

Allgrove Syndrome: Report of Two Cases

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Abstract: Allgrove syndrome or Triple A syndrome is a rare autosomal recessive disorder. The mutation affects the AAAS gene localized on chromosome 12. It combines alacrima, achalasia and adrenal insufficiency. Neurological signs can be associated. It usually occurs during the first decade of life. Treatment is symptomatic based on hormone replacement, artificial tears and surgery. We report two cases of a brother and a sister, whose parents are first cousins and have the full form of this disease with neurological signs. We will study physiopathological, clinical, genetic and therapeutic aspects of this syndrome.

Keywords: Allgrove, Triple A, Achalasia, Alacrima, Adrenal insufficiency.

INTRODUCTION

Allgrove syndrome or “Triple A syndrome” is a rare inherited autosomal recessive disease caused by mutations in the AAAS gene located on chromosome 12. It is characterized by the clinical triad of adrenal insufficiency, achalasia and alacrima. Majority of patients develop neurological disorders during evolution [1]. We report two cases of a brother and a sister with this disease. The clinical, pathophysiologic, therapeutic and genetic features of this syndrome will be discussed.

CASE REPORT

Case 1

It is a case of a 16 old-year girl, youngest in a family of three children, born of a consanguineous marriage. Parents are first cousins. The clinical history dates back to 3 years of age by the installation of a deep asthenia, convulsive episodes related to hypoglycemia and diffuse melanoderma. The diagnosis of peripheral adrenal insufficiency was made and the girl was put under hydrocortisone. An alacrima was also observed. At the age of 15 years, she presented a progressive and total dysphagia with weight loss of 12 kg in 3 months. The œsogastroduodénal transit confirmed the diagnosis of achalasia by objectifying a defect relaxation of the lower sphincter (Fig. 1). Two years later, she underwent Heller’s intra mucosal meatotomy with a good evolution. The child was sent to us after surgery. Her phenotype was particular with microcephaly, dental defects and deformation of the nail of big toes in the form of stairs (Fig. 2 and 3). She had rhinism. It weighed 28 kg (- 4, 5 DS) for a small size of 1.47 cm (- 2, 5 DS). Blood pressure decreased from 110 / 70 mmHg sitting at 90 / 60mmHg standing. Neurologically, we noted amyotrophy of thenar,

hypothenar and interosseous (Fig. 4) with a peripheral neurogenic and pyramidal syndrome. The electromyogram (EMG) noted sensory and motor demyelinating and axonal polyradiculoneuropathy. Ophthalmologic examination confirmed the total alacrima, basal and reflex. The genetic study is ongoing. The patient is currently under hydrocortisone and artificial tears.

The patient underwent a therapeutic education and addisonien card was handed to her. The outcome was favorable in terms of weight: 7 Kg taken in 4 months. However, the patient often discomforts related to orthostatic hypotension. A Fludrocortisone treatment is considered.

Case 2

It is a case of a 28 old-year young patient, who is the big brother of the girl. He was followed from the age of 5 years for peripheral adrenal insufficiency. It was revealed by convulsive episodes secondary to hypoglycemia, melanoderma and a marked weight loss. He had surgery at the age of 17 years for achalasia after dysphagia and vomiting. This patient also presents an alacrima, a microcephaly and orthostatic hypotension (120 mm Hg/ 70 sitting and 100 mm Hg/ 50 standing). Its weight was 49 Kg with a size of 1.58 m so the BMI was 19.5 kg/m². Neurologically, he had a pyramidal tetra irritation with diffuse muscular atrophy. Like his sister, the EMG confirmed the similar neurological anomalies. Ophthalmologic examination objectified basal and reflex alacrima.

Our patient is symptomatic treatment with hydrocortisone and artificial tears. He received therapeutic education and an Addison card.



Fig. 1: Barium meal study showing dilatation of the distal oesophagus and almost complete obstruction at the gastro-oesophageal junction (the bird's beak or rat's tail sign)



Fig. 2: dental defects



Fig. 3: Nail malformation in stairs



Fig. 4: Thenar and hypothenar amyotrophy

DISCUSSION

Allgrove syndrome has been reported for the first time in 1978 by Allgrove in two patients with symptoms of adrenocorticotrophic hormone (ACTH)-resistant adrenal insufficiency, alacrima and achalasia [2]. Its incidence is unknown until now, but hundred cases described in the literature [3]. Classically, there is no predominance of sex except for some authors, the boy is more affected [3, 4]. The clinical evolution is progressive and classical characteristic triad is rarely assembled immediately [4].

Alacrima is the most constant clinical manifestation and the earlier [5]. It is often observed by the parents at the lack of reflex tears but can be asymptomatic. It concerns both the basal and reflex tear secretion that may be complicated by keratitis in the absence of treatment. It is confirmed by the Schirmer test or break up time. Alacrima seems secondary to a progressive degenerative disease of the cholinergic innervation of the lacrimal secretory vegetative system [6]. Other ophthalmologic signs were described as hypoesthesia, optic atrophy, anisocoria and disorders of pupillary motility by cranial nerve [7, 8].

Achalasia is typically observed in 75% of cases [9]. It proves usually by vomiting, dysphagia or pulmonary complications due to tracheal false routes [6]. According Allgrove *et al.*, biopsy performed post mortem demonstrates the absence of ganglion cells and nerve fibers in the lower part of the esophagus [2].

Adrenal insufficiency is the third sign of the triad. The age of discovery is variable, often during the first year of life, often asymptomatic until adulthood [4]. The revealing signs can be hypoglycemic accidents, profound asthenia and melanoderma. The glucocorticoid component dominates the adrenal defect due to ACTH resistance. However, an association with

mineralocorticoid insufficiency can be seen in 15% of cases [9]. Our two patients had complete form of the syndrome, adrenal insufficiency was the first manifestation of the disease, alacrima was early and achalasia was found at the age of adolescence, 15 years in the first case and 17 years in the second. Characteristic triad of Allgrove syndrome is frequently associated with other particular neurological signs. Some authors have proposed the term of "4 A syndrome" [10]. Some of these signs are attributed in part to the complications of hypoglycemia [10]. This may be an abnormality of the central nervous system with a progressively worsening mental retardation, epilepsy and neurosensory disorders [8, 11]. Cranial nerves anomaly can be observed causing rhinism and lowering the velum. Other rarer abnormalities have been described as amyotrophic lateral sclerosis [1, 12]. Autonomic nervous system disorder is observed in 30% [6]. It occurs mainly as orthostatic hypotension like our patients, abnormalities of cardiovascular reflexes and sexual impotence [6, 8]. The peripheral nervous system anomaly is the least documented in the literature [13]. Wallet *et al.* reported four cases with symptoms suggestive of a hereditary poly- neuropathy or distal spinal amyotrophy. Neuropathy in this syndrome is predominantly motor and axonal in preferential ulnar territory [14].

Other clinical signs may include palmoplantar hyperkeratosis, cutis anserina, fungiform papillae of the tongue and incomplete dermatoglyphes are present in 20% of cases [15]. Short stature, microcephaly, hypophosphatemic rachitis can also be present.

In the first case, we found short stature and poly malformation syndrome. Some patients have alacrima and achalasia without adrenal insufficiency. This "alacrimia- achalasia" syndrome has been described as a separate entity by some authors [14].

Allgrove syndrome is inherited as an autosomal recessive disorder as evidenced by the achievement of both sexes and absence of achieving parents [1]. Pathophysiological hypothesis of this syndrome is debatable, Weber and al demonstrated a connection between D12S1629 and D12S12 markers of Allgrove syndrome gene "AAAS gene" located on the 12q13 chromosome. This gene encodes a protein called ALADIN (ALacrima, Achalasia, adrenal Insufficiency, Neurologic disorder) [8, 16]. According Hadj Rabia *et al.* and Handschug K *et al.*, many AAAS gene studies have been published subsequently and showed that Allgrove syndrome and syndrome "achalasia, alacrimia" are the same entity [17, 18]. Genetic analysis looking for mutations in the AAAS gene is ongoing in our two patients. The gene expression is ubiquitous, but notably high in the adrenal gland, gastrointestinal tract and brain [19]. Variability of the severity and age of

onset of this disease among patients with the same mutation and the same genetic background suggests that other factors may be involved.

Treatment is symptomatic in Allgrove syndrome with a tear substitution, a glucocorticoid for adrenal insufficiency associated with fludrocortisone if there is mineralocorticoid failure. Achalasia is treated by esophageal dilatation or Heller's cardiomyotomy [1].

CONCLUSION

Allgrove syndrome is a rare disease but should be considered in any patient with an abnormality of the triad. Do not forget to look carefully neurological signs that are frequently associated. Early diagnosis allows symptomatic therapy to improve the life quality and avoid the complications that can be life-threatening.

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