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Case Report

Allgrove Syndrome (Triple-A Syndrome): A Case Report from North India

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Abstract

Triple-A syndrome, also known as Allgrove syndrome, is an uncommon disorder which is inherited as an autosomal recessive disorder. About 100 cases have been described in literature. The three AAA comprises adrenal insufficiency secondary to adrenocorticotropic hormone (ACTH) resistance, achalasia cardia, and alacramia. We are reporting a case of a 10-year-old boy diagnosed as triple-A syndrome with ACTHresistant adrenal insufficiency, achalasia cardia, and alacrimia. He has alacramia since birth, and at the age of 7 years, he was diagnosed to have achalasia cardia. He developed the symptoms of adrenal insufficiency at the age of 9 years. Allgrove syndrome might be underreported in literature as the diagnosis requires high index of suspicion. In our patient, there was a delay of 3 years after the initial diagnosis of achalasia cardia. The diagnosis of Allgrove syndrrome should be considered in every child presenting with alacremia or achalasia cardia.

Keywords: Achalasia, adrenal insufficiency, adrenocorticotropic hormone resistance, alacremia, nervous system

Introduction

Allgrove syndrome, which is also called Triple A syndrome, was first reported by Allgrove *et al*. in 1978 in two pairs of siblings from different families. All of them were having adrenal insufficiency and achalasia cardia, and three of them had alacrimia.[1] Involvement of nervous system including central, peripheral, or autonomic nervous system has been frequently found in these patients.[2] Most of the patients present during the latter half of the first decade of their life. History of sibling death is also present in significant proportion of patients.

Allgrove syndrome is a rare disease; case reports have been reported from different parts of the world. It is transmitted in an autosomal recessive fashion. The gene responsible for the syndrome AAAS gene (achalasia adrenocortical insufficiency and alacrimia syndrome) has been localized to the chromosome 12q13, which encodes ALacrimia Achalasia aDrenal insufficiency Neurologic disorder (ALADIN) protein.[3]

Case Report

A 10-year-old boy was referred to Rajiv Gandhi Centre for Diabetes and Endocrinology for evaluation of hyperpigmentation. He had diffuse hyperpigmentation all over body including the palmar creases, knuckles, tongue, and oral mucosa for the past 2 years. He was also complaining of reduced appetite, occasional nausea, asthenia, fatigue, and failure to thrive. He is a product of consanguineous marriage, born full term by normal vaginal delivery at home. His two younger siblings (one brother and one sister) died within 1 month of their birth, cause of death is not known, but they have recurrent vomiting. Parents noticed lack of tears during crying since infancy in this patient, but they did not consult any one.

At the age of 7 years, he developed gradual onset difficulty in swallowing, especially for liquids, for which he was evaluated, a diagnosis of achlasia cardia was made, and Heller's esophagomyotomy was done. He was relieved of dysphagia after operation.

On examination, there was no pallor, cyanosis, clubbing, and icterus. Generalized hyperpigmentation including

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pigmentation of tongue, oral mucosa, and palmar creases was present [Figure 1]. His height was 123 cm, weight was 16.0 kg, and body mass index (BMI) was 10.40 kg/m^2; blood pressure was 94/56 mm Hg, and there was no postural drop. Systemic examination including neurological examination was unremarkable. Schirmer's test revealed dry eye (2 mm at 5 min, normal >5 mm).

Routine blood investigations were done which showed normal complete blood counts, blood urea nitrogen, creatinine, electrolytes (Na+ 135, K+ 4.0), and liver function test. Nerve conduction studies were normal. Tuberculin test was negative. Plasma aldosterone concentration and plasma renin activity were not measured, as the patient was normotensive without any postural drop and his electrolytes were also normal.

8 AM serum cortisol was 2.16 μg/dl and failed to increase after intravenous injection of 250 mg of synacthen (3.5 μg/dl at 30 min, normal >20 μg/dl). Adrenocorticotropic hormone (ACTH) level was 1324 pg/ml. Noncontrast computed tomography of the adrenal glands was normal with no visible calcification or adrenal enlargement.

A diagnosis of primary adrenal insufficiency was made. On the basis of ACTH-resistant adrenal insufficiency, achalasia cardia, alacrimia, a diagnosis of Allgrove syndrome or triple-A syndrome was made. Genetic testing of AAAS gene mutation was not done, as it was not available at our institute. A normal computed tomography scan of adrenals with negative tuberculin skin test ruled out the possibility of adrenal tuberculosis. He was started on oral hydrocortisone tablets 10 mg after breakfast and 5 mg in the evening, and he was also prescribed artificial tears. The patient showed remarkable improvement in his appetite and weight, and his hyperpigmentation was also reduced.

Discussion

Allgrove syndrome is a rare disease where description is mostly limited to case reports. Allgrove syndrome is transmitted in autosomal recessive fashion; the genetic locus is AAAS gene located on chromosome 12q13 that encodes for ALADIN protein. These mutations lead to a truncated protein leading to basic pathophysiology of Allgrove syndrome.[4] There is a marked variability in phenotype of genetically confirmed triple-A syndrome.[5] Patients of Allgrove syndrome do not have any structural abnormality in their cells, suggesting that mutations in AAAS lead to functional impairment.[6]

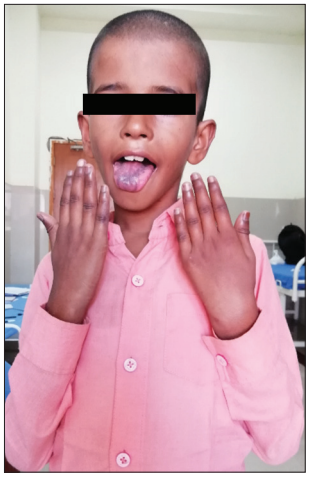

Figure 1: Hyperpigmentation of the tongue and knuckles

The clinical features of Allgrove syndrome are ACTHresistant adrenal insufficiency, achalasia, alacrimia, and variable neurological involvement. The earliest clinical feature in literature is alacrimia which is present since birth in our patient. The usual presentation of Allgrove syndrome is during the latter half of the first decade of life. Achalasia cardia occurs in up to 75% of cases; patients usually present with dysphagia, weight loss, and heartburn.[7] Age of occurrence of adrenal insufficiency is variable, it can present early in life with severe hypoglycemia, or it can present later with hyperpigmentation, failure to thrive, nausea, and recurrent vomiting. The death of two younger siblings of our patient was possibly due to adrenal insufficiency. The peculiar feature of adrenal insufficiency in Allgrove syndrome is primary adrenal insufficiency with normal mineralocorticoid function.[7] The presence of normal electrolyte and absence of postural hypotension in our patient point toward the preservation of mineralocorticoid function. An involvement of neurological system including central, peripheral, and autonomic nervous system has been described in a significant number of patients. Neurological involvement is a late phenomenon as compared to other core manifestations of Allgrove syndrome. Polyneuropathy with distal distribution is a common presentation of nervous system involvement.[8] Other neurological manifestations include involvement of autonomic system, mental retardation, amyotrophy, parkinsonism, ataxia, dementia, dystonia, and chorea. The cause of neuropathy in Allgrove syndrome is not clear. At present, there is no connecting pathological link between achalasia, alacrima, and adrenal unresponsiveness to ACTH in the Allgrove syndrome. ACTH has been found to have some neurotropic effect, and its receptor gene may provide some clues to elucidate the association of the three central features of this syndrome.[9] In case reports, Allgrove syndrome has been described in association with microcephaly, short stature, dysmorphic features, palmoplantar hyperkeratosis, osteoporosis, and long QT syndrome.[10]

Conclusion

Allgrove syndrome is a multisystem disorder with cardinal features suggestive of alacrimia, achalasia cardia, and adrenal insufficiency that can appear at any time from infancy to childhood. The prognosis of health and quality of life can be significantly improved with early diagnosis and treatment. The diagnosis must be considered in any child presenting with achalasia cardia or alcremia as this will enable early diagnosis and treatment of adrenal insufficiency and it may be lifesaving.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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