

Allgrove Syndrome: A Frequently Under-Diagnosed ALS Mimic

Sir,

Allgrove (Triple A) syndrome is a rare, autosomal recessively inherited syndrome characterised by achalasia, alacrima, adrenal insufficiency and a progressive neurological dysfunction.^[1] Afflicted individuals usually manifest with 2–4 of these symptoms and most cases have no positive family history.^[1] Mutations in *ALADIN* gene located on chromosome 12q13 are responsible, which can be identified by genetic analysis.^[2]

A 46-year-old gentleman, born of non-consanguineous marriage, presented with progressively increasing difficulty in getting up from squatting position and lifting arms overhead for the past 20 years associated with nasal intonation and difficulty in swallowing solids and liquids.

These were complicated by recurrent dyspepsia, whose evaluation lead to a diagnosis of achalasia in 2017, for which he was operated. He developed complaints of severe grittiness and dryness of eyes for the past 5 years and has been taking lubricating eyedrops. He developed an erectile dysfunction for the past 3 years, whose evaluation lead to a diagnosis of azoospermia. He was medically managed without any symptomatic relief. There was no history of sensory loss or bowel/bladder complaints.

Examination revealed a significant postural hypotension with prominent wasting of the small muscles of hand (abductor digiti minimi > first dorsal interossei) and tongue, with fasciculations. Pupils were normal in size but sluggishly reactive. Power in the proximal and distal joints bilaterally was grade 4/5 and 5/5 on the Modified Research Council

scale, respectively. Grade 1 spasticity was present in all limbs; deep tendon reflexes were brisk and plantars were extensor.

His routine blood investigations were normal. Serum cortisol was low but adrenocorticotropic hormone levels were normal. Extractable nuclear antigen profile was negative. Schirmer's test was positive in both eyes (<5 mm). Nerve conduction studies revealed an axonal neuropathy with electromyography suggestive of preganglionic neurogenic involvement in the cervical and lumbosacral segments. Autonomic function tests revealed severe sympathetic and parasympathetic involvement. MRI brain and spine were normal. Next generation clinical exome sequencing from the blood revealed a homozygous *c.C43A/p.Gln15Lys* missense mutation on exon 1 of the *ALADIN* gene on Chromosome 12 confirming a diagnosis of Allgrove syndrome.

Allgrove syndrome was first described in 1978 in two pairs of siblings (OMIM database number 231550)^[3] and was characterized by achalasia, alacrima and ACTH-resistant adrenal insufficiency.^[3] Thereafter, multiple additional features have been described including central and peripheral nervous system involvement (CNS/PNS), hyperkeratosis, short stature, microcephaly, xerostomia, and angular cheilitis/glossitis.^[3-5] It results from mutations in the *ALADIN* gene that encodes for a ubiquitous WD-repeat protein, which has the highest expression in the gastrointestinal tract, adrenals and the brain.^[2] The clinical features vary according to the type of mutation. The mutation in our patient was the same as in Family 1 by Houlden H *et al.*^[1] (Exon 1, Gly 15 Lys) and had similar features.^[1] However, insertions and deletions are commoner, with missense mutations accounting for only 10% cases.

Our patient had all four cardinal symptoms (seen in only 30–40% cases), which made the diagnostic suspicion easy. Long-standing disease invariably leads to autonomic nervous system involvement, which manifests as erectile dysfunction, orthostatic hypotension and pupillary abnormalities. Peripheral nerve involvement is predominantly motor, and for unknown reasons, and have more severe ulnar involvement.^[1] These were seen in our patient.

A spectrum of neurological findings can occur in patients with Allgrove syndrome and it should be suspected in any patient presenting with features of CNS/PNS dysfunction with achalasia, alacrima and/or adrenal insufficiency. Although, no definitive treatment modalities exist, early diagnosis can lead to proper counselling, management and incorporation into research trials, which can hopefully provide a future cure.

Learning points

1. Allgrove syndrome: *ALADIN* gene- Alacrima, achalasia, adrenal insufficiency and neurological disorder
2. Allgrove syndrome should be suspected in any patient presenting with amyotrophic lateral sclerosis (ALS)-like presentation with one of the above symptoms

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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