

A case of late-onset allgrove syndrome presenting with predominant autonomic dysfunction

Debmalya Sanyal, Shakya Bhattacharjee¹

Department of Endocrinology, KPC Medical College and Hospital, 1F, Raja Subodh Chandra Mullick Road, Jadavpur, ¹General Medicine, Peerless Hospital, 360, Panchasayar, Kolkata, West Bengal, India

Abstract

Allgrove Syndrome or triple A syndrome is a rare familial multisystem disorder characterized by achalasia, alacrima and adrenal insufficiency. The objective was to describe a case of 4A syndrome where autonomic dysfunction was the presenting feature. A 22-year-old male presented with erectile dysfunction and loss of spontaneous morning erections for six months. He was having nocturnal diarrhea and recurrent postural dizziness for three months. He was found to have hyperpigmentation at pressure points, postural hypotension and other features of autonomic dysfunction. Laboratory investigations and imaging studies revealed hypoadrenalism, achalasia, alacrima and peripheral neuropathy. Autonomic neuropathy-related features persisted even after correction of hypoadrenalism. Based on clinical features and investigation he was diagnosed as a case of 4A syndrome presenting with autonomic dysfunction. Allgrove or 4A syndrome should be considered as a rare differential diagnosis of someone presenting with features of autonomic neuropathy.

Key Words

Alacrima, autonomic, achalasia, neuropathy

For correspondence:

Dr. Shakya Bhattacharjee, Department of General Medicine, Peerless Hospital, 360, Panchasayar, Kolkata – 700 094, West Bengal, India. E-mail: shakyadoc@rediffmail.com

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Introduction

Allgrove Syndrome or triple A syndrome is a rare familial multisystem disorder characterized by achalasia, alacrima and adrenal insufficiency due to Adreno cortico trophic hormone (ACTH) insensitivity, usually presenting in the first decade of life.^[1,2] Manifestations in adult patients are rarely reported.^[1] When autonomic neuropathy is there it is called 4A syndrome and when both autonomic neuropathy and amyotrophy are present, it is called 5A syndrome. We report a case of adult-onset Allgrove syndrome presenting with features of predominantly autonomic dysfunction.

Case Report

A 22-year-old recently married male, born to non-consanguineous parents, presented with erectile dysfunction and loss of spontaneous morning erections for six months, but

with normal libido. He was having irregular bowel movement including nocturnal diarrhea for three months along with recurrent postural dizziness on standing from supine position. He had occasional palpitation, gustatory sweating, decreased sweating and tingling, numbness of both distal extremities. He had persistent redness and itching of eyes for the last six months along with decreased tears while crying for two years.

He had no history of nausea, vomiting, dysphagia, weakness or thinning of limbs, nasal intonation of voice, difficulty of vision, nasal regurgitation of food. There was no past history of seizure, shock, hypoglycemia or any major illnesses like tuberculosis or similar episode in childhood. He was on no regular drug therapy. His family history was insignificant.

On clinical examination he had hyperpigmentation of skin, especially of creases of palm and sole, buccal mucosa, both his eyes were congested. He had normal testicular volume (18 ml, bilaterally) and secondary sexual characters (pubic hair was Tanner stage P5, axillary hair was present). His resting pulse rate was 104/min, blood pressure on supine posture was 122 / 84 mmHg with a postural drop of 32/20 mmHg on standing with no compensatory tachycardia on repeated occasions.

His neurological examination revealed normal higher mental function, cranial nerves, cerebellar functions, pupillary reflex and fundoscopy. There was no wasting of muscles or

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fasciculation with normal muscle tone. Tendon reflexes were normal except diminished ankle jerks bilaterally. He had bilateral flexor plantar responses. He had decreased pinprick and vibration senses distally in both hands and feet.

His complete blood count, ESR, blood urea, serum creatinine, calcium, magnesium and liver function tests were normal. Fasting blood glucose (80 mg/dl) was with normal serum sodium (139 meq/l) and potassium (3.8 meq/l). Serum cortisol was low-1.8 mcg/dl (normal-6.2-19.4) with very high 8 AM plasma adrenocorticotrophic hormone (ACTH) of 1871 pg/ml (normal 7.2-63.3 pg/ml). Synthetic ACTH (synacthen) stimulation test failed to raise the plasma cortisol-3.4 mcg/dl (normal >18). Computed tomography (CT) scan abdomen showed normal adrenal sizes. Chest X-ray was normal and Elisa for HIV was negative. Thyroid function tests, TPO antibodies, prolactin, leutinizing hormone (LH), follicle stimulating hormone (FSH) were within normal limits. Nerve conduction velocity (NCV) study of all four limbs suggested distal motor polyneuropathy with axonopathy with features of sensorimotor neuropathy.

Even after full replacement with oral hydrocortisone (20 mg/day) the postural hypotension (28 mm Hg) and resting tachycardia (108/min) persisted. His serum aldosterone levels and plasma renin activity were normal. Suspecting autonomic dysfunction in view of persistent postural hypotension other clinical tests for autonomic dysfunctions were performed. His heart rate variation with deep breathing was 9 beats/min (normal ≥ 15), heart rate response (30:15 ratio) to standing was 1.01 (normal ≥ 1.04) and valsalva ratio (heart rate response to valsalva maneuver and was abnormal at 1.11 [normal ≥ 1.21]). His diastolic response to sustained handgrip was 8 mm Hg (normal ≥ 16).

Ophthalmological evaluation revealed significant reduction of tear film bilaterally. Schirmer's test was positive, 4mm (normal > 10mm) but tear film break-up time was normal confirming the diagnosis of alacrima. A barium swallow esophagus showed narrowing of the lower esophageal sphincter constriction with dilatation of the esophagus above suggestive of achalasia cardia. Esophageal manometry revealed mean resting LES pressure >60 and absent relaxation to wet swallows. There were simultaneous contractions to wet swallow and spontaneous esophageal body contractions confirming the diagnosis of achalasia.

Presence of autonomic dysfunction, adrenal insufficiency, alacrima and asymptomatic achalasia was consistent with the diagnosis of Allgrove's syndrome. The patient was treated with replacement dose of oral hydrocortisone (20 mg/day) and topical eye lubricants. On regular follow-up at 18 months his lethargy and weakness improved and pigmentation decreased significantly but autonomic dysfunctions and peripheral neuropathy persisted. He also developed symptoms of achalasia like occasional vomiting and dysphagia.

Discussion

Allgrove syndrome, a rare disorder is usually diagnosed in the first decade of life but it has a variable age of onset and

presentation. Allgrove syndrome, commonly presents during the first decade of life with dysphagia due to achalasia or severe hypoglycemic or hypotensive attacks, related to adrenocortical insufficiency or rarely dryness of eyes due to alacrima. Onset of adrenal insufficiency or other features may be rarely delayed to adulthood. Patients presenting with Allgrove syndrome in adulthood are rarely reported. In contrast to children, adult-onset Triple A syndrome is dominated by neurological symptoms with minor gastrointestinal and endocrinological symptoms rendering the diagnosis difficult.^[3] Alacrima is diagnosed by Schirmer's test while achalasia cardia and adrenal insufficiency are best diagnosed by esophageal manometry and post-ACTH stimulated cortisol levels respectively.^[4] Our patient presented with mostly autonomic features, along with alacrima and undiagnosed adrenal insufficiency without any symptoms of achalasia. Alacrima is not a usual presenting feature but is claimed to be the earliest and most consistent feature.^[4]

Allgrove syndrome is characterized by mutation(s) in AAAS gene, located on Chromosome 12q13 coding for ALADIN protein. Most mutations produce a truncated protein, although missense and point-mutations have also been reported. Some patients with Triple-A syndrome may not have mutations in AAAS. There is no specific genotype-phenotype correlation.^[4,5] The exact cause of peripheral neuropathy in Allgrove syndrome is not clear but a defect in ACTH receptors on neurons/glia cells leading to demyelination was proposed.^[1,6] Globally, the pathology may be due to a progressive loss of cholinergic function throughout the body. Dysfunction of melanocortin receptor signaling is also a possibility as melanocortin receptors are known to regulate adrenal and skin exocrine gland function.^[2] Our patient had low cortisol, very high ACTH confirming glucocorticoid deficiency due to ACTH resistance. The glucocorticoid deficiency is probably due to degeneration of zona fasciculata, mineralocorticoid function is usually normal as in our patient, as he had normal electrolytes serum aldosterone and plasma renin activity. Dysfunctional esophageal autonomic nerve plexus and degeneration of nerve fibers is postulated as the etiology of dysphagia, with c-AMP as the possible neurotransmitter.

Neurological features of Allgrove syndrome include sensorimotor polyneuropathy, amyotrophy, dysarthria, ataxia, optic atrophy, intellectual impairment and autonomic dysfunction. In a series of eight patients from France all showed features of peripheral neuropathy.^[3] Other neurological features described in various studies include cognitive deficits, pyramidal syndrome, distal muscular atrophy, hyperreflexia, cerebellar dysfunction, dysautonomia, neuro-ophthalmological signs, bulbar and facial symptoms and microcephaly.^[2,3,7] Extrapyrmidal symptoms are rare and parkinsonism is the commonest type described but Jacob *et al.*, from Kerala reported two siblings of familial Allgrove's syndrome presenting with chorea and dystonia.^[7]

In our case symptoms of autonomic and peripheral neuropathy and alacrima predated achalasia symptoms. He had persistent autonomic dysfunction symptoms in the form of erectile dysfunction, bowel irregularity, gustatory sweating, decreased sweating and postural hypotension, palpitation even after full steroid replacement. Autonomic dysfunction in our case

seemed to involve cardiac sympathetic and parasympathetic, cholinergic sympathetic (sudomotor), parasympathetic lacrimotor and pelvic parasympathetic (erectile function). Previously autonomic dysfunction in Allgrove's syndrome was said to be restricted to cholinergic neurons but there are a few reports of noradrenergic autonomic nervous system involvement.^[1] Sympathetic dysfunction may be due to involvement of autonomic ganglia and nicotinic Ach receptors, thus affecting both sympathetic and parasympathetic functions. In our case nerve showed axonal variety sensory neuropathy. Kimber *et al.*, also confirmed the presence of axonal degeneration in Sural nerve biopsy of two Allgrove syndrome patients.^[1]

This patient had 4'A' variant of Allgrove syndrome-autonomic dysfunction, adrenal insufficiency, alacrima and asymptomatic achalasia, but there was no amyotrophy. Allgrove's syndrome may be an underdiagnosed rare cause of multisystem neurological disease in adults and it must be considered as a differential diagnosis. Adrenal insufficiency, alacrima or achalasia cardia are important non-neurological clues to the diagnosis and should be evaluated even if asymptomatic.

Early recognition of the syndrome presenting in adult life permits prompt treatment of unrecognized alacrima, achalasia and adrenalin insufficiency leading to significant improvement in weakness and quality of life.

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