Brief Communication

The " Double A" phenotype: Portending Allgrove's syndrome and averting adrenal crisis

Soumik Goswami, Ajitesh Roy, Rana Bhattacharjee, Shivaprasad K. S., Partha P. Chakraborty, Chitra Selvan, Anubhav Thukral, Kaushik Biswas, Sujoy Ghosh, Satinath Mukhopadhyay, Subhankar Chowdhury

Department of Endocrinology, SSKM and IPGMER Kolkata, India

ABSTRACT

Introduction: Allgrove's syndrome is a rare autosomal-recessive disorder with only about 70 cases reported thus far and is characterized by alacrima, achalasia, and ACTH insensitivity among other clinical features. However, it has a widely variable clinical presentation, which may result in such cases remaining undiagnosed. **Objective:** To report a patient with impending Allgrove's syndrome and to highlight the importance of clinical suspicion in diagnosing the same. **Materials and Methods:** A 2.5-year-old girl was diagnosed with impending Allgrove's syndrome on the basis of clinical presentation, barium swallow study, Schirmer's test, and hormonal evaluation. **Results:** A 2.5-year-old girl, born of non-consanguineous marriage, presented with failure to thrive and developmental delay with occasional vomiting on taking solid or semi-solid food for past 6 months. Examination revealed stunted weight (SDS of -4.4) and height (SDS of -4.76), and barium swallow showed presence of achalasia. On direct questioning, her mother mentioned presence of decreased tears on crying since birth, and Schirmer's test confirmed the presence of dry eyes. Baseline ACTH was slightly elevated with normal basal and post-ACTH stimulation serum cortisol. Based on these findings, impending Allgrove's syndrome was diagnosed with a plan for follow-up study of adrenal function. Conclusions: Allgrove's syndrome may be an under diagnosed disorder as aclarima is often overlooked. However, a high index of clinical suspicion may help in avoiding adrenal crisis by diagnosing the condition early.

Key words: Achalasia, Alacrimia, adrenal insufficiency, Allgrove's syndrome

Introduction

Allgrove's syndrome or Triple A syndrome was first described by Allgrove and colleagues in 1978 in two pairs of unrelated siblings and is characterized by achalasia, alcrima, and adrenocorticotrophic hormone (ACTH)-resistant adrenal failure.[1] A number of associated features have been described including progressive central, peripheral, and autonomic nervous system abnormalities, palmo-plantar and punctate hyperkeratosis, short stature, osteoporosis, xerostomia, angular cheilitis, glossitis and fissured tongue, and microcephaly.[2] Inheritance is autosomal-recessive, and many have consanguineous parents. The syndrome has been linked to mutations in the AAAS gene located on chromosome 12 q13 whose product is ALADIN (alacrima-achalasia-adrenal insufficiency-neurologic disorder).[2] Globally, the pathology may be due to a progressive loss of cholinergic function or dysfunction of melanocortin receptor signaling, and the glucocorticoid deficiency is probably due to degeneration of an initially normal zona fasciculate.[3]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.104095

Clinical presentation is widely variable. The glucocorticoid deficiency is not apparent at birth but develops over the first two decades of life (usually before puberty) and has even been reported as late as in the fifth decade.[4] Alacrima is usually present from early infancy and is the earliest and most consistent feature. Symptoms of achalasia may appear in individuals as young as five months or as late as early adulthood. Most cases present with classic symptoms of primary adrenal insufficiency, including hypoglycemic seizures and shock in the first decade.[5]

Corresponding Author: Dr. Soumik Goswami, Department of Endocrinology, SSKM and IPGMER Kolkata, India.
E-mail: dr.soumikgoswami@gmail.com

The actual incidence is difficult to determine because of the variable presentation, including unexplained childhood death due to adrenal crisis and mild disease that is not apparent until adulthood, and there are only about 70 published cases in medical literature. We are reporting this case with the intent of adding to the meager literature and highlighting the role of clinical suspicion in diagnosing the condition.

A 2.5-year-old girl, the second child of a non-consanguineous marriage, presented with failure to thrive with occasional vomiting on taking solid or semi-solid food for the past 6 months. She had an uneventful perinatal period but had delayed achievement of her developmental milestones. There was no history of long-standing fever, diarrhea, gluten sensitivity, seizure, loss of consciousness, or visual disturbance. On examination, she was found to weigh only 7 kg (Weight SDS of -4.4) and had a stunted height of 73 cm (Height SDS of -4.76). Rest of the general and systemic examination including that of the nervous system was normal, and she had a BP of 90/60 mm Hg. An upper GI endoscopy was normal, but barium swallow showed the presence of bird beak narrowing of lower end of esophagus with proximal dilatation, suggestive of achalasia cardia. Subsequently, on direct questioning, her mother mentioned presence of decreased tears in her eyes on crying since birth and a history of transient dryness of eyes of her elder brother, which had spontaneously resolved in his infancy. Schirmer's test was done, which showed wetting of 6 mm and 9 mm in right and left eye, respectively, confirming the presence of dry eyes (normal is > 10 mm). The palpebral portion of the lacrimal gland was not visible on double eversion of upper eyelid suggesting alacrima, and slit-lamp examination was normal. Investigations showed a hemoglobin of 10 gm%, TLC 10900/cmm, N68 L25 E5, platelet 3.2 lakh/cmm, hypochromia and anisocytosis on peripheral smear study; random plama glucose 81 mg%, creatinine 0.5 mg/dl, calcium 10.5 mg/dl, albumin 4.9 g /dl, SGPT/SGOT 29/41, and ALP 142 U/L. Hormonal evaluation revealed FT4 1.01 g/dl, TSH 1.56 μIU/ml, 8 A.M. serum cortisol 7.57 μg/dl, ACTH 80.2 pg/ml (normal is up to 60 pg/ml) and 1 hour post-Synacthen serum cortisol 30 μg/dl. The hormonal profile was suggestive of early or evolving ACTH insensitivity with normal adrenal function at that moment. She underwent esophageal balloon dilatation, with CRE balloon of 8-10-12 mm, with relief of her gastrointestinal symptoms and was prescribed topical ocular lubricants. A repeat esophageal dilatation was done after two weeks as per gastroenterologist's advice. We planned to biochemically evaluate her pituitary-adrenal axis at 6 monthly intervals or earlier if clinically indicated and monitor her auxologic parameters.

Esophageal achalasia is a rare disease and when present, should always prompt elucidation of history suggestive of alacrima. In Allgrove's syndrome, alacrima is usually present from birth or early infancy but is often unrecognized at presentation necessitating direct questioning and relevant investigations for the same. The presence of achalasia and alacrima as initial presentation of this syndrome is less frequent, and achalasia-alacrima syndrome was once defined as a separate clinical entity, although later haplotype analysis showed it to be a variant of the triple A syndrome. Allgrove's syndrome is an under diagnosed disorder, and a high degree of clinical suspicion is required to identify the same. Being conversant with the variable presentation of the syndrome is of utmost importance for the clinician, as effective management results in a normal lifespan.

Our patient, by virtue of her atypical presentation, gave us the rare opportunity to portend impending full-blown Allgrove's syndrome and initiate requisite monitoring to avert adrenal crisis

References

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978;1:1284-6.
2. Houlden H, Smith S, De Carvalho M, Blake J, Mathias C, Wood NW, *et al.* Clinical and genetic characterization of families with triple A (Allgrove) syndrome. Brain 2002;125:2681-90.
3. Marks D, Bruce A, Boston MD. Allgrove (AAA) syndrome. eMedicine J 2001;2.
4. Kimber J, McLean BN, Prevett M, Hammans SR. Allgrove or 4 "A" syndrome: An autosomal recessive syndrome causing multisystem neurological disease. J Neurol Neurosurg Psychiatry 2003;74:654-7.
5. Kasar PA, Khadilkar VV, Tibrewala VN. Allgrove syndrome. Indian J Pediatr 2007;74:959-61.

Cite this article as: Goswami S, Roy A, Bhattacharjee R, Shivaprasad KS, Chakraborty PP, Selvan C, *et al.* The "double a" phenotype: Portending allgrove's syndrome and averting adrenal crisis. Indian J Endocr Metab 2012;16:S367-8.

Source of Support: Nil, **Conflict of Interest:** No.