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Allgrove Syndrome: A Case Report

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Allgrove syndrome (triple A syndrome) is an autosomal recessive disorder characterized by achalasia, alacrima and adrenocorticotropic hormone (ACTH) resistant adrenal insufficiency. It is a multisystem disease and in addition to cardinal manifestations, associated features especially neurologic problems, must be detected and treated.

In this case report, we report a 17 year-old boy diagnosed as having Allgrove syndrome with predominant symptoms of achalasia and additional features consisting of short neck, long eye lashes, unexplained fever and chills, reduced visual acuity because of amblyopia, thenar and hypothenar atrophy and abnormal opposition of fingers.

If necessary screening with stimulatory tests in patients with unexplained features such as long eye lashes, short neck, muscle atrophy, nasal speech, skin and neurologic abnormalities and hyperkeratosis, should be recommended.

Key Words: Allgrove syndrome, Achalasia, Alacrima, Addison, Adrenocorticotropin insensitivity syndrome.

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Introduction

In 1978, Allgrove et al. first described two pairs of siblings with a combination of the symptoms of ACTH-resistant adrenal insufficiency, achalasia of the cardia, and alacrima.[1] Over the following years, about one hundred patients with the triad of adrenal insufficiency, achalasia, and alacrima have been reported, and the name "triple A syndrome" became established. [2,3] This syndrome can be associated with neurologic, skin, bone and skeletal problems. We report here a triple A syndrome with additional features.

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Case Presentation

The patient, a young single man studying in the last year of high school, was a 17 year-old boy with a chief complaint of dysphagia for the past 6 years, mildly progressive to solid materials and intermittent to liquids.

Ten months before admission, the patient suffered several episodes of chills and fever, up to 40°C with approximately 30 minute durations. All investigations revealed no definite results regarding source of fever; 2 months before admission his complaint of dysphagia became severe and he was reffered to a gastroenterologist, upper GI endoscopy and manometry were performed. Due to achalasia of cardia, dilatation of cardia was considered. At the same time, during an episode of chills and fever, he became ill and hypotensive, and unresponsive to IV fluid therapy. Clinically suspected of adrenal insufficiency, hydrocortisone and fludrocortisone were administered for the adolescent.

The patient's past medical history was positive for recurrent nasal polyps and alacrima from childhood. No history of hypoglycemia, seizure, deafness, neuromuscular disorders and cardiac disease was present. His family history was negative, and his parents were related. Physical examination revealed he had short stature (160 cm), short neck, nasal speech, dry conjunctiva and red eyes, long eyelashes, multiple facial acne, hyperpigmentation of buccal mucosa, high arched palate and palmar and solar hyperkeratosis. Neurologic examination showd thenar and hypothenar muscle atrophy, reduced force of abduction and adduction of fingers, abnormal opposition of fingers, abnormal gag reflex, generalized hyperreflexia, and reduced left side visual acuity; the left eye's visual acuity was 2/10 (amblyopia) and the right eye was 10/10. In fundoscopy, primary optic neuropathy was present. ENT examination revealed nasal septum deviation without deafness. Other physical examinations including the heart, lungs, abdomen and external genitalia were unremarkable.

The patient was admitted for therapeutic intervention; all laboratory tests were normal for complete blood count, sedimentation rate, renal function test, liver function test, electrolytes, calcium profile, serum iron, TIBC, ferritin, peripheral blood smear (Malaria, Borellia), blood sugar, blood and urine cultures, Wright and Widal tests, VDRL, Anti Geliadin Abs, AntiEndomysial Abs, Hepatic viral markers, FANA, Antids DNA and coagulation profile and negative for infectious or colagen vascular diseases.

Basal serum cortisol (6 am) was 1.5 (Normal range 10-20 μg/dL), T_4: 6.5 (4.5-12.8) μg/dL, T_3: 88 ng/dL (80-230), TSH: 0.8 mU/L (0.2-5), T_3R uptake: 32% (25-37) and LH, FSH, PRL, testostrone were normal. Serum ACTH was 80 pmol/L (20-80). Stimulatory tetracosactide test results (IM) showed no increase in serum cortisol; 1, 4, 8, 12, 24 hour after injection, cortisol levels measured were 2, 0.8, 1.7, 1.7 and 1.9 μg/dL.

Upper GI endoscopy revealed food debris in the dilated esophagus, severe (pinpoint) stenosis of lower esophageal sphincter due to spasm (achalasia) and normal stomach. Esophageal manometry was suggestive of achalasia. Brain, hypophysial (dynamic-coronal sections), thoracic and abdominal CT scan including adrenal cuts showed no pathology. Paranasal sinuses x-ray and lateral sella view were normal. Audiometry and ECG was normal. EMG and NCV were compatible with axonal type sensorimotor polyneuropathy. Slit lamp examination and fluorescein were normal. Shirmer test was suggestive of alacrima. Bone age was 16 years and 6 months.

Discussion

Reported here is a case with Allgrove syndrome with unusual features. Additional features observed in our patient were long eyelashes, thenar and hypothenar muscle atrophy, amblyopia, recurrent chills and fever could have been due to autonomic dysfunction. The first presentation of this syndrome, six years ago, was achalasia and dysphagia, followed by Addison crisis 2 months ago, and in the most recent admission we found a positive history of alacrima; some additional features were also observed that had not been previously reported.

Allgrove syndrome can be clearly distinguished from familial glucocorticoid deficiency forms by the presence of additional features; it manifests itself during the first decade of life with severe hypoglycemic episodes that can cause sudden death. Although in most cases hypoglycemia and hyperpigmentation lead to diagnosis, alacrima or hypolacrima is probably the earliest and most consistent sign. The majority of patients have isolated glucocorticoid deficiency, but in about 15% mineralocorticoid production may also become impaired at a later time.[2-4] Adrenal insufficiency does not occur immediately postnatally but results from a progressive disorder leading to hypofunction of the adrenal gland at a variable time after birth. Patients with isolated familial glucocorticoid deficiency have extremely low plasma epi-

nephrine concentrations,[5] which may cause low resting systolic blood pressure and an exaggerated pulse rate response to upright posture, and contribute to fasting hypoglycemia. Our patient had episodes of hypotension responsive to corticosteroid (adrenal crisis) but without hypoglycemia.

Achalasia of the cardia occurs in about 75% of all cases, the age of onset ranging from 0.5 to 16 years; in one rare report, the onset was in 3 month-old siblings.[6,7] In fact , achalasia and gastric atonia lead to recurrent or chronic pulmonary disease as a result of aspiration; achalasia can be a predominant feature of this syndrome.[8]

The neurologic system including central, peripheral, and autonomic nervous system may be involved. Impairment of the central nervous system has been seen in the form of mental retardation that can be progressive, with optic atrophy, clumsiness, ataxia, dysartria, parkinsonism and hyperreflexia. Sensorineural deafness may occur. In some patients, a characteristic hypernasal speech has been reported. Muscle hypotonia, muscle weakness, progressive distal muscular atrophy, pes cavus, loss of deep, sensibility, and other sensory impairments have been reported. About 30% of all patients suffer from autonomic impairment.[9-11] All parts of neurologic systems were involved in our patient and we believe that thenar and hypothenar atrophy is a presentation of localised distal muscular atrophy.

In about 20% of all patients, skin abnormalities are present comprising hyperkeratosis of palms and soles with fine palmar creases. Other features are significant short stature, microcephaly, osteoporosis, lack of eyelashes, dysmorphic facies with long narrow face, long philtrum, down-turned mouth, and thin upper lip, poor wound healing, scoliosis, long QT syndrome, hyperlipoproteinemia type IIb.[12-14]

Regarding the pathogenesis, patients with Allgrove's syndrome have mutations in the AAAS (Alacrima, Achalasia, ACTH, resistent Adrenal insufficiency Syndrome) gene, located on chromosome 12q13, which encodes for the Alacrima-Achalasia-Adrenal Insufficiency Neurologic disorder (ALADIN) protein.[15,16] Most of the reported mutations produce a truncated protein, although missense and point-mutations have been reported. [17,18] In one study, patients from families with the same mutation showed significant clinical variability, [17] and in another, there was little genotype-phenotype correlation.[19] A recent report of a case showed a mutation in exon 7 (p.R194X) of the AAAS gene; this is a novel mutation and has not been found in any other family so far.[20] We are not sure if this kind of mutations can explain additional symptom seen in our case, regarding the clinical variability and weak genotype phenotype correlation in this syndrome. As noted above, lack of eyelashes has been reported previously but there are no reports of long eye lashes. It is possible that this is an incidental finding or an unusual feature, one that we cannot explain the etiology of.

We started glucocorticoid and mineralocorticoid replacement therapy for Addison and prescribed artificial tears for symptomatic alacrima. For treatment of achalasia, esophageal dilatation was done, three months after treatment, the patient was stable and free of symptoms.

As noted above, Allgrove syndrome is a multisystem disease and in addition to cardinal manifestations, associated features especially neurologic problems, must be detected and treated.

Because Addison's disease is a life threatening disease and without replacement therapy multiple morbidity may occur, it is vital to recognize the symptoms and signs; if necessary screening with stimulatory tests in patients with unexplained features such as long eye lashes, short neck, muscle atrophy, nasal speech, skin and neurologic abnormalities and hyperkeratosis, should be recommended.

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