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CASE REPORT

A Case Report of Allgrove Syndrome with Hypodontia

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ABSTRACT

Allgrove syndrome is one of the rare hereditary disorders with autosomal recessive inheritance. Mutation in AAAS gene on chromosome 12q13 encoding ALADIN protein leads to alacrima, achalasia, adrenal insufficiency and multiple rare features.

We present a case of allgrove syndrome diagnosed on history and examination with alacrima evident at the age of 6 months, achalasia and adrenal insufficiency at the age of 3 years and 11 years respectively, dental variations i.e., missing of permanent premolars and malformed lateral incisors at the age of 10-11 years. In this particular case report, association of this syndrome with congenitally missed permanent premolars and malformed lateral incisors has been established which is a novel and rare feature observed in allgrove syndrome patients. Patients with allgrove syndrome usually manifest alacrima, achalasia and adrenal insufficiency during the first two decades of life.

Key Words: *Adrenal insufficiency, Achalasia, Alacrima, Dental involvement, Allgrove syndrome, Hypodontia*

INTRODUCTION

Allgrove syndrome is rare hereditary disorder inherited as autosomal recessive pattern. Most patients have consanguineous parents. Main characteristics of this syndrome include ACTH resistant adrenal insufficiency,[1] alacrima and achalasia mostly in the first two decades of life. Mutation of AAAS gene on chromosome 12q13 which codes for a WD repeat regulatory protein ALADIN,[2] is the cause of this syndrome.[2] It was first described by Allgrove in 1978, also called Triple a Syndrome (achalasia, adrenal insufficiency and alacrima). Later, various autonomic abnormalities were reported with Allgrove syndrome and it was named as 4A syndrome (adreno-cortical insufficiency, achalasia of cardia, alacrima and autonomic abnormalities). Since then many cases of 4A syndrome have been reported with significant variability in the clinical presentation. Additional associated features include developmental delay, muscle weakness and speech delay.[3] There is family history of sudden infant death syndrome and consanguinity.[4]

This article reports a case of Allgrove syndrome of an 11 years old presenting with adrenal insufficiency, alacrima, achalasia and congenital loss of permanent teeth, developmental delay and mild intellectual disability.

CASE REPORT

An 11 - years old male born to consanguineous parents, presented to pediatrics emergency department with 2- days, history of high grade intermittent fever, sudden in onset, associated with rigors and chills and relieved by antipyretics. There was one episode of generalized tonic clonic seizures for 1 day, associated with uprolling of eyes, frothing from mouth, urinary and fecal incontinence. Duration of seizures were less than 5 minutes, and was followed by short post-ictal state. Fits were controlled by intravenous

diazepam. There was no history of cough, ear discharge, respiratory distress, rash, body swellings, joint pains, trauma, weight loss, urinary or gastrointestinal symptoms. No past or family history of fits, headache, dizziness or early morning headache.

Mother narrated that her child cries without tears since birth, artificial tears of methylcellulose were advised by ophthalmologist. On ophthalmological evaluation, fundal glow was normal but a small corneal opacity in left eye was seen. B-scan of both eyes was unremarkable. Schirmer tear test was suggestive of alacrima.

He also had a complaint of recurrent episodes of vomiting and difficulty in swallowing solid food since the age of 9 months. In view of feeding difficulty mother added more liquids and semi solids in his diet. Barium meal showed smooth narrowing of gastro-esophageal junction and esophageal dilatation proximal to the junction (fig 1). On upper GI endoscopy esophageal biopsy was taken which showed signs of esophagitis at the lower end. Dietary advice was given without any surgical intervention.

He developed progressive darkening of the skin around lips, knees and elbow joints (fig 2) at the age of 4 years. There was no history of recurrent vomiting, diarrhea, dehydration or hospital admissions. Patient achieved almost all the developmental milestones at normal age except running (achieved at 3 years of age) and delayed dentition. He was unable to run and had a staggering gait with frequent falls while running. In addition he had nasal twang since childhood. He was vaccinated according to EPI schedule

On examination his vital signs were HR 100/min, BP 90/60 mmHg without orthostatic hypotension, RR 20 breaths/min, temperature 101^{O}F, capillary refill time <2 sec. and spO2 was 98%. His height was 148cm (at 75th centile), weight 25kg (at 10th centile). GCS was 15/15, Patient was cooperative during examination. CNS examination revealed hyper-reflexia, mild ataxia and nasal twang .He had hyperpigmentation of the skin, lips, knees and elbow joints. Psychosocial evaluation (table 1) was done in view of his aggressive behavior and stubbornness. His WISC-R score (50-55) after neuropsychiatric evaluation showed mild to moderate intellectual disability. He was referred for behavioral therapy and special education.

Baseline investigations: Random blood sugar 40 mg/dl, Complete blood count showed hemoglobin 11.2, Total Leukocytes count 13.9×10^3, platelet count of 175×10^3. Serum electrolytes: sodium = 132 mg/dl, potassium = 4.9 mg/dl, chloride = 97 mg/dl, calcium = 9.4 mg/dl. Renal and liver function tests were normal. Chest x-ray, abdominal ultrasound, ECG was normal. Urine complete examination was normal and there were no urinary ketones or reducing substances. Serum cortisol level was 6.0µg/dl at 8 a.m (normal 6-28 µg/dl) and serum ACTH level was 1193 pg/ml (references range, 10–60 pg/ml. Slide for malarial parasites was negative. Fundoscopy was normal.

CSF examination showed clear fluid, with normal cytology, proteins 30mg/dl and glucose 79mg/dl. CT abdomen showed adrenal atrophic changes and renal parenchymal changes. MRI brain (fig 3) showed focal meningeal thickening around the right cerebrum but no intra-axial or brain parenchymal changes were seen Blood culture and urine culture were negative.

He had congenital missed teeth, ortho-pantomogram (OPG) (fig 4) showed missed second permanent premolars (hypodontia) with malformed lateral incisors. EMG and nerve conduction studies were done for ataxia, which showed normal results. ACTH stimulation test was done by giving intravenous 250 micrograms tetracosactrin, 30 minutes and 60 minutes values were 3.2 and 4.5 µg/dl, respectively.

Patient was admitted in ICU, Hypoglycemia was corrected with 10% IV dextrose infusion. Ampicillin and ceftriaxone was started empirically and were discontinued after negative culture reports. Patient improved when hydrocortisone was given on trial basis for adrenal insufficiency. Patient was discharged on oral hydrocortisone and fludrocortisone along with artificial tears. Parental counseling was done about disease course, complications and stress management (high dose hydrocortisone) to prevent any fatal event in patient and to immediately report if any of the disease symptoms appear in other siblings. Patient was kept under follow-up for regular evaluation.

Diagnosis of allgrove syndrome was made on the basis of alacrima, achalasia, ACTH resistant adrenal insufficiency (raised ACTH and low cortisol) and mental retardation.

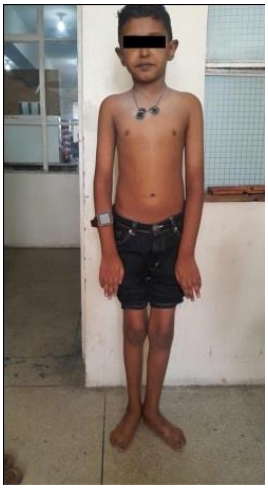
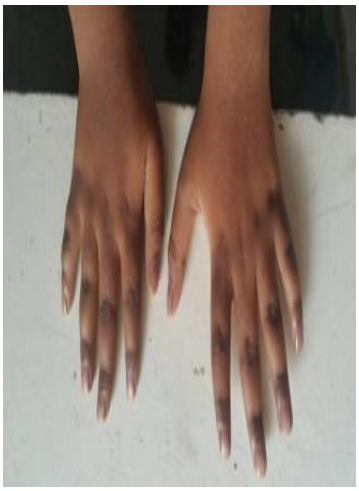


Fig 1a: Hyperpigmentation of lips, nipples, knee joints.

Fig 1b: hyperpigmentation of elbow joints



1c: hyperpigmentation of dorsum of proximal and distal interphalangeal joints and metacarpophalangeal joints

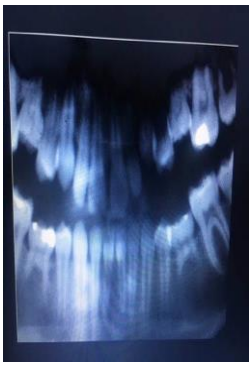


Fig 2: OPG showing congenitally missing second permanent premolars incisors

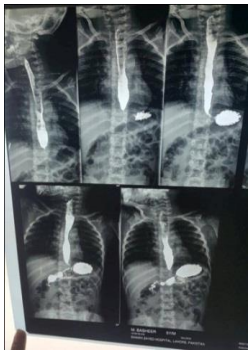
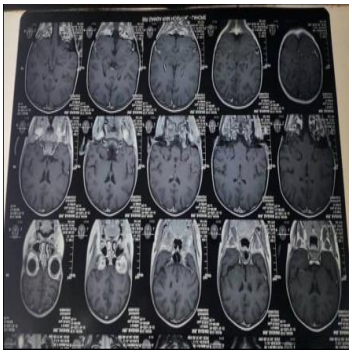


Fig 3: Barium swallow of patient, showing smooth narrowing at gastro-esophageal junction with mild proximal dilatation and hold up of contrast



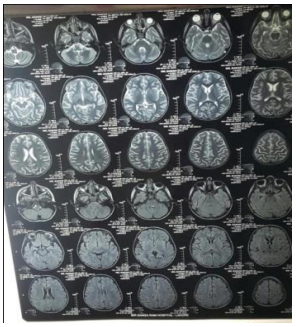


Fig 4: MRI brain with contrast, occasional sites of focal meningeal thickening around right cerebrum, suggesting meningeal inflammation. No intra-axial or brain parenchymal lesion seen otherwise.

TABLE 1: Psychosocial evaluation of patient)

Features/ Skills	Patient's Condition
Motor skills and self-help skills	Appropriate self help skills, difficulty in running
Social skills	Appropriate
Cognitive development	Average
Comprehension	Appropriate
School adjustment	Not adjusted to school since he entered school
Pre-morbid temperament	Good, co-operative
Parents	Living together
Mutual relationship of parents	Good

DISCUSSION

Allgrove syndrome or Triple-A syndrome is a rare autosomal recessive disorders which usually presents with three features i.e alacrima, achalasia cardia and ACTH resistant adrenal insufficiency.[1] Since it is an inherited disorder, patients usually present in early childhood but are often misdiagnosed and mismanaged. Primary adrenal insufficiency leads to asthenia, misdiagnosed as tiredness or muscle fatigue. Sudden stress leads to hypoglycemia and/or hypotension with syncope ending up in sudden death. Alacrima is well tolerated in these patients and often remains undiagnosed, until detailed evaluation is done. Ophthalmic symptoms can be easily managed by the use of artificial tears[5]. Achalasia leads to esophageal dys-motility and dysphagia especially for liquids. Patients may present with persistent vomiting and even shock. Patients of Allgrove syndrome can have developmental delay, mental retardation with central and peripheral neurological signs and symptoms, ataxia, dysarthria hyper-nasal speech, dysmorphic facial features, hearing deficit, xerostomia, and palmo-plantar hyper-keratosis .[6,9] Other reported features include microcephaly, short stature, palmar and plantar hyperkeratosis, osteoporosis and long QT syndrome.[7,8,10,11] Aftab S, et al. reported hypertensive encephalopathy with Allgrove syndrome in Pakistan.[12]

Very few cases have been reported showing dental abnormalities in association with Allgrove syndrome[13] but this feature has not been mentioned in literature yet. Our case also has congenitally missed permanent premolars and malformation of lateral incisors at the age of 11 years. Razavi Z, et al[13] reported two families of Allgrove syndrome. Two girls in first family became totally edentulous by 13 years of age but no dental abnormality was observed in cases from second family. Vucicevic-Boras V, et al[14] reported dental abnormalities in Allgrove syndrome. Vahedi M, et al[2] reported classical triad of Allgrove syndrome but with normal set of teeths. Authors have concluded that significant clinical variability exist among these patients. Dental abnormality is also a feature of Allgrove syndrome but further work is needed in this regard.

Rare associations seen in our case were hyper-reflexia on neurological examination and hyper-nasal speech and ataxia. .Some features e.g. polyneuropathy, muscle wasting, delayed puberty, osteoporosis and hypertensive encephlopathy are late presentations and are seen in adulthood,[5.] Pjatient is now on regular follow-up for early detection and management of late complications of Allgrove syndrome.

We emphasize that Allgrove syndrome is a multisystem disease and the cardinal manifestations may appear at any time from infancy to adulthood.

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