Allgrove Syndrome: A Little Common Clinical Presentation

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Abstract The Allgrove syndrome or triple A is a rare inherited autosomal recessive syndrome. The presence of the clinical triad type alacrima, achalasia and Addison's disease is sufficient for the diagnosis. We report the case of a family, the sister and the brother, respectively 11 and 19 years old, from a 1st degree consanguineous marriage and who presented the characteristic signs of the Allgrove syndrome with 2 features: a growth hormone deficiency for the sister and congenital bone malformations for the brother. To our knowledge these characteristics have not been described previously.

Keywords Allgrove syndrome; Achalasia; Alacrima; Adrenal insufficiency; Growth hormone deficiency; Congenital bone malformations

1 Introduction

The Allgrove syndrome or triple A is a rare inherited autosomal recessive syndrome. It was reported for the first time in 1978 by Allgrove (Allgrove et al, 1978). The presence of the clinical triad type alacrima, achalasia and Addison's disease is sufficient for the diagnosis.

2 Case report

We report the case of a family, the sister and the brother, respectively 11 and 19 years old, from a consanguineous marriage of the 1st degree. In the family history, we found a brother who died at the age of 2 years in a clinical picture evoking a salt-losing syndrome and a sister, 26 years old, apparently in a good health. There are no similar cases in the family. The pregnancy was normal for both the sister and the brother, vaginal delivery at term, normal psychomotor development and proper vaccination.

2.1 Observation 1

The sister entrusted to us by the pediatric department at the age of 08 years for a cushingoid appearance. She was followed for alacrima, apparently from birth, under treatment (artificial tears), adrenal insufficiency diagnosed at the age of 3 years, in favor of weight loss with significant melanoderma and impaired general condition and under treatment (hydrocortisone 30 mg /day), and a megaesophagus diagnosed in favor of gastroesophageal reflux, surgery at the age of 07 years. Moreover, the academic performance of the child was just average.

The clinical examination revealed a cooperating child with clear signs of overdosing of hydrocortisone type cushingoid aspect, weighting more than 2 SD, a size less than 2 SD, Tanner pubertal stage S1 and P1, and a normal neurological examination without other signs of endocrine involvement.

Laboratory tests showed: urinary free cortisol = 348 µg/j (32-243, high), FT4 = 1.15 pmol/l (0.93-1.7), TSH =1.7IU/L (no deficit), antithyperoxidase antibody = 2.92 (<34IU/ml), bone age=3years (delay of 5 years compared to the chronological age). Neurological examination: a normal EEG, an axonal sensorimotor polyneuropathy at the EMG (vitamin E and monitoring), a normal cerebral MRI. After adjustment of hydrocortisone doses (20 mg / day), weight decreased with the disappearance of the cushingoid appearance without catch-up growth. The growth retarded becoming important, an exploration looking for another cause of this delay showed no villous atrophy at the duodeno-jejunal biopsy, FT4= 1.36 ng/dl, TSH=2IU/L (no deficit),
GH/glucagon=1.54 ng/ml (low), GH/insulin=1.60 ng/ml (low), hypothalamic-pituitary MRI-no anomalies detected. The Diagnosis of total growth hormone deficiency, apparently idiopathic, was retained and the patient was put under physiological doses of growth hormone. With this treatment, the child was able to catch his growth retardation (-0.2 SD) with a normalization of her bone age.

2.2 Observation 2
The brother, 19 years old, consulted in our department on its own initiative for a suspected adrenal insufficiency with a picture of melanoderma with asthenia, weight loss and low blood sugar during fasting. In his history, he has regained alacrimia (under artificial tears) since a young age and megaesophagus operated at the age of 06 years.

The clinical examination revealed a patient with melanoderma and asthenia, thin (BMI = 14.69 kg/m²) with a tooth spacing, precordialgia, orthopnea associated with pectus excavatum, scoliosis and flat feet without other signs of endocrine or neurological impairment.

Laboratory tests showed: plasmatic cortisol = 138 ng/ml (low), ACTH=190pg/ml (very high), FT4=12.7 pmol/l, TSH=2.04 IU/L, (no deficit). The diagnosis of primary adrenal insufficiency has been established and the patient was put under 25 mg/day of hydrocortisone and addressed to the pneumology and the cardiology departments for its funnel chest but also to the physical medicine and rehabilitation department for a scoliosis and flat feet.

Neurological examination: a normal EEG, an axonal sensorimotor polynymopathy at the EMG (vitamin E and monitoring), a normal cerebromedullar MRI.

Medical imaging:
- chest CT: chest deflection of the anterior wall.
- X-ray of the spine: lumbar scoliosis and kyphosis.
- X-ray of feet: hallux valgus with bilateral malformation of the two middle toes of both feet (amputation of the 2nd phalanx).
The patient underwent surgical repair of pectus excavatum (sternochondroplasty, Ravitch type) and an orthopedic treatment for flat feet.

3 Discussion

The Allgrove syndrome or triple A combines alacrimia which is the first sign (Ornek et al., 2002), achalasia which is present in 75% of cases (Clark et al., 1995; Philip et al., 1996), Addison's disease due to ACTH resistance (Lanes et al., 1980), a progressive neurological impairment (central autonomous and peripheral nervous system) as well as other signs such as small size, palmoplantar hyperkeratosis, fissured tongue and microcephaly (Clark et al., 1998). The Allgrove syndrome should be considered in any alacrimia of the child or a young subject. The Allgrove syndrome is caused by a mutation of a gene located on chromosome 12 in position 12q13 and ensures the synthesis of ALADIN protein which is a regulatory protein (Orrell and Clark, 2002). The diagnosis is often made in childhood (case of our 2 patients) but sometimes in adulthood (Azoug et al., 2015; Pedreira et al., 2004). Our two patients had complete triple A syndrome and the alacrimia was the first symptom, as reported in the literature (Azoug et al., 2015; Ornek et al., 2002). The consanguinity (1st degree) in the case of this family is also found in 87.5% of cases in Azoug’s study (Azoug et al., 2015). This consanguinity on the one hand and the other sister free from the disease in the other hand, confirm the autosomal recessive transmission. Moreover, the brother died at the age of 2 years in a clinical picture evoking salt loss syndrome suggests that it might be carrying the disease. Otherwise, the small size has been described in the Allgrove syndrome, however, no growth hormone deficit has been, to our knowledge, reported to date. It is the same for bone defects, never previously described. The latest sign described and published is syringomyelia (Bizzari et al., 2013). These two unusual situations (GH deficiency and bone malformations) need a special attention even we cannot certify if they are a part or not of the triple A syndrome.

4 Conclusion

The Allgrove syndrome is more common in our country. We should be vigilant in case of an adrenal insufficiency in young patients with alacrimia and we have to report any unusual sign to identify the triple A syndrome and screen the index cases and their family. Indeed, the Allgrove syndrome is a very disabling disease due to the motor neurological impairment and sometimes to death by the hypoglycaemia unawareness without forgetting the academic and the social failures.

Author’s contributions

By signing this letter each of us acknowledges that she or he participated sufficiently in the work to take public responsibility for it.

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