

# Allgrove's Syndrome with Early Onset Neuropathy - A Rare Presentation

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## ABSTRACT

**Introduction:** Allgrove's syndrome or Triple-A syndrome is an extremely rare multi-system disease with autosomal recessive inheritance characterised by cardinal features of adrenal insufficiency due to adrenocorticotropic hormone resistance, achalasia, and alacrimia. Amongst the wide variety of multi-system manifestations of this disease, neurological symptoms appear during the second decade or later.

**Case report:** We here in report a rare case of Triple A syndrome who presented with early-onset neuropathy at 9 years of age with the complaints of dysphagia, hyperpigmentation and gait disturbances.

**Conclusion:** Allgrove's syndrome or Triple-A syndrome is a rare multi-system disease in which the cardinal symptoms may appear at any time from infancy to adulthood. Therefore, early diagnosis and prompt treatment can lead to a significant improvement in a patient's quality of life.

**Keywords:** Triple-A (AAA) syndrome, Allgrove's Syndrome, Adrenal Insufficiency, Paediatric, Genetic.

## INTRODUCTION

First described by Allgrove et al<sup>1</sup> in 1978, Allgrove's syndrome is a rare autosomal recessive disorder due to mutations in the AAAS gene, located on chromosome 12q13, which encodes a protein called ALADIN.<sup>2,3</sup> Apart from the cardinal features of adrenal insufficiency, achalasia and alacrimia this disease can present with a wide variety of manifestations and is frequently associated with late neurological manifestations due to the involvement of central, peripheral or autonomic nervous systems.<sup>4</sup> We herein report a case of a 9-year-old male child with Triple A syndrome who presented to us with early-onset neuropathy.

## CASE REPORT

A 9-year-old male child born out of a non-consanguineous marriage presented to us with complaint of difficulty in swallowing for both solids and liquids since the age of 4 years. This difficulty in swallowing was more for solid foods as compared to liquids and progressive with associated nasal regurgitation of feeds. Parents also noticed increased pigmentation of the tongue since the age of 6 months and of skin since the age of 5 years. The patient developed difficulty in walking at the age of 6 years which started as dragging of the right limb while walking, difficulty in climbing and getting down the stairs, gradually to difficulty in getting up from sitting position for the last two and half years. Parents did not notice any weakness in the upper limb. He also complained of supra-umbilical pain abdomen for the last 4-5

months, occurring every 10-15 days and was not related to any changes in bladder and bowel movements. Mother also informed that patient has decreased tears from eyes while crying since birth.

Physical examination revealed an active and cheerful child with normal pulse rate, pulse volume, respiratory rate and temperature. Blood pressure was 78/50 mmHg which was below 5th percentile. There was diffuse hyperpigmentation of the body especially on tongue and limbs with palmoplantar hyperkeratosis. No abnormality was detected on cardiovascular, respiratory and per abdomen examination. Neurological examination revealed nasal speech and mild intellectual disability with muscle wasting and a clumsy gait. The tone was slightly increased in all four limbs with normal power at all joints and hyperactive deep tendon reflexes. Bilateral plantar reflexes were mute.

Haemogram, renal function tests, serum electrolytes, liver function tests, and fasting plasma glucose were within normal limits. Basal serum cortisol (8:00 AM) was very low (<0.50 µg/dL; normal range: 4.30-22.40 µg/dL) and the plasma adrenocorticotropic hormone (ACTH) levels were markedly elevated (>1250 pg/mL; normal range: <46.00 pg/mL). TSH levels were also raised (11.5 mIU/L on 1st & 9.4 mIU/L on repeat test) and were suggestive of hypothyroidism. Growth hormone levels were within normal limits. On ophthalmologic examination, Schirmer's test was found positive (<3mm). UGI endoscopy showed dilated upper part of oesophagus with increased pressure of Lower oesophageal sphincter with visible peristalsis in oesophagus and were suggestive of achalasia (Figure 1,2). USG abdomen revealed right renal concretions and bilateral cryptorchidism. Echocardiography was normal. Nerve conduction tests revealed peripheral neuropathy.

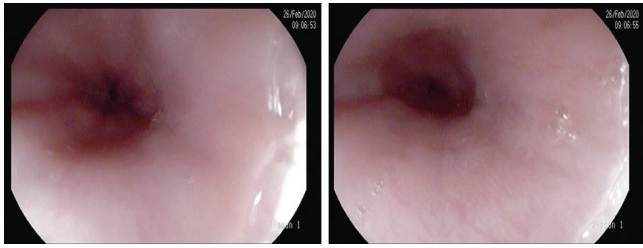
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**Figure-1 & 2:** UGI endoscopy

On the basis of primary adrenal insufficiency, alacrimia, achalasia cardia, and peripheral neuropathy a diagnosis of Allgrove's syndrome was made. Genetic studies and oesophageal manometry could not be done due to non-affordability. The patient was treated with a replacement dose of oral hydrocortisone (10 mg/m<sup>2</sup>/day), tablet thyroxine, topical eye lubricants and physiotherapy. Endoscopic dilatation of oesophagus was done for relief of achalasia symptoms. The child has been following up with us and is doing fine.

## DISCUSSION

Exact prevalence of Allgrove's syndrome is unknown due to its limited description as case reports in world literature. However, in 2003, Jacob et al mentioned in their report that approximately 70 cases have been reported worldwide.<sup>5</sup> It is a rare cause of adrenal insufficiency inherited in an autosomal recessive pattern. It consists of a triad of alacrimia, achalasia cardia and adrenal insufficiency<sup>1</sup>. The molecular basis of this rare autosomal recessive disorder is the mutated AAAS gene, located on chromosome 12q13, that codes for ALacrima Achalasia aDrenal Insufficiency Neurologic disorder (ALADIN) protein, a constituent of the nuclear pore complex that has been shown to be linked in its pathogenesis<sup>2,3</sup>. It can also be associated with various autonomic and neurologic manifestations.<sup>4,6</sup>

General manifestations of this disease include isolated glucocorticoid failure, hypoglycaemia, weakness, fatigue, anorexia, gastro-intestinal symptoms such as nausea, vomiting, constipation abdominal pain, diarrhoea, salt craving, postural dizziness, weight loss, hypotension, hyperpigmentation, vitiligo, electrolyte disturbances, anaemia, eosinophilia, hypothyroidism, alacrima and achalasia, palmoplantar hyperkeratosis, short stature, gonadal failure, microcephaly, osteoporosis, pes cavus and neurological abnormalities including autonomic, sensory and motor neuropathies.<sup>1,3,7</sup>

Alacrimia<sup>3,8</sup> is usually considered the earliest manifestation as was seen in our patient. Adrenal insufficiency and achalasia are usually manifested during the first decade of life. Achalasia of the cardia occurs in about 75% of cases and in older children/adults it usually manifests as dysphagia, especially for liquids. In our patient achalasia developed at the age of 4 years. Adrenal insufficiency is also an early manifestation and manifests as severe hypoglycemic or hypotensive attacks during childhood which may lead to sudden death.<sup>4,8</sup> The adrenal insufficiency in Allgrove syndrome is a unique form of primary adrenal insufficiency

with preservation of mineralocorticoid production.<sup>7,9</sup> In our patient, the documentation of normal electrolytes indicated normal mineralocorticoid production.

Neurological manifestations appear at a later age usually in the second decade of life as reported by many authors previously.<sup>5,9,10</sup> However, in our patient neurological manifestation in form of gait disturbance appearing in the first decade of life i.e at 6 years of age, was one of the chief presenting complaints. Distal sensorimotor polyneuropathy is a common manifestation. Other neurological manifestations include prolonged nerve conduction, muscle weakness, distal limb atrophy, progressive spastic tetra-paresis, deafness, mental retardation, optic atrophy, ataxia, dysarthria, hypernasal speech, dementia, parkinsonism, dystonia, and chorea.<sup>5,7,9,10</sup>

In our case, the patient sought medical help for the complaints of dysphagia, hyperpigmentation and gait disturbances. On the detailed evaluation of history and examination, other findings were identified and diagnosis of Allgrove syndrome was made and medical therapy was started. Genetic studies might be required in cases with atypical presentation.

Although there is no treatment for this disease, hormone replacement therapy to treat adrenal insufficiency, artificial tears (to improve eye irritation, reduce eye blink rate and prevent eye infections and corneal ulcers), application of a balloon to dilate the lower oesophageal sphincter and physiotherapy for limbs may be used to relieve the symptoms.

## CONCLUSION

Allgrove's syndrome or Triple-A syndrome is a rare multi-system disease with autosomal recessive inheritance and the cardinal symptoms may appear at any time from infancy to adulthood. Although neurological symptoms usually appear in second decade or later, it might be seen earlier as in our case. Therefore, early diagnosis and prompt treatment can lead to a significant improvement in a patient's quality of life.

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