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Case Reports

Allgrove Syndrome (Triple-A Syndrome): A Case Report

SULTANA YEASMIN[1], SULTANA NADIRA RAHMAN[2], RABI BISWAS[3]

Abstract:

Allgrove syndrome (also known as Triple-A syndrome) is a rare disorder with autosomal recessive inheritance. About 100 cases have been described in literature. Triple-A syndrome includes ACTH resistant adrenal insufficiency, alacrima, achalasia cardia. This syndrome may affect the autonomic nervous system; in that case it is called 4A syndrome. We are reporting a case of 5-year-1-month old diagnosed as Triple–A syndrome with adrenal insufficiency and alacrima. He had alacrima since birth and developed symptoms of adrenal insufficiency since 3 years of age. We diagnosed the case on the basis of suggestive clinical features, low serum cortisol, high ACTH and whole exome sequencing. As it is a rare disease, we should query about other symptoms of Triple-A syndrome if a patient present with adrenal insufficiency. Early detection and adequate treatment can reduce morbidity and mortality.

Keywords: *Allgrove syndrome (Triple–A syndrome), adrenal insufficiency, alacrima, achalasia cardia.*

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Introduction:

Allgrove syndrome was first reported by Jeremy Allgrove in 1978 in two pairs of siblings from different families. All of them were having adrenal insufficiency and achalasia cardia, three of them had alacrima.[1] Genetic basis of this syndrome is mutation in AAAS gene located on chromosome 12q13 which codes for ALADIN protein (Alacrima, Achalasia, Adrenal insufficiency and Neurological disorder).[2] These mutations produce a truncated protein leading to basic pathophysiology of Allgrove syndrome. Alacrima is the earliest manifestation with adrenal insufficiency; other manifestations appear in later childhood or adolescence. High index of suspicion can diagnose Allgrove syndrome earlier; our case is an example.

1. Registrar, Department of Paediatric Endocrinology and Metabolic Disorder, Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh.
2. Assistant Professor, Department of Paediatric Endocrinology and Metabolic Disorder, Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh.
3. Associate Professor and Head, Department of Paediatric Endocrinology and Metabolic Disorder, Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh.

Correspondence: Dr. Rabi Biswas, Associate Professor and Head, Department of Paediatric Endocrinology and Metabolic Disorder, Bangladesh Shishu Hospital and Institute, Sher-E-Bangla Nagar, Dhaka-1207, Mobile: 01715287817, Email: rabibiswasdr@ gmail.com,

Case Report:

A 5-year-1-month old boy was referred to Department of Endocrinology and Metabolic disorder, Bangladesh Shishu Hospital and Institute, Sher-E- Bangla, Dhaka for evaluation of hyperpigmentation. He had generalized blackening of skin over whole body for last 2 years followed by generalized weakness, fatigue, excessive salt craving for last 6 months. He also had history of one episode of afebrile generalized tonic clonic convulsion, persisted 3-4 minutes 6 month back. On query, mother gave history of lack of tear during crying since infancy, but they did not consult with physician. He had no history of regurgitation, choking or coughing related to feeding. He was second issue of consanguineous parent, delivered by LUCS at term with average birth weight. His other sibling was healthy.

On examination, he was active without any anaemia, jaundice, dehydration or facial dysmorphism . Skin survey revealed generalized hyperpigmentation including perioral, gum, buccal mucosa, tongue, knuckles, palmar and plantar creases was present. [figure-1] Vitals revealed- pulse 96/min, pulse volume good, blood pressure 90/60 mm of Hg and there was no postural drop. His height 107 cm, -0.4SD, weight 17 kg, -0.6SD, BMI was 16.34 kg/m^2, falls at 50^{th} centile. Nervous system was examined meticulously, which showed no abnormality.

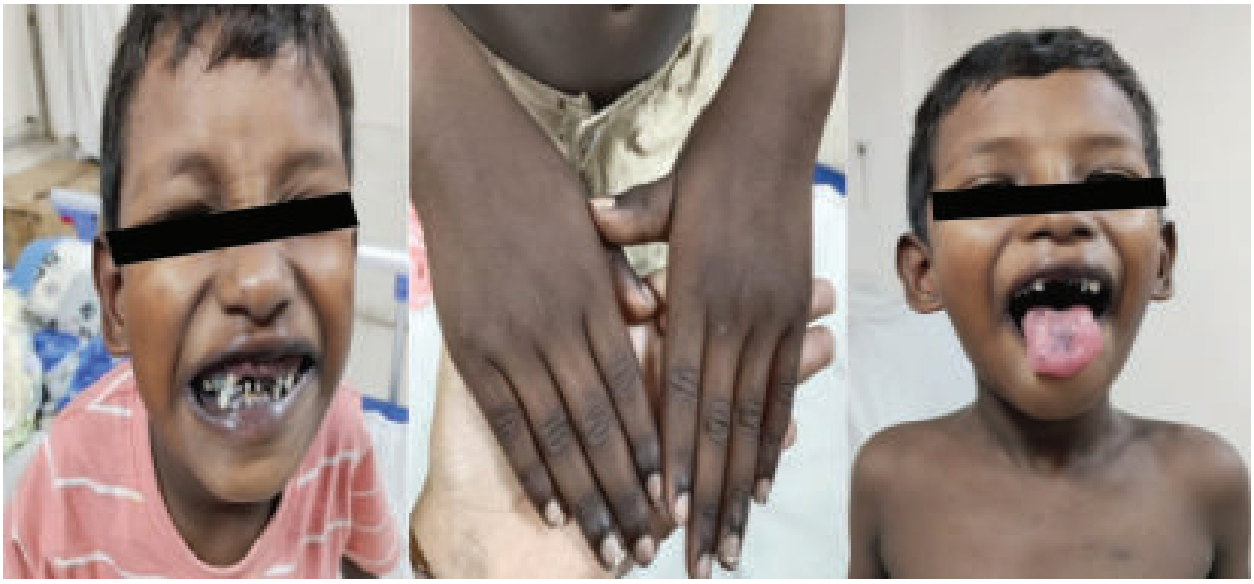
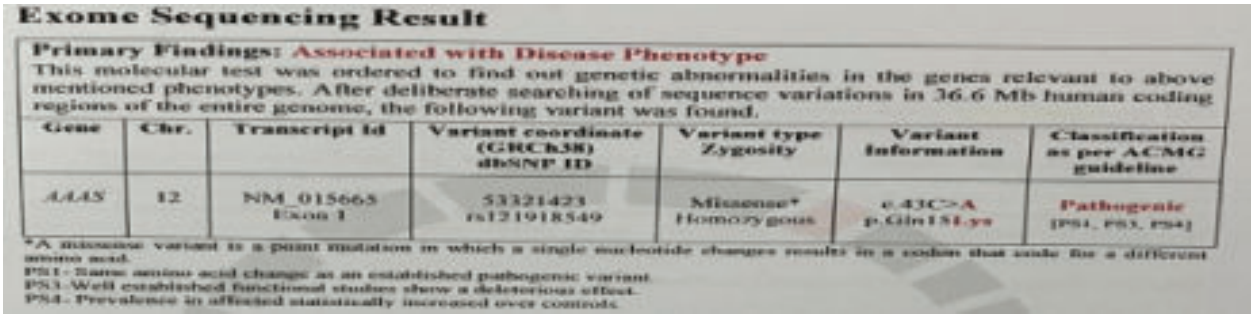


Figure 1: *Hyperpigmentation in perioral, gum, knuckles, tongue*



Exome Sequencing Result

Primary Findings: Associated with Disease Phenotype

This molecular test was ordered to find out genetic abnormalities in the genes relevant to above mentioned phenotypes. After deliberate searching of sequence variations in 36.6 Mb human coding regions of the entire genome, the following variant was found.

Gene	Chr.	Transcript Id	Variant coordinate (GRCh38) dbSNP ID	Variant type Zygosity	Variant Information	Classification as per ACMG guideline
AAAS	12	NM_015665 Exon 1	53321423 rs121918549	Missense* Homozygous	c.43C>A p.Gln15Lys	Pathogenic [PS1, PS3, PS4]

*A missense variant is a point mutation in which a single nucleotide changes results in a codon that code for a different amino acid.

PS1- Same amino acid change as an established pathogenic variant.

PS3-Well established functional studies show a deleterious effect.

PS4- Prevalence in affected statistically increased over controls.

Figure 2: *Whole Exome sequencing shows mutation in AAAS gene located on 12*

Routine blood investigations revealed normal complete blood count, arterial blood gas analysis and serum electrolytes (Sodium-137mmol/L, Potassium-3.91mmol/L, Chloride- 102mmol/L), Random blood sugar- 6.8mmol/L, Basal serum cortisol at 8 am was low (46nmol/L; normal range 101-690 nmol/L), plasma ACTH was markedly elevated (1200pg/ml; normal range 8.3- 57.8 pg/ml) but plasma renin activity normal.

Primary adrenal insufficiency was established on the basis of low basal cortisol and markedly elevated ACTH level. We took consultation from ophthalmologist regarding alacrimia. Finally, we did whole exome sequencing, which showed missense mutation of AAAS gene chromosome 12.

On the basis of primary adrenal insufficiency, alacrima and genetic study, finally we diagnosed the case as Allgrove syndrome.

We started Tab Hydrocortisone 5mg 8 hourly (20mg/m^2/day) after meal. After 2 months of treatment, patient showed remarkable improvement in clinical features as well as biochemical parameter.

Discussion:

Allgrove syndrome is a rare hereditary disorder, estimated prevalence is 1 in one million.[3] Alacrima is the earliest manifestation, which was present since birth in our patient. Although alacrima is usually overlooked, but when it is associated with complications like corneal ulcer, keratopathy, orbital cellulitis it become major concern,[4] that is evident in case report of Roy S et al.[5] There were no features of such complications in our patient.

Adrenal insufficiency usually manifests in first decade of life. Patient can present with recurrent vomiting, hypoglycaemic seizure, shock, hyperpigmentation of skin and mucous membrane, developmental delay. An episode of hypoglycaemic seizure occurred in our case. Severe hypoglycaemia, hypotension can cause sudden death.[4] The unique feature of adrenal

insufficiency in Allgrove syndrome is that mineralocorticoid activity is preserved, it may be impaired in 15% of patients.[6] In our patient normal electrolyte level, normal plasma renin activity indicates normal mineralocorticoid activity.

Achalasia cardia occurs in up to 75% cases, usually present with regurgitation, choking or cough during or after feeding, dysphagia, weight loss and heart burn.[7] Barium swallow, oesophageal manometry are well established investigation for diagnosis of achalasia cardia.[8] As our patient having no any clinical features of achalasia cardia, we didn't do further investigation.

Neurological involvement is a late manifestation of Allgrove syndrome. It involves central, peripheral, autonomic nervous system. Distal sensory motor neuropathy is common presentation.[9] Nerve conduction study can be done to find out any neuropathy.

Monitoring of visual acuity, tonometry, fundus by an opthalmologist is recommended yearly.[10] Patient should be followed up initially 3 monthly then after becoming clinically and biochemically stable 6 monthly for lifelong by an endocrinologist.[11] Genetic study is confirmatory test, which is done in our case. There is no definitive treatment, symptomatic treatment and genetic counselling is the main stay of management. Hormonal replacement by hydrocortisone for adrenal insufficiency, lubricating drops and emulsion locally at eye for alacrima and achalasia can be treated by surgical intervention.

Conclusion:

Allgrove syndrome is a genetic multisystem disease. Cardinal features may present from infancy to childhood, so if a patient present with one of the three cardinal features, we should search other features. Early diagnosis and treatment can reduce morbidity and can save life from sudden death due to hypoglycaemia or shock.

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