Case Report

Triple-A Syndrome (Allgrove Syndrome) in Iranian Children: Report of 4 Cases

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ABSTRACT

Allgrove syndrome also known as triple-A syndrome is an autosomal recessive disorder characterized by alacremia, achalasia and ACTH-resistant adrenal insufficiency. Although this syndrome is rare, herein we report four cases with different clinical manifestations. They were referred to the gastrointestinal ward during a one year period with complaints of vomiting and dysphagia. The diagnosis of triple-A syndrome was confirmed after careful evaluations for vomiting.

Keywords: **Achalasia; Alacremia; Adrenal insufficiency**

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INTRODUCTION

Allgrove syndrome (Triple A or AAAs) is a rare autosomal recessive disease characterized by ACTH-resistant adrenal insufficiency (Addison disease), Achalasia of the cardia, Alacremia and sometimes neurologic abnormalities (1). This syndrome was first reported in 1978 (2) and its incidence is unclear (3), The gene for this disease localizes to 12q13, however most cases of Triple-A syndrome have no family history (4). The clinical features are heterogeneous (2). Herein we report four patients with this syndrome who referred to the gastrointestinal ward of Children's Medical Center Hospital, Tehran University of Medical Sciences for evaluation of dysphagia and vomiting.

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CASE REPORTS

Case 1

A 9 year-old male was admitted to the pediatric GI ward for evaluation of persistent dysphagia and vomiting. At the age of two, the patient initially referred to the pediatric GI ward with recurrent vomiting and inability to consume solid foods. A barium swallow study showed dilated esophagus, bird beak appearance and slow esophageal emptying. Upper GI endoscopy revealed non-relaxation of the LES with the inability to pass the endoscope into the stomach. The patient responded to pneumatic dilatation of the LES and was diagnosed with achalasia. At the age of three, the patient gradually developed hyperpigmentation of his skin and buccal mucosa, with a recurrence of vomiting. Following a thorough assessment, he was

diagnosed with adrenal insufficiency without salt loss The patient was prescribed hydrocortisone. Thereafter, vomiting and anorexia subsided and the patient began to gain weight.

After questioning his parents, they revealed that he had alacremia since birth which was confirmed following evaluation by an ophthalmologist.

Case 2

A 4 year-old age female patient was referred to the pediatric GI ward for therapeutic intervention. At age of 2 years, 8 months, the patient was admitted to the endocrinology ward with complaints of vomiting, hypotension, hypoglycemic convulsion and hyperpigmentation of her skin and buccal mucosa. Lab data supported a diagnosis of Addison's disease without salt loss. The patient responded well to hydrocortisone therapy, but at the age of 3 years, 3 months, she developed dysphagia and recurrence of vomiting. Barium swallow under fluoroscopy showed a dilated esophagus, with slow esophageal emptying, decreased peristalsis and a typical bird beak appearance. Endoscopy revealed non-relaxation of the LES, a dilated esophagus and mild erythema of the lower third of the esophagus. Therefore, with a diagnosis of achalasia, pneumatic dilatation was performed with significant improvement in her signs and symptoms.

The patient had alacremia since birth which was confirmed by an ophthalmologist. She received artificial tears for resolving corneal dryness.

Case 3

A 4 year-old child was admitted to the pediatric Endocrinology Ward 2.5 years ago because of failure to thrive, recurrent vomiting, hypotension and hyperpigmentation of the skin and buccal mucosa. After laboratory evaluations, non-salt-loss Addison's disease was confirmed. The patient received hydrocortisone with some improvement. However, six months later vomiting recurred and the patient refused to eat solid foods. Barium swallow under fluoroscopy showed a typical bird beak and rat tail appearance which suggested achalasia. Endoscopy revealed mild dilatation of the esophagus, non-relaxation of the LES and the endoscope was unable to be passed into the stomach. With a diagnosis of achalasia, pneumatic dilatation of LES was performed with significant improvement. The patient has had no tear production since infancy. Alacremia was confirmed by an ophthalmologist and artificial tears were administered for frequent blinking.

Case 4

A 4 year-old male child was referred to the pediatric Out patient Department for recurrent vomiting, weight loss and lethargy since one year previous. He had refusal to feed, particularly with solid foods and hyperpigmentation of his lips and buccal mucosa, but not skin. Echocardiography was unremarkable. Barium swallow under fluoroscopy showed delayed passage of barium from the LES and a bird beak appearance. Endoscopy revealed non-relaxation of the LES with difficult passage of the endoscope into the stomach. With a diagnosis of achalasia, pneumatic dilatation was done with marked improvement.

After assessment for hypotension and hyperpigmentation of the lips and oral mucosa, Addison's disease was confirmed. The patient was administered hydrocortisone. He has had alacremia since birth which was confirmed by an ophthalmologist.

Patients' laboratory data are given in Table 1.

Table 1: Laboratory data before treatment.

Investigation	Case 1	Case 2	Case 3	Case 4
ACTH*(Pg/mL)	157.0	269.2	457.0	380.0
Cortisol*(µg/dL)	2.0	1.3	2.5	2.2
Na (meq/L)	133	135	139	136
K (meq/L)	4.1	4.8	5.2	4.9
BUN (mg/dL)	11	17	22	18
Cr(mg/dL)	0.7	0.5	0.7	0.6
BS(mg/dL)	78	43	63	77
Renin*(ng/mL.h)	1.7	3.2	2.7	4.1

*Normal range: ACTH = 7.9-66.1 pg/ml; Cortisol = 4.5-22 µg/dl; Renin = 0.5-6 ng/(ml.h)

DISCUSSION

We have presented four cases of classic Triple-A syndrome that all were referred to the GI Ward of the Children's Medical Center Hospital, affiliated with Tehran University of Medical Sciences for management of vomiting and dysphagia. The inheritance of this rare syndrome is autosomal recessive but most cases have no family history. RNA blotting experiments reveal marked expression in neuroendocrine and gastrointestinal structure which are predominantly affected in Triple-A syndrome, supporting the hypothesis that mutation in the gene of AAAs syndrome are responsible for this disease (1).

The earliest manifestation of Triple-A syndrome is alacremia which is a progressive disorder that can take years to develop into a full-blown clinical picture (5). It is the earliest and the most consistent sign of allgrove syndrome (6), that usually presents from early infancy but is often missed by parents.

Patients with triple-A syndrome manifest with ophthalmic manifestations other than alacremia. Brooks et al. presented a 12 year-old female case of triple-A syndrome with decreased tear production, no spontaneous tearing, inappropriate accommodation and superficial punctate keratopathy that needed frequent ocular lubrication (7). In our study all patients had alacremia since a few months after birth, but was not noted by parents. The patients had no abnormalities in accommodation and keratopathy, however complaints of frequent blinking existed in two cases that needed artificial tear drops for resolution.

Patients with triple-A syndrome can manifest signs of autonomic nervous system dysregulation which include: decreased lacrimation, pupillary abnormality, orthostatic hypotension, sexual impotence in adults, disturbances in heart rate and abnormal reaction to intradermal histamine (7).

ACTH resistant adrenal insufficiency is another important part of Triple-A syndrome (8). The age of presentation and severity are different. In some patients, adrenal insufficiency presents as early as one year of age and in some cases as late as the third decade of life (6). Classic symptoms are hypoglycemic seizure and shock as well as skin manifestations that include hyperpigmentation, hyperkeratosis and fine fissuring of the palms and soles (3). Diaz et al. have reported a case of Triple-A syndrome with adrenal insufficiency that developed at the age of 3 years, six months (6). Pedreira and Zacharin have reported a case of Triple-A syndrome with symptoms of dizziness and collapse that started at the age of 36 (2). The ages of presentation of adrenal insufficiency in our patients were: 3, 2.8, 1.5 and 4 years of age, respectively. In two patients adrenal insufficiency was diagnosed before achalasia, in one patient simultaneously, and in another patient after the diagnosis of achalasia. Two patients had frank episodes of fainting, hypotension and hypoglycemia, but the other two had milder symptoms.

In Triple-A patients, mineralocorticoid function is usually normal, however Werder et al. found a case with subnormal aldosteron response (9). In our report all four patients had normal aldosteron activity.

Triple-A patients also have hyperpigmentation of the skin, genitalia and buccal mucosa (3), which was true for our patients with the exception of one who did not have skin hyperpigmentation, but presented with hyperpigmentation of the genitalia and buccal mucosa.

Achalasia is a devasting problem of triple-A syndrome that mostly appears between the ages of 6 months to 16 years. It presents with symptoms of dysphagia, vomiting, weight loss and irritability (6). Pedreira reported a 37 year-old patient with triple-A syndrome with achalasia that presented 20 years before their diagnosis (2). This late diagnosis must emphasize the importance of physician assessment of adrenal function in patients with alacremia and achalasia (2) Etemadifar reported one patient with triple-A syndrome that had symptoms of vomiting, dysphagia, abdominal pain and weight loss which presented from the age of 3, almost simultaneously with their signs and symptoms of adrenal insufficiency (generalized hyperpigmentation of the knees, elbow and buccal mucosa) (8). In our study signs of achalasia developed at 2, 3.3, 2 and 4 years of age, respectively.

Neurologic manifestation of triple-A syndrome only occurs in some patients, predominantly in adults with signs and symptoms of progressive neurologic degeneration (3). Aghajanzadeh et al. presented two cases (16 and 17 years-old) of triple-A syndrome with neurologic manifestations that included: hyperreflexia,

dysarthria and palatopharyngeal incomptetence (10). None of our patients until now have had signs of neurologic disease. However because of the potential neurologic involvement in later years of life, precise neurologic examinations will be needed.

Triple-A syndrome can also present in adulthood. Disease manifestations in adults are the signs and symptoms of adrenocortical insufficiency that include: hypoglycemia, weakness, fatigue, anorexia, nausea, vomiting, postural dizziness, weight loss, hypotension, hyperpigmentation, electrolyte disturbance, and signs of achalasia and alacremia. Other clinical features are palmoplantar hyperkeratosis, gonadal failure, and short stature. In adults, neurologic abnormalities are more common of which the signs are: autonomic, sensory and motor neuropathies, dysarthria, progressive spastic tetraplegia, distal limb atrophy, deafness, mild mental retardation, optic atrophy and cerebellar ataxia (8). Some patients have specific facial characteristics which include a long thin face, long philtrum, microcephaly, and down turned mouth with narrow upper lip (10).

Each patient with achalasia or adrenocortical insufficiency must be tested periodically for gastrointestinal, adrenocortical and neurological involvement, in particular autonomic abnormalities. Patients should be questioned about alacremia and its presence confirmed by an ophthalmologic examination.

CONCLUSION

Triple-A syndrome is a rare autosomal recessive disease which consists of alacremia, achalasia of the cardia and ACTH-resistant adrenal insufficiency. Each patient with achalasia who develops signs of hypotension, hypoglycemia, lethargy and/or hyperpigmentation of the skin and buccal mucosa should be evaluated for this syndrome. Careful neurologic examination is also needed in these patients. Patients should be directly questioned about a history of alacremia.

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