient's quality of life. Adrenal failure is the most important determinant in the prognosis of the disease in terms of its diagnosis and treatment.Thus,earlier diagnosis and timely intervention helps in reducing the morbidity and mortality.

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