

Triple A syndrome presenting with myopathy: An Egyptian patient

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ABSTRACT

Triple A syndrome (Allgrove syndrome) is a rare, autosomal recessive disorder characterized by Adrenocorticotrophic hormone resistant adrenal insufficiency, Alacrimia, Achalasia of the oesophageal cardia, progressive neurological degeneration and occasionally autonomic instability (making it 4A syndrome). Reported neurological abnormalities included developmental delay, ataxia and polyneuropathy with sensory, motor and autonomic components, long-tract degeneration, parkinsonism and mild dementia.

In this paper we report a 13 year old boy with Allgrove syndrome presenting with muscular weakness that was confirmed by EMG studies. To our knowledge, muscle disease in Allgrove syndrome was not reported before.

Key Words:

Allgrove syndrome, triple A syndrome, alacrimia, cardiac achalasia, adrenal insufficiency.

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INTRODUCTION

Triple A syndrome (Allgrove syndrome) is a rare, autosomal recessive disorder characterized by adrenocorticotrophic hormone (ACTH) resistant adrenal insufficiency, alacrima, achalasia of the esophageal cardia, progressive neurological degeneration and occasionally autonomic instability¹. The syndrome was first reported by Allgrove in 1978 when they described two pairs of sibs (3 boys and 1 girl) with glucocorticoid deficiency and achalasia of the stomach cardia. Three had defective tear formation (alacrima) and one showed other signs of autonomic dysfunction.²

The condition is associated with impairment of the central, peripheral and autonomic nervous systems. Progression of neurological symptoms has been reported with worsening of peripheral neuropathy, dementia, long tract degeneration, dysarthria and ataxia³. In this paper we report a 13 year old boy with Allgrove syndrome presenting with muscular weakness that was confirmed by EMG studies. To our knowledge, muscle disease in Allgrove syndrome was not reported before.

CASE REPORT

A 13 year old boy, seventh in order of birth of one and half cousin marriage presented to the genetics clinic with a

four year history of headache, excessive fatigue, difficulty in walking and climbing the stairs and recurrent fainting attacks. This was accompanied by continuous pain and recurrent ulcers in both eyes. One year ago, the patient started to have recurrent attacks of vomiting.

On examination, his height was 140 cm (-3SD), weight was 28 kg (< - 4 SD). He had long thin face, long philtrum, deep seated eyes and darker skin than the rest of family members especially around the lips and knuckles. Chest, heart and abdominal examination showed no abnormalities (Figures. 1, 2). Neurological examination showed wasting, slight hypotonia, diminished deep tendon reflexes and weakness of proximal muscles of upper and lower limbs.



Figs. 1,2: Anteroposterior view of the patient showing the darkness around the lip and the knuckles.

Morning cortisol level was 2.7 $\mu\text{g/dl}$ (normal level: 4.3- 22.4), ACTH was more than 1250 pg/ml (normal level: 10-60), sodium level was 132 mmol/L (normal: 138-145), potassium level was 5.9 mmol/L (normal:3-5). TSH: 3.94 $\mu\text{IU /ml}$ (normal: 0. 33-5.5), free T4; 1.1 ng/dl (0.8-1.9).

Digital computed radiography of barium swallow of the oesophagus showed mild gastro-oesophageal reflux. Ophthalmological examination showed bilateral alacrimia. EMG studies for abductor pollicis brevis, right biceps, and right extensor hallucis brevis muscles showed no spontaneous activity at rest. On mild contraction, motor unit action potentials were of small amplitude, prolonged duration and occasional polyphasia and early recruitment, with full interference pattern on maximum. Nerve conduction velocity of both median and right tibial nerves revealed normal distal latencies with nerve conduction velocity and average amplitude for CMAPs. These findings were suggestive of a myogenic pattern. Audiometry, CT brain and EEG were all normal.

DISCUSSION

Neurological abnormalities in Allgrove syndrome was first reported by Ehrich et al.⁴ in 1987 in two brothers with severe developmental delay, short stature, microcephaly, ataxia and optic atrophy⁴. Furthermore, follow-up of the patients originally described by Allgrove et al.² showed that they had developed neurologic manifestations, including polyneuropathy with sensory, motor and autonomic components, long-tract degeneration, parkinsonism, and mild dementia³. Although our patient did not have any of the previous

neurological manifestations, he had typical symptoms and signs suggestive of muscle disease. This was confirmed by electromyogram and nerve conduction studies.

Muscle weakness could be explained by the long-term undiagnosed adrenal insufficiency which makes a major contribution to reduced motor function and quality of life. But unlike other neurological disorders associated with adrenal insufficiency, neurological change with Allgrove syndrome was reported to be extremely slow⁵. Our patient had the onset of muscle weakness very early (at the age of nine years) which is against the theory of long-term adrenal insufficiency.

Distinct facial appearance of Allgrove syndrome includes long thin face with a long philtrum, narrow upper lip, down-turned mouth and microcephaly⁶. Except for microcephaly, these features were typical to our patient.

Alacrima is the most consistent feature of this syndrome and is usually the earliest manifestation⁷. This was evident in our patient who had persistent complaint of eye pain and redness and was not diagnosed with alacrima till his presentation to our clinic. Other reported ophthalmic manifestations include keratoconjunctivitis sicca, corneal melts, lacrimal gland atrophy, pupillary abnormalities including sluggish pupils, tonic pupils with hypersensitivity to dilute miotics, accommodative dysregulation, amblyopia and optic atrophy.^{1,8}

Our patient had both glucocorticoid and mineralcorticoid deficiency. Most patients in the literature reported had glucocorticoid deficiency with normal

mineralocorticoid function, but deficiency has been reported in only 15% of patients.⁹

The orthostatic hypotension that was reported by our patient could be explained by abnormal cardiovascular reflexes (progressive loss of cholinergic function) due to autonomic dysfunction.¹⁰

Although our patient did not develop cardiac achlasia yet, it is known that other authors reported Allgrove patients who had only 2 of the 3 features, with variable neurological defects¹¹. This was further confirmed by Prpic et al.¹² who demonstrated marked phenotypic variability in 3 patients with genetically confirmed triple-A syndrome. Two patients had achalasia, alacrima, and adrenocortical deficiency as well as neurologic and autonomic dysfunction. The third patient had only achalasia and neurologic dysfunction. All patients were homozygous for mutations in the AAAS gene. In the patient with isolated achalasia, the diagnosis of triple-A syndrome could only be made on the basis of the molecular genetic analysis of the AAAS gene. The authors proposed that the diagnosis of triple-A syndrome should be made on the basis of molecular analysis of the AAAS gene and may therefore include patients with 1 or 2 of the 3 main symptoms.¹²

Achalasia was also reported to have a variable, often insidious presentation. Dysphagia may be present for years before the diagnosis of achalasia is made and may be present as gastroesophageal reflux.¹³

Unlike ACTH resistance syndromes (familial glucocorticoid deficiency), triple A syndrome is not due to mutations in the ACTH receptor, but it has some fea-

tures of a contiguous gene syndrome¹⁰. The triple A syndrome is due to mutations in the AAAS gene whose product is ALADIN (alacrima-achalasia-adrenal insufficiency neurologic disorder); located on chromosome 12q13.^{1,8}

In conclusion, patients with triple A syndrome often reports to a specialist with one complaint and the association may remain unsuspected, leaving the patient prone to complications like Addisonian crisis, recurrent aspiration and failure to thrive. All children presenting with one of the three symptoms should be screened for triple A syndrome. Neurological manifestations of Allogrove syndrome may include muscle disease.

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