ALLGROVE'S SYNDROME: CASE REPORT AND LITERATURE REVIEW

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يعني هذا التقرير باثنين من المرضى إحداهما عمره عشر سنوات والأخر ثمانية عشر عاما.
يشكو المريضان من صعوبة في البلع بدأت مبكرا، أظهرت الفحوصات المخبرية والأشعة الملونة والمقطعية وكذلك الفحص السريري للعيون والأعصاب وتنظير المريء وجود متلازمة الجروث لدى المريضين ، وقد تم علاج الضيق في منطقة الفؤاد عن طريق التوسعة بالمنظار مع إضافة عقار الكورتيزون.
استجاب المريضان جيدا للعلاج وتحسنت حالتهما واستعادا نشاطهما المعهود0

الكلمات المرجعية : متلازمة الجروث ، المتلازمة الثلاثية , تضيق فؤاد المريء , عدم وجود الدموع , خال الأعصاب الطرفية , قصور الغدة الكظرية , توسع البالوتي للفؤاد المريئي ، علاج الكرتيزون.

This report concerns two brothers aged 10 and 18 years with long-standing dysphagia that started at age three and six years respectively. They had been diagnosed as achalasia and treated accordingly. The appearance of additional symptoms and clinical signs required further investigations including abdominal sonography, esophago-gastroduodenoscopy, barium swallow, esophageal manometry, computerized tomography (CT) of abdomen and brain, biochemical profiles, and neurologic and ophthalmic evaluations. The results of these extensive investigations along with the clinical evaluations were consistent with Allgrove's syndrome.
Glucocorticoid therapy was initiated. The management consisted of pneumatic cardiac dilatation and initiation of cortisone treatment. The patients' response was impressive and they resumed most of their usual activities.

Key Words*: Allgrove's syndrome, Triple A syndrome, Achalasia, Alacrima, Autonomic neuropathy, Adrenocortical impairment, Pneumatic dilatation, Steroid therapy.*

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INTRODUCTION

Allgrove's or Triple A syndrome, which was later on named "4A" syndrome is a rare autosomal recessive condition characterized by alacrima, achalasia, autonomous neuropathy and ACTH insensitivity among other features. The syndrome usually presents during the first decade of life with dysphagia, while other signs may be delayed until adulthood.

Allgrove and his colleagues first described this syndrome in 1978 in two unrelated pairs of siblings (aged 4 and 6 years).[1] All four had achalasia and Adrenocortico- Tropic Hormone (ACTH) insensitivity, three suffered from impaired lacrimation and one had autonomic dysfunction. The onset of adrenocortical impairment is usually before puberty. However, the preservation of cortisol secretion till the third decade has been reported. The syndrome may manifest itself during the first decade of life, with severe hypoglycemia or hypotensive attacks, which may lead to sudden death. Allgrove's syndrome may be an underdiagnosed multi-system disorder in which achalasia and alacrima are the most valuable clinical signs to reach the diagnosis.

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Catastrophic complications can be prevented with adequate cortisol and specific measures such as cardiac pneumatic dilatation or myotomy along with other supportive management. The prognosis for health and quality of life can be significantly improved.

CASE NO. 1

An 18-year-old boy was brought to our Emergency Room with deterioration of general health, cachexia and weight loss. He was bedridden, had stool and urine incontinence and complained of progressive difficulty of swallowing for some months. He is the first child of healthy non-consanguineous parents and product of full-term delivery. He remained well until the age of 3 – 4 years. Later on, the family noticed the progressive nasal speech and anorexia and lack of weight gain with frequent regurgitation. He was taken to a local hospital. Based on the results of barium studies and gastroscopy, achalasia was diagnosed. The patient was subjected repeatedly to esophageal cardiac dilatations.

Due to the poor response and general health deterioration, the patient was referred to a tertiary hospital for further management. After three years of follow-up, for some social reasons, his father stopped taking him to that hospital and started taking him to different hospitals. Finally, he was brought into our hospital with the above-mentioned presentations. The father was appreciative of his son's tolerance by saying that despite all the problems, he had not seen any tears shed by his son.

Apart from his younger brother who had a milder form of similar symptoms, the other siblings, parents and relatives were all free of symptoms.

On examination, he was cachectic, wasted and bedridden (Figure 1). The nasal speech of the young boy was understood only by his parents. He was pale with hyper-pigmentation of skin, gums, and palmar creases. His face was long and thin with narrowed upper lips down-turned mouth and microcephaly. His blood pressure was 80/50 mmHg. The joint motions were limited because of muscle contractures, spastic tetraparesis with mild ataxia, deep tendon reflexes were increased in all four limbs. His basic investigations showed moderate anemia of hemoglobin (Hb) of 10 g/dl. Urea and electrolytes were normal. Cortisol level at 8 am was less than 1.1 ug/dl and ACTH was

Figure 1*: Patient during admission in the hospital*

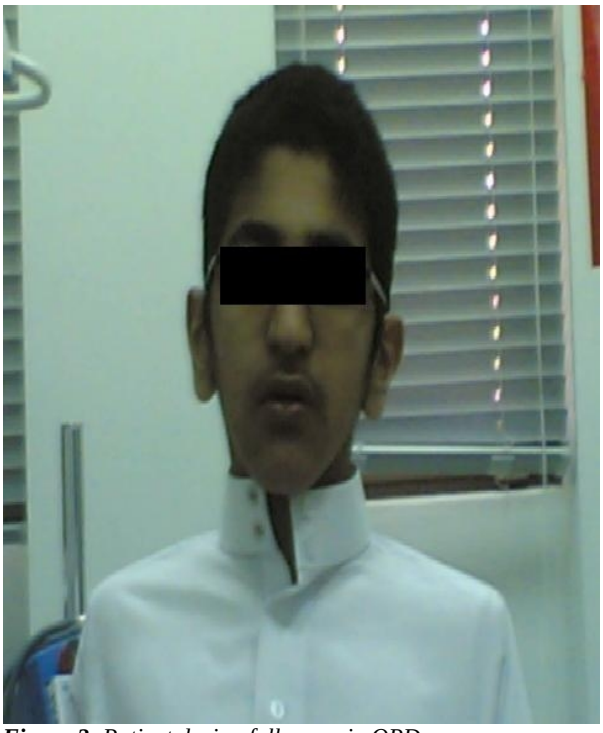

Figure 2*: Patient during follow-up in OPD*

54.1. Adrenal imaging studies did not reveal any abnormality. Barium swallow study and esophageal manometry features were consistent with achalasia. He was seen and evaluated by an ophthalmologist and Schirmer's test was needed. This revealed dry eyes i.e. alacrima while, CT brain and orbit tomography showed reduced lacrimal gland tissue.

His management included full supportive therapy that included hydration, nutrition, physiotherapy and artificial tears. The achalasia was managed by two sessions of pneumatic dilatations and he was kept on 10 mg prednisone/day as a maintenance dose. During one year of follow-up, he exhibited significant

improvement and was able to eat well, walk without any support and he gained 25 kg weight i.e., his body mass index (BMI) increased from 13.3 to 21.3 (Figure 2).

CASE NO. 2

This 10-year-old boy is the brother of the previous case. His main presentation was frequent regurgitation, weight loss and failure to thrive. At the age of three, his physical examination revealed an under-developed child with nasal speech. At the age of four, the diagnosis of achalasia was established and he was subjected to Heller's surgery.

He was found to be thin, underweight and microcephalic. The following investigations were performed in our hospital: Barium swallow, esophageal manometry which indicated achalasia and upper GI endoscopy which showed good functioning myotomy.

Ophthalmic examination revealed positive Schirmer test. Based on the clinical appearance, achalasia as well as alacrima, an early and slow progressing Allgrove's syndrome was diagnosed. His electrolytes, blood glucose, cortisol and ACTH were all within normal limits. He is on regular follow-up and not on any medication.

DISCUSSION

Allgrove's syndrome is considered an autosomal recessive disorder with variable presentations.[1-2] Recent studies have identified mutation in the AAA syndrome of a candidate gene on chromosome 12q13 in such patients.[3] Prpic et al (2003) demonstrated the marked phenotypic variability in three 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 suffered from achalasia only and neurologic dysfunction. All patients were homozygous for mutations in the triple A syndrome gene.[3] The age of onset of symptoms is variable, the syndrome usually presenting during the first decade of life with dysphagia or severe (occasionally fatal) hypoglycemic or hypotensive attacks related to adrenocortical insufficiency.[4-5]

In our two cases, achalasia was the initial alarming symptom causing vomiting, dysphagia, recurrent chest infection and failure to thrive, which required frequent hospital admissions. These symptoms were noticed at the age of three and six respectively, which helped in reaching the diagnosis of achalasia. The association of dry eyes together with achalasia was an important clinical sign in support of Allgrove's syndrome. Both patients had proven alacrima, which impressed the parents as high pain threshold and tolerability. Lacrimal gland CT (orbital tomography) may be helpful in establishing the diagnosis. The biopsy obtained from his gland may show neuronal degeneration and depletion of secretory granules in the acinar cell.[5,6]

Conjunctival congestion and irritation should be the only sign of alacrima which could be confirmed by the Schirmer's test.

Nasal speech is another additional common feature which was present in these two brothers. The younger one had no debilitating finding and had a normal life and good school performance.

The index case had areas of hyper-pigmentation, most obvious over the buccal mucosa and gums. Skin pigmentation varies and is often missed since it requires careful examination. Peripheral motor and sensory neuropathy reveal muscle wasting, hyperreflexia, dysarthia, nasal speech, ataxia and autonomic dysfunction.[6-8] All these signs were present in the first case contributing significantly to his morbidity.[9-10] Adrenocortical function was preserved in Case 2 while the index case was remarkably affected with a typical pattern of ACTH insensitivity. ACTH insensitivity due to adrenocortical atrophy is the resultant clinical picture. Baseline ACTH, cortisol level and ACTH stimulation test are used to evaluate adrenal insufficiency. Glucocorticoid replacement therapy seems to have no influence on the development and progression of neurological features.

Etiology of the neuropathy in Allgrove's syndrome is obscure. At present, no explanation for the association of achalasia, alacrima and adrenal unresponsiveness to ACTH in the triple A syndrome is available. It has been thought that the ACTH receptor gene would provide the link to explain the association of the three main features of the syndrome, since there is evidence that ACTH has some neuropathic effects.[11, 12]

Imaging studies such as ultrasonography, computerized tomography and magnetic resonance might be informative if neurological abnormalities are noticed. Contrast swallow study, esophagoscopy and manometry give the definite diagnosis of achalasia and should be considered among the preliminary investigations for the diagnosis.

In both patients, achalasia was established. The index case responded to graded pneumatic

dilatation and his younger brother had open cardiomyotomy at age four (six years prior to the diagnosis of Allgrove's syndrome). Careful replacement of glucocorticoids in patients with adrenal insufficiency and management of achalasia either via endoscopic or surgical approach are cornerstones of the treatment.

In long term follow-up of adults, increased risk of Gastroesophageal reflux (GER) and its epitheloid changes have been reported.[13] Myotomy with antireflux procedure will, therefore, be a better choice and in case of pneumatic dilatation, a small dose of proton pump inhibitors (PPIs) might be needed. Additionally, the usage of artificial tears and application of topical lubricants with other supportive therapy can improve the general outcome.

During one year follow-up, our index case patient showed impressive improvement. He is able to perform his daily routines without any support, communicates well and has gained 25 kg. His brother is on follow-up without any pharmacological support.

CONCLUSION

Allgrove's syndrome may be an underdiagnosed disorder. A high index of suspicion is required when patients present with such complex symptoms as failure to thrive (dysphagia), crying without tears (alacrima), nasal speech and seizures (hypoglycemia). It may be associated with neurological disturbance. Diagnosis can be confirmed by esophageal manometry, ophthalmic assessment, biochemical study and neurological evaluation. Effective management can result in near normal life span.

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