Case Report

TRIPLE A (ALLGROVE) SYNDROME

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Abstract: Allgrove syndrome is a rare autosomal recessive disorder characterized by classic triad of Achalasia cardia, Alacremia and ACTH-resistant adrenal insufficiency. Although Addison's disease is the essential component but various combinations of other major findings are often seen involving nervous system. Patients generally present with adrenal insufficiency diagnosed during an inter-current illness. Other clinical features such as alacremia, dysphagia with recurrent vomiting may precede adrenal insufficiency for some time. Here, we present case of a 5 year-old boy who presented with complaints of recurrent vomiting and dysphagia. In last admission tendency towards low blood sugar was noticed and there was some concern about pigmentation of lips. This paper highlights early features of this syndrome and the importance to include Allgrove syndrome in the presence of any of two features, progressive dysphagia Alacremia or symptoms of primary adrenal insufficiency.

Key words: Achalasia, Alacremia, Adrenocorticotrophic insufficiency, Allgrove syndrome

Introduction

Triple A syndrome was first described by Jeremy Allgrove and colleagues in 1978.[1] It is a rare disorder and real incidence is not known. It presents with features such as hypocortisolism, absence of tears, swallowing difficulties.[2] It usually present during the first decade of life mostly with classical features already mentioned but sometimes may present with life threatening episodes of severe Hypoglycemia and hypotension. Cholinergic dysfunction and autonomic tests are usually disturbed with a significant deviation from normal values.[3]

Globally, the pathology of this syndrome may be due to a progressive dysfunction of cholinergic function throughout the body tissues. Alternatively, this disorder may represent an ACTH resistance caused by dysfunction of melanocortin receptor signaling pathway. This explains most of clinical features of the disorder. As melanocortin receptors are known to regulate adrenal function and skin exocrine gland function.[4]This disorder is caused by mutation in AAAS gene on chromosome l2ql3 which encodes ALADIN protein (a part of nuclear pore complex) resulting in an impaired protein function[5].

Case Report

A 5 years old boy presented to our hospital in OPD with complaints of recurrent vomiting and progressive dysphagia for last 7- 8 months. He had difficulty in swallowing solids but tolerate liquid diets. Our patient had poor appetite with easy fatigability, muscular aches and pains. There is history of one elder sibling death 4 months ago due to dehydration and shock, which was diagnosed as Addison's disease at a tertiary care unit in Lahore.

There was progressive dryness of conjunctive with reduced tear formation. There was no history of fainting spells or fits. His physical examination revealed a lean thin, alert, well cooperative and comfortable child. He had obvious pallor & hyperpigmented lips and gingival (fig.1). He was afebrile with heart rate 11O/min, Blood pressure 100/70mmHg and Respiratory rate 35/min. His weight was 16.5 Kg, Height 102 cm and OFC 50cm (All below 50th centile). Other examination was unremarkable.His investigations revealed haemoglobin ll.3g/dl (microcytic hypochromic Red blood cells), total leukocytes 8.87x l03 uL, platelet

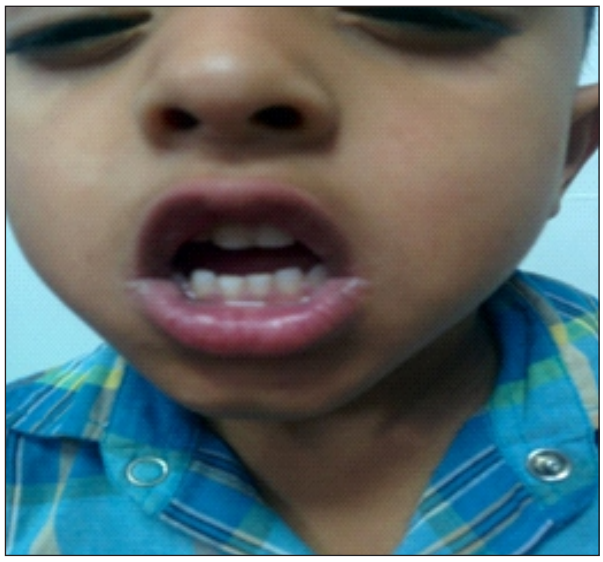

Fig.1. Hyperpigmentation of lips and gingivae.

count 335 x l03/uL and Blood sugar was 52mg/dl. Serum electrolytes, renal function test, liver function tests and urine complete picture was normal. The serum ACTH and Cortisol were initially done at 8:00am. Serum ACTH was high with value of 103 pg/ml (normal cut off 6-50 pg/ml) and random serum cortisol was 12ug/dl (normal cut off 6-23ug/dl) Then ACTH stimulation test was done to check for response of adrenal glands.

ACTH stimulation Test:

- Sample (0) before ACTH Cortisol 14.4 ug/dl.
- Sample (1) after 30 min 32 ug/dl.
- Sample(2) after 60 min 36 ug/dl.

These values document suboptimal response ACTH stimulation. In a normal person a threefold rise of cortisol is expected after standard ACTH stimulation.

Contrast studies upper barium series showed narrowing of lower esophagus giving it a bird-beak appearance and delayed esophageal emptying. Heller's Myotomy was done successfully after surgical consulation. He was put on stress dose Hydrocortisone 50 mg/m2 per day in DD for 5 days to avoid crisis during surgical stress. Ophthalmic evaluation also proved dry conjunctiva and signs of irritation due to absence of tear production. Artificial tears and lubricant were prescribed for use on regular

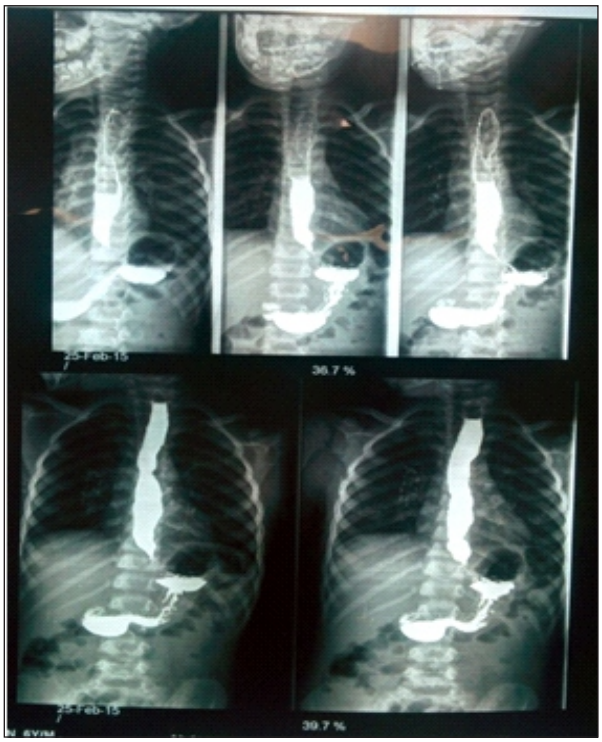

Fig-2: Barium meal Showing Esophageal Achalasia.

basis. Patient responded well to the surgery and he was able to take liquid and solid diets during the hospital stay without any vomiting. He was discharged with advice of stress dose of hydrocortisone and close follow up to pediatric endocrine clinic.

Discussion

We have presented a case who presented in Fatima memorial hospital with vomiting and dysphagia. The lips and buccal hyperpigmentation along with irritation of eyes and decreased lacrimal production made us to think of a rare syndrome which has characteristic triad of achalasia, alacremia and ACTH-resistant adrenal insufficiency- triple-A syndrome. This is an inherited familial disorder that usually manifests within the first decade of life with alacrima and/or achalasia, followed by glucocorticoid deficiency.[6] Alacremia which is a progressive disorder that can take years to develop into a full-blown clinical picture. It is the earliest and the most consistent feature of allgrove syndrome that usually presents from early infancy but is often missed by parents.[7] The term achalasia means "failure to relax" and refers to the inability of the lower esophageal sphincter (a ring of muscle situated between the lower esophagus and the stomach) to open and let food pass into the stomach resulting in dilated esophagus with retained saliva, liquid, and undigested food particles in the absence of mucosal stricturing or tumor.[8]

Incidence is unknown but it is an extremely rare syndrome with an autosomal recessive inheritance. The probable risk in future pregnancies is 25%. No evidence suggests that gender affects the frequency. It affects all races and can have variable presentation (1). The prevalence of Allgrove syndrome is unknown, only scattered family and case reports were noted in the literature. The primary cause of mortality is unrecognized adrenal crisis. In Allgrove syndrome, usually increased ACTH level is found in blood while cortisol level is subnormal and/or showing disturbance in diurnal variation due to ACTH resistance.[9] Our case showed high baseline ACTH and normal cortisol level in blood but a subnormal cortisol levels in the blood after ACTH stimulation test. This shows an evolving peripheral adrenal insufficiency. Patients with triple-A syndrome can manifest signs of autonomic nervous system dysregulation which include: decreased lacrimation, pupillary abnormality, orthostatic hypotension, sexual impotence in adults, disturbances in heart rate and abnormal reaction to intradermal histamine.[10] Autonomic disturbances associated with same

Genetic mutation led to suggestion of 4A (Allgrove) syndrome, the fourth A represents autonomic dysfunction.[4] Cases of cardiac arrhythmia have been described grown up because of autonomic involvement.Haoufadi et al, reported two cases in the same family, both of them had neurological involvement in the form of amyotrophy of thenar, hypothenar and interosseous with a peripheral neurogenic and pyramidal syndrome. Their electromyogram (EMG) noted sensory and motor demyelinating and axonal polyradiculoneuropathy.[11] These cases along with three primary features Alacremia, Achalasia peripheral adrenal insufficiency also had postural hypotention and microcephaly. In the literature, peripheral nervous system anomaly is the least documented association of Algrove syndrome.[12]Treatment is symptomatic in Allgrove syndrome with a tear substitution, a glucocorticoid for adrenal insufficiency associated with fludrocortisone if there is mineralocorticoid failure. Achalasia is treated by esophageal dilatation or Heller's cardiomyotomy.

Conclusion

Allgrove syndrome is a rare disease but each patient with achalasia who develops with signs of hyperpigmentation of the skin and buccal mucosa should be evaluated for the AAA syndrome. Careful neurologic examination is also needed in these patients. Patients should be directly questioned about a history of decreased tear production.

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