INTRODUCTION

Allgrove syndrome, also known as triple-A syndrome, is a rare familial multisystem autosomal recessive disorder. It is characterised by triad of alacrima, achalasia and adrenal insufficiency due to adrenocorticotropin hormone (ACTH) resistance. If it is associated with autonomic dysfunction, it is termed as 4-A syndrome. This syndrome is caused by a mutation in the Achalasia - Addisonism - Alacrima (AAAS) gene on chromosome 12q13 encoding the nuclear pore protein ALADIN. A 5-year boy presented with history of fits and altered sensorium for one day. His vomiting progressively worsened; and for the last one year, it was associated with heart burn and regurgitation of food particles. On direct asking, the mother gave history of no tear formation on crying. There was no family history of any pigmentation of body, absent tears or repeated vomiting in any of his siblings or other family members.

Here, we are reporting a 5-year boy who was diagnosed as Allgrove syndrome with autonomic hypertensive crises.

CASE REPORT

A 5-year male child presented to Emergency Department of The Children's Hospital and The Institute of Child Health, Lahore with complaints of headache, vomiting, fits, and altered sensorium for one day. He had a product of consanguineous marriage with two healthy siblings. There was a past history of progressive darkening of skin and repeated vomiting since six months of age. His vomiting progressively worsened; and for the last one year, it was associated with heart burn and regurgitation of food particles. On direct asking, the mother gave history of no tear formation on crying. There was no family history of any pigmentation of body, absent tears or repeated vomiting in any of his siblings or other family members. On admission, he was a sick afebrile child with respiratory rate of 24/minute, pulse rate of 100/minute and blood pressure of 160/90 mm Hg. Height was 96 cm (< 3rd centile) and weight was 13 kg (< 3rd centile). He had generalised hyperpigmentation involving oral mucosa and palmer creases with normal external genitalia. His CNS examination revealed GCS of 12/15, grade II papilledema, and normal tone, power and deep tendon reflexes. He had no sign of meningeal irritation with bilateral down going planters. Rest of systemic examination was normal. In Emergency, he was managed as Addison disease with meningoencephalitis and was given intravenous fluid, antibiotics, hydrocortisone and Mannitol. After stabilisation, he was shifted to Paediatric Endocrinology Department.

Investigations showed normal complete blood count, renal function test, liver function test, C-reactive protein and Blood culture. Cerebrospinal fluid examination and magnetic resonance imaging of brain was also normal. Blood glucose level was 70 mg/dl, serum sodium was 143 meq/l, serum potassium was 2.7 meq/l and arterial blood gas analysis showed metabolic alkalosis. His
hormonal profile showed raised serum ACTH > 1250 pg/ml and decreased serum Cortisol < 1 ug/dl at 8:00 am, with normal serum Renin (0.3 pg/ml), serum Aldosterone (40.69 pg/ml) and 17 hydroxy-progesterone (0.03 ng/ml). His eye examination showed tear breakup film time > 10 seconds, suggestive of alacrimia. Barium swallow showed bird beak appearance, suggestive of achalasia (Figure 1).

During stay in Paediatric Endocrine Department, he had episodic hypertension, for which he was thoroughly worked up. He had normal USG abdomen with no evidence of renal artery stenosis on Doppler. His echocardiography was normal. His nerve conduction studies (NCS) and electromyography (EMG) was also normal. He was tested for autonomic instability, which showed no obvious orthostatic hypotension and normal heart rate variability on Valsalva maneuvre.

On basis of ACTH resistance (raised ACTH, decrease cortisol, normal renin and normal aldosterone), achalasia and alacrimia, he was diagnosed as Allgrove syndrome. Molecular genetic study for detection of mutation in AAAS gene was not done due to its unavailability in Pakistan. His episodic hypertension seemed to be due to autonomic instability and responded to B-blocker.

After correcting his electrolyte imbalance, his surgery for achalasia was done under stress steroid dosage. His surgery went uneventful with smooth post-operative recovery. His investigations before discharge showed normal serum sodium (140 meq/l), potassium (3.8 meq/l), and arterial blood gas analysis. He was discharged on oral hydrocortisone (15 mg/m2/day), topical eye lubricant, and B-blocker. On follow-up after 3 months, his pigmentation had decreased, gained 3 kg weight with normal blood pressure, electrolytes (serum sodium=142 meq/l, serum potassium=3.7 meq/l) and arterial blood gases (PH=7.38, HCO₃=22 meq/l, PCO₂=39 meq/l).

**DISCUSSION**

Allgrove syndrome or Triple-A syndrome is a rare autosomal recessive multisystem disease which consists of a triad of alacrima, achalasia and ACTH resistance. In some cases, it is associated with sensory and/or autonomic instability and termed as 4A syndrome. It is named as Allgrove syndrome as it is first time reported by Allgrove et al. in 1978.1,3 It has varied age of different symptoms. Alacrima typically present in early infancy. Symptoms of achalasia reported as early as 6 month of age. Adrenal insufficiency is not present at birth but can develop at any age within first two decades of life. Skin of these patients may show hyperpigmentation, hyperkeratosis, and fissuring of palm and soles.2

Alacrima in Allgrove syndrome occurs due to structural abnormalities in lacrimal gland and autonomic dysregulation. Alacrima is confirmed by Schimers test or tear break-up time. If left untreated, it can lead to band keratopathy and corneal ulceration.4 In this case, alacrima is confirmed by tear break-up time.

Glucocorticoid deficiency due to ACTH resistance is second component of this syndrome.5 This patient also had low cortisol and high ACTH (glucocorticoid deficiency) with evidence of normal mineralocorticoid activity (normal serum renin and aldosterone level), confirming ACTH resistance. Persistant hypokalemic metabolic alkalosis in our patient seems to be due to repeated vomiting, which settled on surgical Heller Myotomy for achalasia.

In this syndrome, achalasia occurs due to decrease in non-adrenergic and non-cholinergic neurons.6 In esophagus, there is lack of neuronal nitric oxide synthase in autonomic plexus. It is surgically treated by Heller Myotomy with or without antireflux medication.4

Neurological manifestation of Allgrove syndrome includes sensorimotor polyneuropathy, autonomic dysfunction, amyotrophy, dysarthria, ataxia, optic atrophy, and intellectual impairment. Some cases also report evidence of cognitive defect, pyramidal syndrome, dital muscular dystrophy, hyperreflexia, cerebellar dysfunction, dysautonomia, neuro-ophthalmological sign, bulbar and facial symtoms and microcephy.5 In this case, there is no evidence of sensorimotor neuropathy. To date, most of the cases of Allgrove syndrome showed autonomic dysfunction in the form of orthostatic hypotension or reduced heart rate variability on Valsalva maneuvre, but this boy presented with episodic hypertension as the manifestation of autonomic instability.
The index patient had 4 A variant of Allgrove syndrome — alacrima, achalasia, ACTH resistance, and autonomic dysfunction. As in this case, early detection and prompt treatment of alacrima, achalasia, adrenal insufficiency, and autonomic dysfunction lead to improvement in quality of life.

REFERENCES