Case Series

Allgrove Syndrome: Case Series on 4A and Triple A Syndrome in Children with Rare Presentation

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Abstract

Introduction: Allgrove or Triple A syndrome is a rare familial multisystem disorder with autosomal recessive inheritance. Usual features include varied combination of alacrima, achalasia cardia, and adrenocorticotrophic hormone (ACTH) resistant adrenal insufficiency along with autonomic dysfunction and other neurological problems in some cases when it is known as 4A syndrome. Basic defect is in the Achalasia Addisonianism Alacrima Syndrome gene (AAAS) located on chromosome 12q13. **Case Details:** This report relates to two unrelated girls aged 7 and 12 years, who presented with orbital cellulitis with acute adrenal crisis and initial episode of nephrotic syndrome, respectively. Both had history of hyperpigmentation of skin, especially palmer creases and knuckles and absence of tear from both eyes while first patient also had autonomic dysfunction. Ophthalmological examination, biochemical evaluations for adrenal function, barium swallow study and magnetic resonance imaging (MRI) of orbits were all consistent with Allgrove Syndrome. Patients were adequately treated for the complications and then put on hormone replacement therapy and ocular lubricants resulting in remarkable improvement on follow up study. **Conclusion:** Despite lack of definitive treatment, supportive treatment and hormone replacement can improve quality of life of Allgrove patients.

Keywords: *4A, AAAS gene, allgrove, cellulitis, nephrotic, orbital, syndrome, triple A*

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Introduction

Allgrove syndrome or Triple A syndrome is a rare autosomal recessive disorder first described by Jeremy Allgrove in 1978 in two unrelated siblings as a triad of alacrima, achalasia cardia and isolated glucocorticoid deficiency.[1] When this is associated with neurologic disorders like autonomic disturbances(neuropathy), it is known as 4A syndrome.[2] It is characterized by mutation(s) in AAAS gene located on chromosome 12q13 which codes for ALADIN protein (Alacrima, Achalasia, Adrenal insufficiency and Neurological disorder).[3] This case series describes uncommon presentations of this rare disorder.

Case Reports

Patient 1

A seven-year-old girl, born out of nonconsanguineous marriage, presented with chief complaints of pain, redness, and swelling of both eyes with high grade fever and occasional giddiness for 2 days. She had history of darkening of skin color, absence of tear, reeling on change of posture, and unexplained bouts of excessive sweating for the last 1 year but without any history suggestive of dysphagia. There was no history of any developmental delay or speech problem. On examination, child was febrile and drowsy, had pulse rate of 160 per minute, and blood pressure (BP) <5th percentile. Her anthropometry was normal. She had redness and swelling of both eyes and hyperpigmentation of skin particularly knuckles [Figure 1a and b] and palmer

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creases. Heart rate variation during deep breathing was subnormal, expiration–inspiration difference of heart rate was 6 bpm (normal >15 bpm), and there was no reflex tachycardia on standing. Her supine posture BP was 90/50 mm Hg while BP measured within 3 minutes of standing was 60/30 mm Hg, suggestive of orthostatic hypotension. Rest of neurological, other systems, and fundoscopic examination were normal. Random blood glucose was 70 mg/dL [normal 60–100 mg/dL], and serum sodium and potassium were normal. Serum cortisol was low 0.39 µg/dL [normal 6.2–19.4 µg/dL], and early morning ACTH was 1250 pg/dL [normal <46 pg/dL]. Synthetic ACTH stimulation test failed to raise serum levels of cortisol. Serum aldosterone and plasma renin activity were within normal limit. Ophthalmological evaluation involved the Schirmer's Test which revealed 2-mm wetting of filter paper strip in both eyes indicating severe dry eye. Tear film breakup time was however normal suggesting alacrima. MRI orbit revealed absence of lacrimal gland. Barium swallow showed bird beak-like narrowing of lower esophagus. Nerve conduction velocity and electromyography studies were normal. Child was started on intravenous (IV) fluids and antibiotics. Hydrocortisone @50 mg/m^2 was given immediately followed by 50 mg/m^2/day continuous IV infusion over 24 hours. As BP stabilized, the child was switched over to oral hydrocortisone at 8 mg/m^2/day in two divided doses. The child's guardian was well counselled about increasing the dose of hydrocortisone to double/triple in times of stress and was advised to use lubricant eye drops. After 8 months of follow-up, severity of hyperpigmentation decreased and no further hospital admission was needed.

Figure 1a: Image showing normal appearance at 2 years of age; redness and swelling of both eyes during illness; hyperpigmentation of skin particularly knuckles

Patient 2

A 12-year-old girl, born out of second-degree consanguineous marriage, presented with chief complaint of drowsiness and anasarca starting from face [Figure 2a] associated with reduced urine output and 3+ proteinuria on dipstick and eventually diagnosed as initial episode steroid responsive idiopathic nephrotic syndrome. She had past history of hospital admissions due to convulsions associated with hypoglycemia and hyponatremia from 5 years of age, darkening of skin color, and absence of tear, but had no history of dysphagia or neurological abnormalities. The child was on sodium valproate for the last 7 years. Examination revealed anasarca, stable vitals, no change of BP with posture, height was <2 standard deviation (SD), and she had hyperpigmentation of skin especially knuckles and palmer creases. Neurological and other examinations were normal.

Random blood glucose was 40 mg/dL, sodium 110 mmol/L [normal 135–145 mmol/L], and potassium 5.6 mmol/L [normal 3.5–4.5 mmol/L]. Serum cortisol was low as 1.2 µg/Dl. Early morning ACTH levels were high as 968 pg/dL and ACTH stimulation test did not elevate serum cortisol levels, suggesting ACTH insensitivity. Serum aldosterone concentration was lower than normal, and plasma renin activity was on higher side. Schirmer's test revealed wetting of filter paper of 6 mm in both eyes, tear film breakup time was normal, and MRI orbit revealed absence of lacrimal glands. Barium swallow showed bird beak-like appearance of

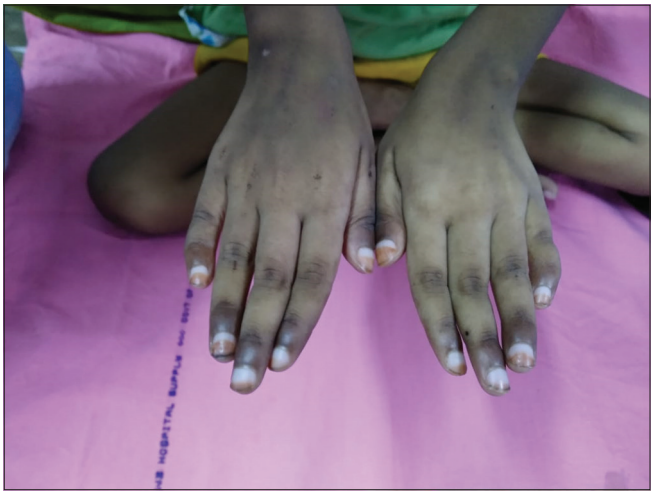

Figure 1b: Image showing change in hyperpigmentation in case 1

Figure 2a: Facial profile of patient 2 with periorbital swelling and diffuse hyperpigmentation

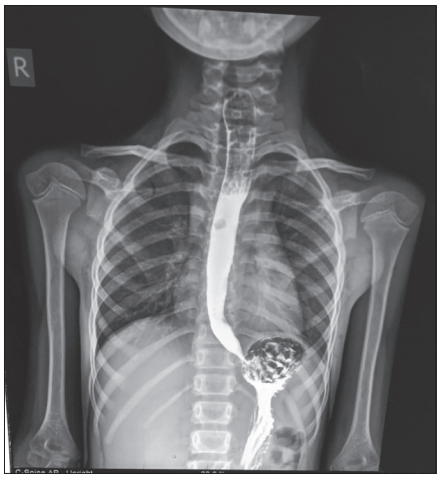

Figure 2b: Barium swallow study of Case2 showing bird beak-like appearance of lower esophagus with narrowing of distal segment and dilation of proximal segment, suggestive of achalasia cardia

the esophagus [Figure 2b]. The child was started on fludrocortisone at 1 mg/day, Prednisolone at 2 mg/kg/day and continued for 6 weeks daily followed by @1.5 mg/kg/day on alternate day for 6 more weeks, valproate was stopped, and lubricant eye drops were advised. Oral hydrocortisone was started after completion of prednisolone therapy. On 1 year of follow-up, the child was on regular hydrocortisone and fludrocortisone, skin color lightened, had one episode of relapse of nephrotic syndrome (treated adequately), was seizure free for 1 year and serum electrolytes, and aldosterone level was normal, so fludrocortisone was stopped without rebound hyponatremia.

Discussion

Allgrove Syndrome is a rare disorder, incidence being one in a million.[4] Classic triad being present only in 70% of cases, while 30% cases have autonomic dysfunction and other neurological impairment and is known as 4A syndrome.[2] Patients usually present within first decade of life with alacrima being the earliest and most consistent feature,[5] followed by achalasia manifesting as dysphagia, hoarseness of voice, or recurrent pneumonia. Although alacrima itself does not concern the patients, associated complications like corneal ulcer or even orbital cellulitis often become serious issues (as in 1st case). Alacrima occurs in most cases due to absent lacrimal gland but may occur in presence of the gland due to impaired cholinergic response.[6] Alacrima is diagnosed by Schirmer's Test where wetting of filter paper <10 mm indicates dry eye and <5 mm severe dry eye. MRI/CT scan of orbit can be done to look for lacrimal gland. In this series, both the patients had absent lacrimal gland. Adrenocortical insufficiency often has a delayed onset even up to adulthood[7] though medical emergencies like hypoglycemia or acute adrenal crisis are not uncommon (as in 2nd case). Isolated glucocorticoid deficiency can occur probably due to degeneration of zona fasciculata of adrenal cortex. Although mineralocorticoid levels are normal in most cases, they may be deficient in a minority of cases. Glucocorticoid deficiency can be assessed by serum cortisol, early morning ACTH levels, and ACTH challenge test which was found to be positive in both the patients. Although mineralocorticoid deficiency is rare, serum aldosterone and plasma renin activity should be assessed in all cases. Neurological involvement is common in adult onset disease and includes one or more of sensorimotor polyneuropathy, autonomic dysfunction, and amyotrophy.[8] There occurs a progressive loss of cholinergic function throughout the body. Dysfunction of melanocortin receptor signaling may be an alternative pathogenesis as they involve skin and adrenal exocrine function.[9] Achalasia occurs due to impaired parasympathetic response at lower esophageal sphincter preventing its relaxation. Esophageal manometry is the gold standard for diagnosing achalasia[5] but barium swallow is a cheaper alternative which shows bird beak-like appearance of the lower esophageal region. Peripheral neuropathy is probably due to a defect in ACTH receptors on neurons or glial cells which leads to demyelination.[10] Nerve conduction velocity study and electromyography reveal any sensorimotor neuropathy or amyotrophy, respectively. Hyperpigmentation is caused by increased production of ACTH and melanocyte stimulating hormone arising from the ACTH precursor proopiomelanocortin. Association between Allgrove syndrome and Nephrotic syndrome may be coincidental, but it is unique and not reported in the literature.

The differential diagnosis of Allgrove syndrome is other causes of adrenal insufficiency including familial glucocorticoid deficiency, adrenoleukodystrophy, and Sjogren Syndrome. Diagnosis can be confirmed by DNA sequencing that reveals mutation in AAAS gene on chromosome 12q13 but may be absent in some cases, so absence cannot rule out the diagnosis of Allgrove syndrome. Genetic mutation study in our cases was not feasible due to financial constraint. Although there is no definitive treatment for this condition, supportive management and adequate hormone replacement can prevent acute emergencies like hypoglycemia or acute adrenal crisis. If achalasia cardia becomes symptomatic, esophageal balloon dilation is preferred over surgery. Lubricant eye drops are used for management of the dry eye. Our first case had alacrima, achalasia, glucocorticoid insufficiency, and autonomic dysfunction suggestive of 4A variety, while second case had alacrima, achalasia, both glucocorticoid and mineralocorticoid deficiency but no neurological abnormalities suggestive of Triple A variety of the disease.

Conclusion

Allgrove syndrome is often under-diagnosed and needs high degree of suspicion for early diagnosis. Prognosis of this conditions is highly dependent on early diagnosis as it can prevent acute emergencies, thus decreasing mortality. Despite lack of definitive treatment, supportive treatment and hormone replacement can improve quality of life of such patients.

Contribution

SR, PG-case management; SB-authored the article; MKD, SDK-critical review

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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