

Allgrove syndrome.

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Abstract

Allgrove's syndrome is characterised by a triad of achalasia cardia, alacrima and adrenal hypoplasia. We present a case of Allgrove's syndrome in a 9 yr old male child who presented with hypoglycaemia and shock. A high index of suspicion is required for prompt diagnosis and management of such cases.

Key words: Adrenal insufficiency, Achalasia cardia, Alacrima

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Introduction

Allgrove's syndrome is a rare cause of adrenal insufficiency transmitted in an autosomal recessive pattern. It was first described by Allgrove et al in 1978 and consists of a triad of achalasia cardia, alacrima and adrenal hypoplasia [1]. Hence, it is also known as Triple-A syndrome. We present a case of Allgrove's syndrome in a 9 yr old male child with the intent of highlighting and adding to the meagre literature on this unusual cause of adrenal failure.

Case report

A nine year old boy, the fourth child of a non-consanguineously married couple, developed gradually increasing hyperpigmentation of whole body since the age of 7 years. Pigmentation was more pronounced at the knuckles, palmar and plantar creases, nails, gums, lips and perioral area. Since the age of 8 years, he also developed difficulty in swallowing which was more for solids and it was associated with vomiting after ingestion of food. He was brought to the hospital emergency with the chief complaints of fever for 3 days and loss of consciousness for 1 day. Fever was associated with chills and increased vomiting. Family history revealed that the patient's brother and sister also had generalized hyperpigmentation beginning at the age of 2 years. Both of them died of undiagnosed illness which manifested as fever and loss of consciousness at the age of around 3 and half years.

On examination, he was found to be severely undernourished. His height was 124 cm (>5th percentile) and weight



Figure 1: Showing external appearance of Allgrove syndrome

was 15 kg (<-3SD). He had abnormal facial features such as an elongated face, with long philtrum and a down turned mouth (Fig 1). Hyperpigmentation of whole body was noticed, especially over bony prominences, nails, creases,

lips, gums and perioral area. Numerous fine palmar creases were noticed. External genitalia were normal. Pupillary size was normal. He had tachycardia and his systolic blood pressure was 64 mm Hg.



Figure 2: Showing achalasia cardia

Investigations revealed a random blood glucose level of 20 mg/dl. His serum sodium was 110 meq/l (137-150) and serum potassium was 4.8 meq/l (3.5- 5.8). His hemogram, QBC and other parameters suggested the possibility of malaria. He was treated with intravenous glucose. Serum sodium level was corrected over a period of 3 days. Malarial infection was treated with inj artesunate and clindamycin. Inj hydrocortisone 5mg/ kg 6 hourly was given as part of emergency supportive management as there was strong suspicion of adrenal insufficiency by above findings. He made rapid recovery.

On recovery, it was found that he had nasal twang to his voice. Neurological examination revealed a normal gag reflex, brisk DTRs, extensor plantar response and clumsy gait.

Patient's serum cortisol during hypoglycemia was 0.026 mcg/dl (6.2- 19.4). Basal 8 am serum cortisol level was 5.57 mcg/dl (6.2- 19.4) after 8 days of treatment. Aldosterone level was found to be 212.05 pg /ml, which was in normal range (25-315). Synacthen test showed a complete lack of response with all three (0, 20 and 60 min) values being below 0.035mcg/dl confirming adrenal cortical failure. The normal expected response is 3 to 5 fold rise in the cortisol at 20 min. Barium swallow confirmed achalasia cardia (Fig. 2) and MRI showed adrenal gland hypoplasia. Schirmer test was indicative of deficient tear production in both eyes.

On the basis of above findings the diagnosis of Allgrove syndrome was made. He was given cortisol replacement therapy, carboxy methyl cellulose eye drops and was referred to pediatric surgeon for management of achalasia cardia. He was put on prednisolone 5 mg/m²/day to start with and subsequently dose was reduced to 3 mg/m²/day, with which his serum cortisol level was maintained within normal range. On follow up after 2 months he had gained 3 kg weight and there was decrease in skin pigmentation.

Discussion

Allgrove and his colleagues first described this syndrome in 1978 in two unrelated pairs of siblings. All four had achalasia and Adrenocorticotrophic hormone (ACTH) insensitivity and three suffered from impaired lacrimation [2].

Allgrove syndrome is characterized by insensitivity to adrenocortico trophic hormone (ACTH) with the majority of patients having isolated deficiency of glucocorticoid, elevated levels of ACTH and normal aldosterone production. But in about 15% mineralocorticoid production may also become impaired at a later time [2]. Other known cause of ACTH insensitivity is familial glucocorticoid deficiency (FGD), which has adrenal insufficiency as sole manifestation. Allgrove syndrome was initially considered to be a variant of FGD since ACTH insensitivity was common to both disorders. However, data from recent studies suggest that Allgrove syndrome is in fact a distinct entity as gene for this syndrome maps to the chromosome 12q13 near type II keratin gene [3] unlike that of FGD which has been found on chromosome 18p11.2 [4]. In addition, mutations in ACTH receptor gene have been found in patients with FGD but none has been identified in patients with Allgrove syndrome. Incidence of this syndrome is unknown and only scattered reports exists in literature. Recent studies implicate mutation in the AAAS gene, which codes for WD repeat protein termed ALADIN, resulting in expression of a truncated protein suggesting loss of function [5].

In view of variable order of presentation and marked phenotypic variation, this association is often diagnosed late, sometimes even in adulthood [6]. The glucocorticoid deficiency is not apparent at birth but develops during the first decade of life and the most frequent initial presentation is a hypoglycemic seizures

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and shock secondary to glucocorticoid deficiency. Most patients have previously unrecognized alacrima at the time of presentation which is typically present from early infancy. Achalasia of the cardia occurs in about 75% of all cases. Symptoms of achalasia may appear in individuals as young as 5 months or as late as early adulthood [7].

Association with autonomic nervous system dysfunction has also led to the suggestion to rename the syndrome as 4A syndrome (adrenal insufficiency, achalasia of cardia, alacrima and autonomic abnormalities) [8]. Specific autonomic disturbances described in this syndrome include abnormal pupillary reflexes, poor heart rate variability during valsalva maneuver, and orthostatic hypotension. A distinct facial appearance associated with Allgrove syndrome consists of a long thin face with a long philtrum, narrow upper lip, and a down-turned mouth [9]. Associated features of the syndrome also include neurological and dermatological abnormalities [7]. A slow neurologic deterioration occurs in many patients which manifests as hyperreflexia, dysarthria, hypernasal speech with palatopharyngeal incompetence, mild mental retardation and ataxia. Hyperkeratosis and fine fissuring of the palms of the hands and soles of the feet represent a unique feature of this syndrome [9]. Hyper pigmentation of gums, lips, pressure points and extensor aspects of phalangeal joints is seen.

In a patient who presents with a serious illness such as malaria it is easy to overlook other causes of hypoglycemia. In the patient reported here, hypoglycemia was as a result of glucocorticoid deficiency exaggerating the manifestations of the infection. It is important to keep a high index of suspicion and look for all possible causes in every patient presenting with hypoglycemia. Features like hyperpigmentation, positive family history and alacrima could lead to diagnosis of unsuspected diseases as in this case. Early recognition of glucocorticoid deficiency will prevent hypoglycemic convulsions, neurological sequelae and death. A careful replacement of glucocorticoids is critical not only to avoid adrenal crisis but also to allow normal growth and development.

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