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Short Communication

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Allgrove (AAA) Syndrome Addison, Achalasia, Alacrimia

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ABSTRACT

Triple A syndrome is an extremely rare syndrome. It is an autosomal recessive disorder characterized by adrenal insufficiency, alacrima and achalasia. 16 patients from different parts of Libya were selected and were studied for the disorder in our Department of Pediatric Endocrinology, Tripoli Medical Centre, Libya. The patients presented with classical signs and symptoms of adrenal insufficiency, ocular symptoms and achalasia which developed subsequently. The diagnosis was based on clinical grounds and some laboratory studies like electrolyte disbalance due to mineralocorticoid deficiency (Adrenal crisis), high base ACTH, low cortisol level and aldosterone levels. Barium swallows demonstrated achalasia of esophagus. Careful replacement therapy with glucocorticoid, topical lubricant for the eyes (artificial tears) and dilatation of the esophagus was performed for dysphagia.

Keywords - *Allgrove; AAA; Pathophysiology.*

INTRODUCTION

Allgrove and colleagues described an inherited familial disorder in 1978. It consists of adrenal insufficiency, achalasia of the esophagus and alacrima AAA syndrome.[1,2] Other authors suggest autonomic disturbance associated with the original Allgrove triad (4A) syndrome is an autonomic disturbance which include abnormal pupillary reflexes, poor heart rate variability and orthostatic hypotension.[1-3]

Pathophysiology

The disease is caused by mutation in AAA S gene on chromosome 12q13 encoding the nuclear gene protein ALADIN near the type II keratin gene cluster.[4-8] The linkage to a region of the genome containing a keratin gene cluster, is particularly intriguing because of the hyperkeratosis of the palms and soles that is observed in several patients.[8] DNA analysis is not useful for the prediction of clinical expression and outcome of the disorder.[8] Further investigations are necessary to evaluate correlation between genotype and clinical phenotype in triple A syndrome.[9]

The pathology of this syndrome may be due to a progressive loss of cholinergic function throughout the body.[10] This disorder may represent a dysfunction of melanocortin receptor signaling which are known to regulate adrenal function and skin gland function.[11,12] While the three main features producing primary morbidities associated with Allgrove syndrome includes mild mental retardation and autonomic neuropathy, ataxia and muscle weakness.[13] A slow neurological deterioration appeared in many patients.

Mullaney *et al.,* 1998 studied a lacrimal gland biopsy on child with Allgrove syndrome and examined the glandular cell with an electron microscope which showed clear evidence of neuronal degeneration associated with depletion of secretary granules in the acinar cells. The reduced or absent lacrimation that accompanied this change frequently lead to dehydration, induced keratopathy that was seen with Rose bengal staining. They reported xerostomia (dry mouth) and its complication only in a few patients with triple A syndrome and suggested salivary function assessment and relevant therapy should be given as necessary in all patients with triple A syndrome.[14]

MATERIALS AND METHODS

This observational study was conducted at the Department of Pediatric Endocrinology, Tripoli Medical Center, Tripoli, Libya.

Children diagnosed with Allgrove syndrome were enrolled and the study was conducted between 1992 to 2006.

Clinical presentation, age, sex, family history of this disease, geographical distribution, investigation proper management and follow up were considered as prime for the studies. Particular attention was given to the growth, developmental progress, heart rate, blood pressure, time needed for surgical intervention, routine eye and mouth examination.

RESULTS

16 patients with Allgrove syndrome were identified and enrolled between 1992- 2006 (10 males and 6 females).

They were belonged to 7 families from different cities of Libya 6 siblings (Alzahra), 2 siblings (Tripoli,

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Soug Alguma), 3 siblings (Sert), 2 siblings (Misrata), 1 young man (Gahrian), 2 other children from different families (Alzawia). The mean age of onset was 3 years (range 7 months - 10 years).

The first case was presented in 1992. 2 patients <1 year (7-10 month), 5 patients (1-5 year), 2 patients (6 -10 years), 7 patients (above 10 years) were presented.

Ocular symptoms associated with conjunctival injection, irritation, photophobia, alacrima were observed in all patients. 11 patients presented the classic symptoms of primary adrenal insufficiency along with hypoglycemic seizures and shock. Skin examination of patients revealed abnormal findings that assisted in confirming hyper pigmentation in 14 patients. Hyperkeratosis and fine fissuring of the palm was observed in 9 patients.

The distinct facial appearance associated with Allgrove syndrome consisted of a long thin face, a long philtrum, narrow upper lip and down turned mouth; these features were seen in 10 patients but were not seen in their unaffected siblings.

The most commonly described abnormal neurological features like hyperreflexia, dysarthria, hypernasal speech were seen in 14 patients. Pes cavus and muscle weakness were also seen in 6 patients. 1 patient aged 25 years old had dementia.

Developmental (walk and speech) delay was observed in 14 patients. All our patients had relatively small head and among them 12, 5, and 8 patients were observed respectively with poor school performance, nocturnal enuresis, and delayed puberty.

Achalasia developed later in 13 patients. Among 3 siblings, one boy presented adrenal crisis at the age one year, achalasia developed at the age of 6 year. The second boy presented alacrima at the age of 14 months and dysphagia developed at the age of 4 year. The third boy 10 months old, presented alacrima only.

Another 2 siblings, one boy presented with hyper pigmentation, alacrima at 3 years and showed achalasia at 11 years. His another sibling (boy) presented with hypoglycemic seizure at 2 years and showed achalasia at the age of 13 years.

One girl (single affected in her family) presented with adrenal crisis at the age one year, achalasia developed at the age of and 11 years. Two siblings, among them one girl presented at the age of 6 years with history of adrenal crisis, achalasia developed at the age of 7 years and her sister presented at the age of 10 years with history of hypoglycemia and eye symptoms, achalasia developed at the age of 11 years. One boy presented at the age of 12 years with history of adrenal crisis and hyper pigmentation, achalasia developed at the age of 18 years and now has dementia at the age of 25 years.

Last family 14 siblings 7 unaffected and 7 affected, one girl unfortunately died when she was 5 years old with adrenal crisis before being diagnosed with a history of alacrimia since infancy. Another all six (4 boys, 2 girls) affected and presented later with achalasia (6 to12 years). They had history of alacrimia in early infancy and generalized weakness and hypoglycemia. The mean age to develop alacrimia is in the first three years of life and achalasia from 10 years to early adulthood.

10 patients underwent surgical intervention Hellers operation. Esophageal dilatation was performed in two patients and four patients were under observation for progression of disease.

Abnormal finding on respiratory examination accompanying achalasia and post-surgical complications was seen in seven patients. Abnormal findings on cardiac examination

Table 1: Shows age of onset *ala*crimation and age of onset achalasia.

Family	Age at presentation	Current age	Age of onset of lacrimation	Age of onset of achalasia
3 siblings-boys	12 months 14 months 10 months	7 years 4 years 10 months	12 months 14 months 10 months	6 years No dysphagia yet
2 siblings-boys	3 years 2 years	18 years 16 years	3 years 5 years	11 years 13 years
2 siblings-girls Single girl Single girl	6 years 1o years 1 year 3years 8 months	8 years 12 years 14 years 4 years 8 months	3 years 3 years 6 years 3 years 8 months	7 years 11 years 11 years No dysphagia yet
6 siblings	14 years (boy) 9 years (boy) 12 years (boy) 7 years (boy) 5 years (girl) 5 years (girl)	30 years 22 years 25 years 14 years 12 years 9 years	<1 year <1 year 3 years 2 years 2 years <1 year	10 years 12 years 12 years 8 years 10 years 6 years
One boy	12 years	25 years	<5 years	18 years

like heart rate variability was not recorded in any patient but orthostatic hypotension were documented in four patients. Dental plagues, gingivitis, atrophic oral mucosa as well as dental caries were revealed in 13 patients. 13 patients have parental consanguinity (first and second degree cousins) although 3 patients have no such family history. Most of our patients had history of electrolyte disturbance during adrenal crisis including (hyponatremia and hyperkalimia) and low blood glucose. Base line ACTH was high in all patients, cortisol levels were low in all patients and serum aldosteron levels were also low.

Barium esophagography is used to demonstrate achalasia of the esophagus and was done in 11 patients. Typically it showed a dilated esophagus. Ultra sound abdomen was done and showed normal adrenal gland. The patients presented with seizure, showed a low base line of blood sugar, therefore lumber puncture was done in some patients to determine cerebrospinal fluid glucose was low as well.

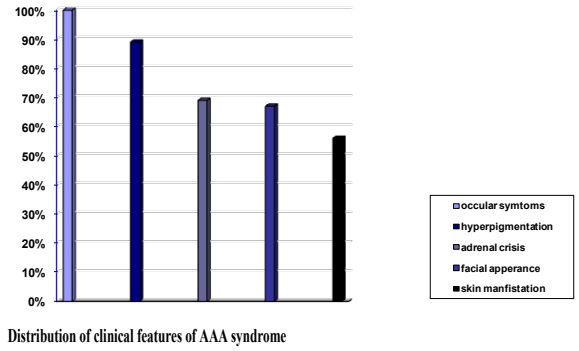

Figure 1: Distribution of clinical features of AAA syndrome.

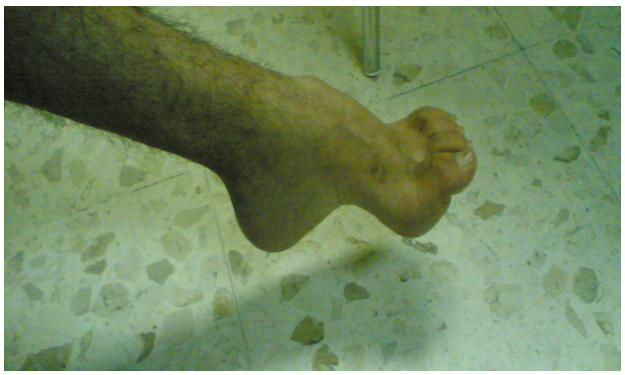

Figure 2: Siblings with AAA syndrome with marked pes cavus.

DISCUSSION

Triple A syndrome (AAA) is an extremely rare syndrome. It is an autosomal recessive disorder characterized by adrenal insufficiency, alacrimia, achalasia, and impairment of central, peripheral and autonomic function. The actual incidence is difficult to determine because of the variable presentation including unexplained childhood death due to adrenal crisis and mild disease that is not apparent until adulthood. Slow neurological deterioration occurs in many patients, this most frequently include mild mental retardation and autonomic neuropathy but may include ataxia and muscle weakness. Careful replacement of glucocorticoids in patients with known adrenal insufficiency is critical to avoid an adrenal crisis and to allow for normal growth in children. Growth must be monitored closely because over treatment with glucocorticoid impairs linear growth. Patients with Allgrove syndrome who undergo surgery must be treated with stress doses of glucocorticoid in the perioperative period. Every patient should always carry the emergency medical information card supplied with it. No specific diet or specific limitation on activity is advised. Achalasia is best managed with surgical correction, monitoring patients for pulmonary complications (due to reflux and aspiration).[15,16] Alacrima is managed with regular application of topical lubricants (artificial tears), an annual ophthalmologic evaluation is helpful in identifying patients with corneal pathology secondary to poor lacrimation. Salivary function assessment and relevant therapy should be performed as necessary in all patients with Triple A syndrome. Provided the patient is managed effectively there is no reason that the patient can not have a normal life span and pear children.

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