Allgrove Syndrome - A Syndrome of Primary Adrenocortical Insufficiency with Achalasia of the Cardia and Deficient Tear Production

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Abstract
Primary adrenal insufficiency is an uncommon disease which has worldwide distribution. The commonest cause in underdeveloped countries is tuberculosis followed by autoimmune destruction of the adrenal gland. We report a case of a 15 years boy who had congenital adrenal insufficiency associated with achalasia of the cardia and deficient tear secretion.

INTRODUCTION
Primary adrenal insufficiency or Addison’s disease is a relatively rare disease, may occur at any age, and affects both sexes equally. Congenital adrenal hyperplasia (CAH) is the most common adrenal disorder of infancy and childhood and is due to recessive mutations that cause one of several distinctive enzyme defects. Much less common than CAH are syndromes secondary to mutation(s) in a key receptor involved in adrenal function. This report highlights a rare case of association of adrenal insufficiency with achalasia and alacrima - Allgrove’s triple A syndrome.

CASE REPORT
A 15 years boy, third child of a non-consanguinous marriage was admitted to this institution in Nov. 2001 for evaluation of fever of two weeks duration and recurrent respiratory infections for six months. Fever was low grade, associated with cough and purulent sputum. No other associated symptoms were present.

He had a history of absent tear secretion while crying since one year of age. He also had pigmentation of face (Fig. 1) tongue and extremities since childhood and it has been increasing during the past three years. He also has decreased weight gain since childhood. There was history of dysphagia mainly for solids and also regurgitation of fluids during night for the past four years. He also gave history of increased fatiguability and tiredness for the past six months. Over the past six months he had recurrent lower respiratory tract infections. He did not suffer from tuberculous infection in the past.
He gave history of occasional watery diarrhea. There was no history of pulmonary tuberculosis in the family. On examination, he was poorly built and nourished. He had bluish black pigmentation of tongue, oral mucosa, teeth, sclera. There was also pigmentation of ear lobes, extremities, knuckles and skin creases and secondary sexual characters were absent. Testicular size was reduced. Blood pressure was 100 mmHg systolic and 60 mmHg diastolic on supine position and 88 mmHg systolic and 60 mmHg diastolic on standing. He was afebrile. Systemic examination did not reveal any abnormality. There were no features of autonomic neuropathy or peripheral neuropathy on clinical examination.

Investigations showed a haemoglobin of 10.5 gm%, TLC - 9800/mm³, DLC-P, L₂, E₂, B₂. Blood sugar : 68 mg%, blood urea : 21 mg%, serum Na : 142, K : 4.6 meq/l.

Peripheral blood smear showed a mild neutropenia, blood culture and sputum culture were sterile, sputum AFB negative, blood widal negative, chest X-ray was normal. Serum ferritin was normal.

Serum cortisol at 8AM was 1.1 µg/dl (N : 11-18). Baseline serum ACTH was 1250 picograms/ml (Normal upto 46).

A barium swallow examination was consistent with achalasia cardia (Fig. 2).

CT scan abdomen (Fig. 3) revealed decreased size of adrenal gland bilaterally (Length 12 mm (20-60 normal); thickness 3 mm (6-10 normal), CT scan of the orbit (Fig. 4) demonstrated decreased size of the lacrimal gland bilaterally.

Ophthalmologic evaluation revealed significant reduction of tear film bilaterally. Schirmer's test was +ve 6 mm (normal > 10 mm). Flourescent stain for corneal ulcer was negative.

The patient was afebrile during the course of hospitalization and was treated symptomatically.

He was put on replacement dose of prednisolone 7.5 mg OD and topical lubricants for local application in the eye. Pneumatic dilatation of the achalasia was done two weeks later.

**DISCUSSION**

Our patient had features of Allgrove syndrome or triple A syndrome, which is an inherited familial disorders in which there is adrenal unresponsiveness to ACTH.

Incidence is unknown but it is an extremely rare syndrome with an autosomal recessive inheritance.¹ The probable risk in future pregnancies is 25%. The primary cause of mortality is unrecognized adrenal crisis. It affects all races and can have a variable presentation.

Age at onset of symptoms is variable. The glucocorticoid deficiency is not apparent at birth but develops over the first two decades of life. Alacrima generally is present from early infancy, while symptoms of achalasia may appear in individuals as young as six months or as late as early adulthood. Most cases present with classic symptoms of primary adrenal insufficiency, including hypoglycemic seizures and shock. Less frequently a child may be evaluated initially for recurrent vomiting, dysphagia and failure to thrive and for ocular
symptoms. Patients may show neurological features like mental retardation, autonomic neuropathy, ataxia, muscle weakness, and peripheral neuropathy.

Dermatologic abnormalities such as palmoplantar hyperkeratosis as well as short stature, microcephaly and osteoporosis may occur.

Genome linkage scans map the syndrome to a 6 cM interval on human chromosome 12q 13 near the type II keratin gene cluster. Pathogenetic mutations have been identified in the ACTH receptor gene in families with isolated familial ACTH unresponsiveness. Whether the ACTH receptor represents the locus of the defect for the triple A syndrome is not known.

The achalasia - alacrima (AA) syndrome has been defined as a distinct clinical entity. It is most likely a varient of the triple A syndrome as shown by haplotype analysis.

Autonomic neuropathy may be associated when it is called the 4A syndrome (adrenal insufficiency, achalasia of the cardia, alacrima and autonomic abnormalities). Autonomic disturbances may include abnormal pupillary reflexes, poor heart rate variability, and orthostatic hypotension.

There is considerable intra and interfamilial variability of severity implying a variable expression of an impaired pleotropically acting gene.

Globally, the pathology may be due to a progressive loss of cholinergic function throughout the body. Alternatively there may be a dysfunction of melanocortin receptor signalling, as melanocortin receptors are known to regulate adrenal function and skin exocrine gland function. The mineralocorticoid function is usually normal although deficiency of mineralocorticoid can occur. The glucocorticoid deficiency is probably due to degeneration of an initially normal zona fasciculata, there being no evidence to support a biologically inactive hormone or an autoimmune process.

Our patient presented with history of absent tear secretion while crying since one year of age. He had no symptoms attributable to hypoglycemia, and mineralocorticoid deficiency was ruled out since the blood pressure and serum electrolytes were normal. Our patient had no ophthalmologic manifestations of deficient lacrimation, which was diagnosed only on the Schirmer test.

He later developed features of achalasia like dysphagia and recurrent respiratory infections. Dysfunctional esophageal autonomic nerve plexus and degeneration of nerve fibres is postulated as the etiology of dysphagia, with c-AMP as the possible neurotransmitter.

Various neurological manifestations like speech and motor delay, optic atrophy, ataxia and microcephaly have been described.

In the absence of neurological abnormalities prognosis is good if the endocrine disturbance is detected early and prompt replacement with steroids is instituted.

Our patient had no clinical features of neurological dysfunction. Electrophysiological studies including nerve conduction studies were not done due to nonavailability. This may be a limitation of the study. Serum cortisol was low, and the radiological studies demonstrated achalasia of the cardia, bilateral adrenal gland atrophy and bilateral lacrimal gland atrophy.

Thus this case report highlights the spectrum of abnormalities that may be associated with primary adrenocortical insufficiency.

REFERENCES
1. Daniel Marks, Bruce A, Boston MD. Allgrove (AAA) syndrome. eMedicine J 2001;2(11).