Section: Pediatrics

Original Research Article

ALLGROVE SYNDROME: A COLLECTION OF CASES FROM THE SAME FAMILY

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ABSTRACT

Triple A (AAA) Syndrome or Allgrove syndrome (AS)(OMIM#231550), is a rare genetic disease. It was first described by Allgrove in 1978. It is an autosomal recessive disorder, characterized by the triad of adrenal insufficiency, achalasia and alacrimia. The triad is frequently associated with progressive neurological impairment and/or mental retardation. It is estimated to affect 1 in 1 million population. Hardly 100 cases are reported till now. We are reporting a family with all siblings affected by this rare disease. 3 children died undiagnosed due to adrenal crisis, 3 are alive but affected at variable degrees due to the same disease. Management depends on the symptoms and not on the diagnosis of the syndrome because this syndrome has different types of clinical presentations, adrenal crisis being the most dreadful. Hence assessment of the adrenal axis and treatment if needed, is the most important management. Till now no case has been reported where a full family is affected.

INTRODUCTION

Even though quite rare, AS is associated with sudden death and progressive cognitive disorder among patients. Microcephaly, long-thin facies with prominent philtrum, orthostasis, hypernasal speech, ataxia, skin thickening with fissuring of palms, and soles are some of the distinct features of AS. In this article, we are reporting 6 siblings affected variably due to this disorder.

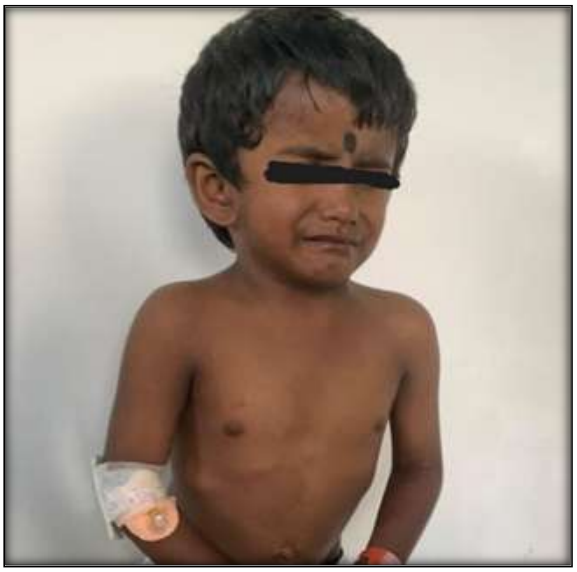

Figure 1: shows the child with generalized hyperpigmentation.

The cases

Case 1

Clinical description:1 year 7 months old boy, born to 2nd degree consanguineous married couple, was admitted in Pediatric ward for fever and loose stool. He was unnaturally dark complexioned compared to his parents. On asking, mother told he was not born so dark but since last 1 year, he is becoming darker. He also had absence of tear, noticed by parents since his 6 months of age. He used to spit out solid food since last 6 months and so he was not gaining weight since then. We considered this to be symptom of achalasia. He was the 1st twin, with an uneventful birth history, developmentally normal, with no history of any major illness or seizure till this admission.

His other twin sister was normal but 3 of his siblings who had expired at different ages. In view of consanguineous parents, alacrimia, Addison's disease (hyperpigmentation) and achalasia, Allgrove syndrome was considered and evaluated for. Management and outcome: He had anaemia Hb-6.4gm/dl, serum Ferritin- 12.3mcg/L (Normal >15mcg/L). He was treated for diarrhoea and then iron deficiency anaemia. His morning serum cortisol was very low (<0.04mcg/dl, N= 5-25mcg/dl) with high level of serum ACTH (>2000pg/ml, N=7.2-63.3pg/ml), but his serum electrolytes (Sodium/Na-146mEq/L, Potassium/K- 3.8mEq/L) and blood sugars (112mg/dl) were normal. His plasma renin

activity (1.2ng/ml/hour, N= 0.2 -4.0ng/ml/hour) and aldosterone (12.1ng/dl, N= 3.5-35.4ng/dl) levels were normal. Schirmer's test for both left and right eye were till 6mm (normal is >10mm), which is considered as moderately dry eyes. Topical lubricant was given to him to keep his eyes moist. Barium swallow test was done but it didn't show any abnormality. He was started on hydrocortisone tablets in divided doses. His skin tone improved with treatment but his feeding difficulty continued. We plan to do further evaluation for it. His whole exome sequence report came positive for homozygous pathogenic variant in exon 10 of the AAAS gene.

CASE 2

Clinical description: 15 years old girl, elder sibling of case 1, was brought by her parents with complaint of difficulty in swallowing food since she was 2 years, initially to solids and currently to both solids and liquids. She was under-weight. She was developmentally normal but had poor scholastic performances. She had dry eyes since last 10 years and her skin complexion was very dark. Management and outcome: Her Barium meal swallow x-ray abdomen revealed narrowing of the distal part of esophagus confirming achalasia.

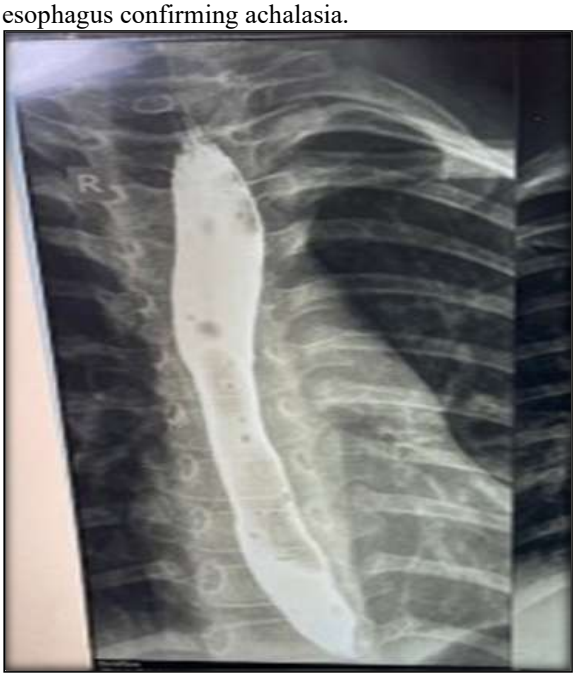

Figure 2: shows beaking of the lower end of esophagus.

She underwent pneumatic dilatation of esophagus thereafter. Her Schirmer's test was 5mm indicating moderately dry eyes. She also had corneal xerosis.

Figure 3: depicts the dry eyes.

She was given lubricant eye drop. On examination she too was dark and was having persistent low blood pressure, not changing with position. Her electrolytes were normal. Morning serum cortisol was very low (<0.04mcg/dl) with high serum ACTH (1000pg/ml). Because of low BP (ranging from 80/62 to 86/68 mm of Hg, checked several times), serum aldosterone (9.6ng/dl) and plasma renin (0.8ng/ml/hour) levels were checked and were found to be normal, so were her ECG and 2D Echocardiography. We contributed her hypotension to be a part of autonomic dysfunction, which is an extended component of Allgrove syndrome. She was given Tablet Hydrocortisone in divided doses. After 6 months of treatment, her skin colour improved, blood pressure was normal, she gained weight as she was able to eat normally. She asked to follow up regularly.

CASE 3

Clinical description: 2 years old female, 2nd twin of case 1, was thought to be normal as initial screening tests with serum cortisol (12.1mcg/dl) and serum ACTH (52pg/ml) levels were normal. She didn't have hyperpigmentation or feeding difficulty. She was brought by parents for hypoglycaemic seizure episode following fever for 1 day. She was developmentally normal. Management and outcome: she had normal blood pressure (98/70mm of Hg) and normal electrolytes (Na-140mEq/L, K-3.7mEq/L). Her morning serum cortisol and ACTH were again checked and were normal. But her ACTH stimulation test with 250 mcg of ACTH showed poor cortisol response (initial Cortisol value- 10.8mcg/dl, 1 hour post stimulation cortisol value- 13.1mcg/dl), suggesting glucocorticoid deficiency during crisis period. Parents were taught to give hydrocortisone tablets during sick days and to come for regular check-up as she can develop other features of Triple A syndrome later on.

CASE 4

Clinical description: 11 years old male child, elder sibling of case 1 was admitted couple of years ago, before case 1. He had fever and cough since last few days. He came to the Emergency department in shock with unconsciousness. His blood sugar was low at presentation. He was also hyperpigmented. Management and outcome: Intravenous fluid and Dextrose were given to him. Unfortunately, he didn't survive and any further evaluation could not be done. We consider that he might had adrenal crisis manifesting as shock and hypoglycaemia.

CASE 5

Clinical description: This 9 years old boy was the step brother of case 1. He was born to the same father but different mother, who was the sibling of the mother of case 1. He had global developmental delay and cleft palate. He didn't have hyperpigmentation. He had fever and seizure. Management and outcome: He was taken to the local hospital, where he was declared as dead. We don't have any reports as he

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was not evaluated for it. We think adrenal crisis and neurological impairment were component of Allgrove Syndrome.

CASE 6

Clinical description: 2 years old another step brother of case 1 and sibling of case 5, who was developmentally normal and not hyperpigmented, died at home following some infection. Management and outcome: He too was not evaluated. But sudden death following some infection, indicates the possibility of adrenal crisis.

The family: The father married both the sisters, who were his nieces, at different times. Two sons from the 1st sister had died. 1 son from the 2nd sister had died and 3 children are alive but affected by Allgrove syndrome at variable degrees. Permission was taken from the parents for publication of their details.

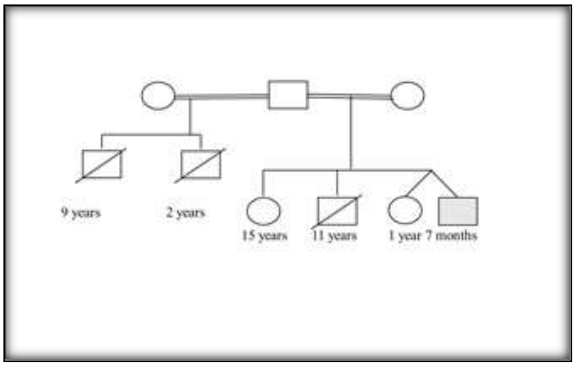

Figure 4: shows the family chart.

DISCUSSION

AS is an autosomal recessive disorder caused by mutation in AAAS gene located on chromosome 12q13, which encodes a nuclear envelope protein ALADIN (alacrimia-achalasia- adrenal insufficiency, neurologic disorder), which is involved in transduction intracellular pathways and is expressed in different human tissues,[1-3] mostly in brain, gastrointestinal tract and adrenal cortex and thus explaining the formation of triad.[4] Mutated ALADIN impairs nucleocytoplasmic shuttling of multi molecular complexes, making the cells susceptible to oxidative stress and leads to selective tissue degeneration.[5-7] But this theory doesn't hold true for all. In few AS patients, AAAS gene mutation is not even found.[8] There is no genotype- phenotype corelation in AS which indicates that environmental factors and other genes can affect the phenotype of AS.[9,10] At least 2 features among the triad, should be present to make a clinical diagnosis of AS and then it is called as "double A syndrome". Involvement of autonomic nervous system (ANS) along with typical features of AS form "4A syndrome" and addition of spinal amyotrophic is coined as "5A syndrome". AS generally manifests in the 1st two decades of life, mean being 5 years. The earliest age of presentation is recorded as a 6 months old baby with ANS involvement.[11] Full triad is present in two- third of patients, 2 symptoms in one-third and only 1 symptom in less than ten percent cases.[12,13] Adrenal insufficiency is present in 85% cases and among them 15% cases have additional mineralocorticoid deficiency. Among the triad any symptom can appear first, followed by the others over the time. This explains AS is a progressive disease. Adrenal insufficiency is the most dangerous symptom leading to sudden death if unrecognised early. Hyperpigmentation with low values of morning serum cortisol and high ACTH value is sufficient to confirm adrenal insult. Sometimes baseline hormone levels can be normal, especially in the early phase of the disease, where an ACTH stimulation test will be helpful to assess the adrenal axis functionality. This adrenal insufficient is typically ACTH resistant. Hydrocortisone alone or with Fludrocortisone tablets should be started for these patients. ANS dysfunction of the lacrimal gland causes impairment of tear formation and even corneal damage.[14] Schirmer test confirms the degree of eye dryness. Artificial tear drop is the treatment. In severe cases, punctal occlusion is the best treatment. If left untreated it can progress to keratoconjunctivitis sicca. Achalasia is a primary motor disorder of the esophagus leading to impairment of lower esophageal sphincter and loss of peristalsis due to imbalance between excitatory and inhibitory neurons.[15] Achalasia leads to repeated aspiration, pneumonia and choking episodes. A barium meal swallow shows narrowing or beaking of the lower oesophageal end. Esophageal manometry remains the confirmatory diagnosis. It shows esophageal muscles fail to contract and the lower oesophageal sphincter fail to relax during swallowing. Heller's myotomy is the surgical treatment where pneumatic dilatation fails to cure achalasia. Prognosis of AS depends on the degree of severity of the disease and associated complications.

CONCLUSION

Due to variable symptoms at various ages, the diagnosis of Allgrove syndrome is extremely difficult. But if any one of the symptoms appears, the patient should be followed in the long term as it is a progressive disease. Undiagnosed adrenal insufficiency is the commonest cause of death in these patients. In our reported family, 3 siblings died due to adrenal insufficiency. Therefore, siblings of an affected patient should always be screened for adrenal insufficiency.

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