Triple A syndrome, a challenging race for the diagnosis in a potentially lethal pathology: a case report

Tiffany Brose[a], Alexandra Bobarnac[b], Sophie Lambert[c], Olivia Bauraind[b], Stéphanie Colinet[b], Isabelle Paquot[b], Marc Dirix[d], Jamil Khamis[e], Florence Roucher[f], Pierre Philippet[g]

[a] Faculty of Medicine, University of Liège, Belgium
[b] Division of Pediatric Gastro-Enterology, Department of Pediatrics, CHC-Montlégia, Liège, Belgium
[c] Division of Pediatric Endocrinology, Department of Pediatrics, CHC-Montlégia, Liège, Belgium
[d] Division of Pediatric Surgery, Department of Surgery, CHC-Montlégia, Liège, Belgium
[e] Division of Pediatric Radiology, Department of Radiology, CHC-Montlégia, Liège, Belgium
[f] Yves Morel Laboratory, Lyon, France
[g] Division of Pediatric Hemato-oncology and Immunology, Department of Pediatrics, CHC-Montlégia, Liège, Belgium

tiffany.brose@chuliege.be

Keywords

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Abstract

Triple A syndrome is a rare disease that associates achalasia, alacrima and adrenal insufficiency. Here we report a case of a 15 year-old girl presenting this typical triad. The symptoms being aspecific, diagnosis was delayed, with a major impact on her growth and development. Despite the rarity of this syndrome, diagnosis must be made as early as possible to avoid lethal consequences (acute adrenal insufficiency, denutrition). We confirmed the diagnosis with imaging and genetic analysis. The patient underwent surgical and medical treatments and was followed to prevent potential complications.

Introduction

The triple A syndrome (TAS, Allgrove syndrome) is a rare disease characterized by a symptomatic triad of esophageal achalasia, adrenal insufficiency and alacrima (1). Achalasia is a primary motor disorder with absence of peristalsis and incomplete relaxation of the lower esophageal sphincter (LES) (2, 3). A few cases of TAS have been described in children and adolescents. Its incidence varies according to the continents and is approximately 0,1/100,000. Diagnosis is often delayed in children because of lower incidence and unspecific symptoms (1, 4).

Case report

A 15-year-old girl was admitted for weight loss and loss of appetite. She had presented feeding difficulties, postprandial vomiting and dysphagia since her third year of life. She had not started puberty. The patient was born at term with intrauterine growth restriction (birth weight: 2500g). She was the fourth of five children of a Moroccan family with consanguineous parents. Her brother died at the age of 13 with similar clinical symptoms. At first clinical examination, she was underweight and pale with muscular hypotrophy (anthropometric measurements: weight 28.7kg (-4SD), height 140cm (-4SD), BMI 14kg/m² (-2SD)), late onset puberty (Tanner stage P1M2) and dental cavities. Additional history showed an absence of tears (Schirmer's test not performed), nighttime gastroesophageal reflux, amenorrhea and an already supplemented primary adrenal insufficiency (hydrocortisone supplementation initiated in 2016 in Morocco at the dose of 15mg/day, corresponding to 16mg/m²/day). Laboratory evaluations showed primary adrenal insufficiency (cortisol 6.5µg/dL [Normal value: 9-21µg/dL] and ACTH 559pg/mL [Normal value: 7.2-63pg/mL] measured in the morning), normal serum sodium (sodium 142mmol/L [Normal value: 136-145mmol/L] and potassium 3.9mmol/L [Normal value: 3.5-5.1mmol/L]), normal glucose (fasting serum glucose 69mg/dL [Normal value: 60-100mg/dL]), anemia, hypoproteinemia, negative inflammatory bowel disease antibodies, negative celiac disease antibodies and normal thyroid function. The high resolution esophageal manometry could not be performed due to poor compliance. The barium swallow (Figure 1) and upper gastrointestinal endoscopy (Figure 2) showed a dilated esophagus and low peristalsis with delayed emptying of the esophagus and gastric inflammation. Anatomical and functional criteria were compatible with esophagus achalasia. The combination of achalasia, adrenal insufficiency and alacrima suggested triple A syndrome. DNA sampling (*AAAS* gene, chr 12q13, mutation ALADIN) identified a homozygous intronic mutation 14 c.1331 + 1G>A (the most common mutation in North Africa). A treatment by proton pump inhibitors (omeprazole 40mg), artificial tears and a high caloric diet was initiated and adrenal supplementation was pursued. After a multidisciplinary discussion, Heller procedure with anti-reflux surgery (Dor gastroplasty) was performed. In the short and medium term, the course of the disease was satisfactory, with a decrease of dyspepsia, dysphagia, postprandial vomiting and food impaction. The growth in height and weight progressed harmoniously with a significant increase of the BMI and the first signs of puberty appeared. After a few years, the evolution was fine without distant complications. Digestive tolerance was good due to the absence of gastroesophageal reflux and dysphagia. The esophageal impedancemetry was normal one year after the surgery.

Discussion

The triple A syndrome is a rare disease usually characterized by a clinical triad of esophageal achalasia, adrenal insufficiency and alacrima (1). Although its name is defined by the triad, the syndrome is phenotypically heterogeneous. Fewer than the three features may be present. Additional features not originally identified, include progressive autonomic (central and peripheral) nervous system deficits (1, 4). The latter symptoms were

not present in our patient, who presented with the usual triad. The etiology of achalasia in TAS appears to be distinct from other forms of achalasia. Although it is a rare condition and epidemiologic data are scant, symptoms of swallowing difficulty and achalasia in TAS usually manifests by the end of the first decade of life and can begin in infancy in contrast to idiopathic achalasia, where a very small minority of patients manifest symptoms before the age of 10. Our patient had presented dysphagia since her third year of life (2, 3).

Mutations in the *AAAS* gene (which codes for the ALADIN protein), located on chr 12q13, accounts for the majority of cases (5). Consanguinity is often described. Transmission is autosomal recessive pattern. In our patient's family, an older brother died at the age of 13, possibly of adrenal insufficiency. Indeed, he presented the same clinical symptoms. The penetrance of biallelic mutations in *AAAS* approaches 100%, though expressivity is variable, possibly due to allelic variation or the existence of yet unidentified genes (1, 5, 6). Diagnosis is often delayed because of the aspecificity of symptoms (vomiting, dysphagia, weight loss, failure to thrive, chest pain, regurgitated food), lower incidence of achalasia than other more frequent pathologies (gastroesophageal reflux disease). Our patient presented with severe growth retardation, probably due to the combination of partial primary adrenal deficiency for years and a long-standing undernutrition (Figure 3). The differential diagnoses that must be excluded when faced with similar symptoms are gastroesophageal reflux, eosinophilic esophagitis, foreign-body ingestion, intrinsic esophageal stenosis, leiomyomatosis, external compression of the esophagus (e.g. esophageal duplication, mediastinal tuberculosis, malignant neoplasms), and eating disorders (anorexia nervosa). The diagnosis must be made as early as possible since long-existing achalasia can cause severe undernutrition, which can be potentially lethal (2, 3). The workup includes biochemistry, X-ray (barium swallow X-ray), esophageal manometry and upper endoscopy. Esophageal manometry allows definitive diagnosis and grading of the achalasia. In our case, radiological and endoscopic characteristics, as well as the alacrima and the primary adrenal deficiency are sufficient to establish the diagnosis. Furthermore, the genetic analysis brought formal confirmation (1, 7, 8). The three primary types of treatment are pharmacological and nutritional (adrenocortical hormone supplementation, symptomatic treatment of alacrima, high caloric diet), endoscopic (botulinum toxin injection into the LES, pneumatic dilatation and stenting, peroral endoscopic myotomy) and surgical (Heller procedure with anti-reflux surgery and feeding gastrostomy) (9,10). Our patient was granted a surgical treatment as first line therapy, due to severe anatomical and nutritional repercussions as well as the late diagnosis. Gastrostomy was not immediately necessary thanks to good surgical tolerance with improving symptomatology, satisfying semi-liquid refeeding leading to acceptable weight gain. Patients should be regularly followed-up to prevent progression toward esophageal cancer or motor disorders with malnutrition.

Conclusion

Triple A syndrome is rare and its prevalence varies among continents. Achalasia in Triple A syndrome may appear earlier in life than isolated achalasia. The symptoms are rather aspecific and the diagnosis is difficult and often delayed. It is essential to quickly confirm diagnosis because the disease can be fatal (acute adrenal insufficiency, malnutrition). Long-term patient follow-up is essential in view of distant complications.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

Figure 1: Barium swallow radiography: major distension of the superior 2/3 of the esophagus with delayed emptying and food stagnation, thin aspect of the inferior 1/3 of the esophagus and of the esogastric junction (« bird's beak »).

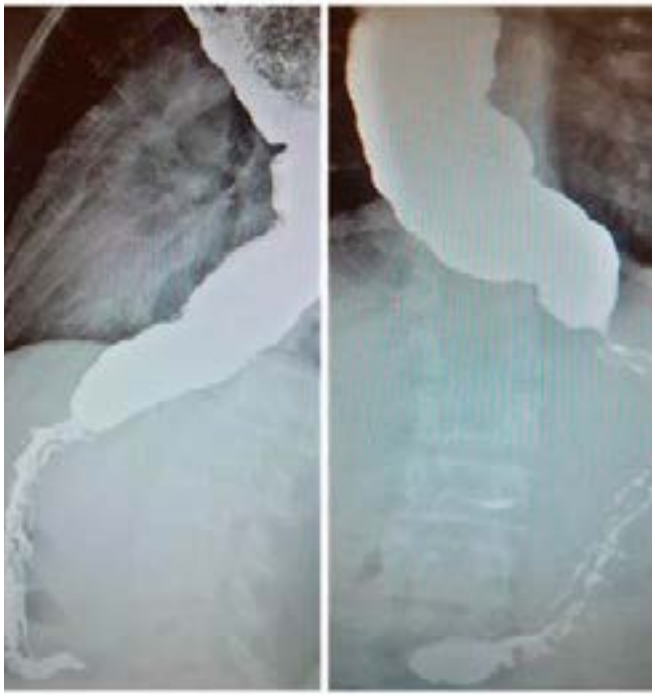


Figure 2: Upper gastrointestinal endoscopy: dilated esophagus and gastric inflammation (nodular aspect).

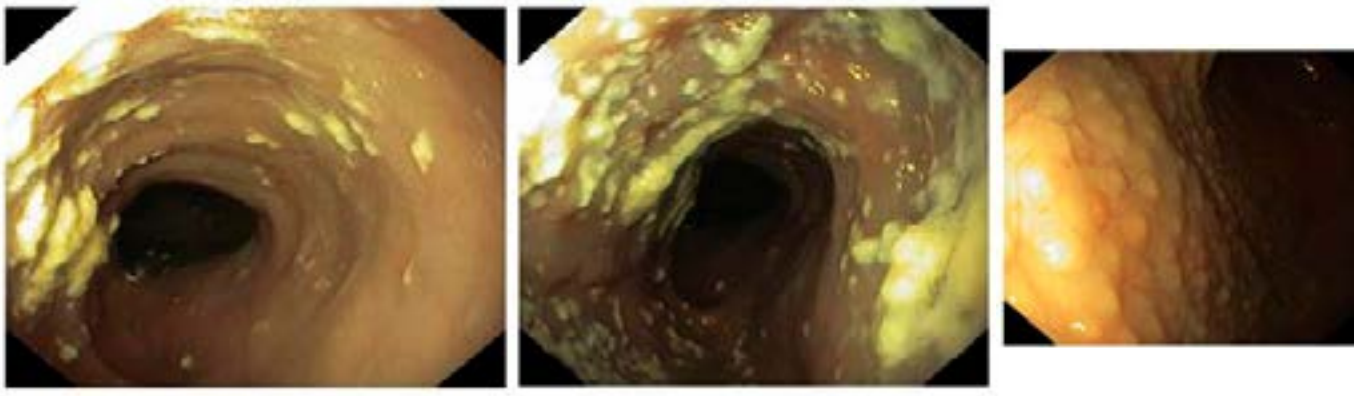
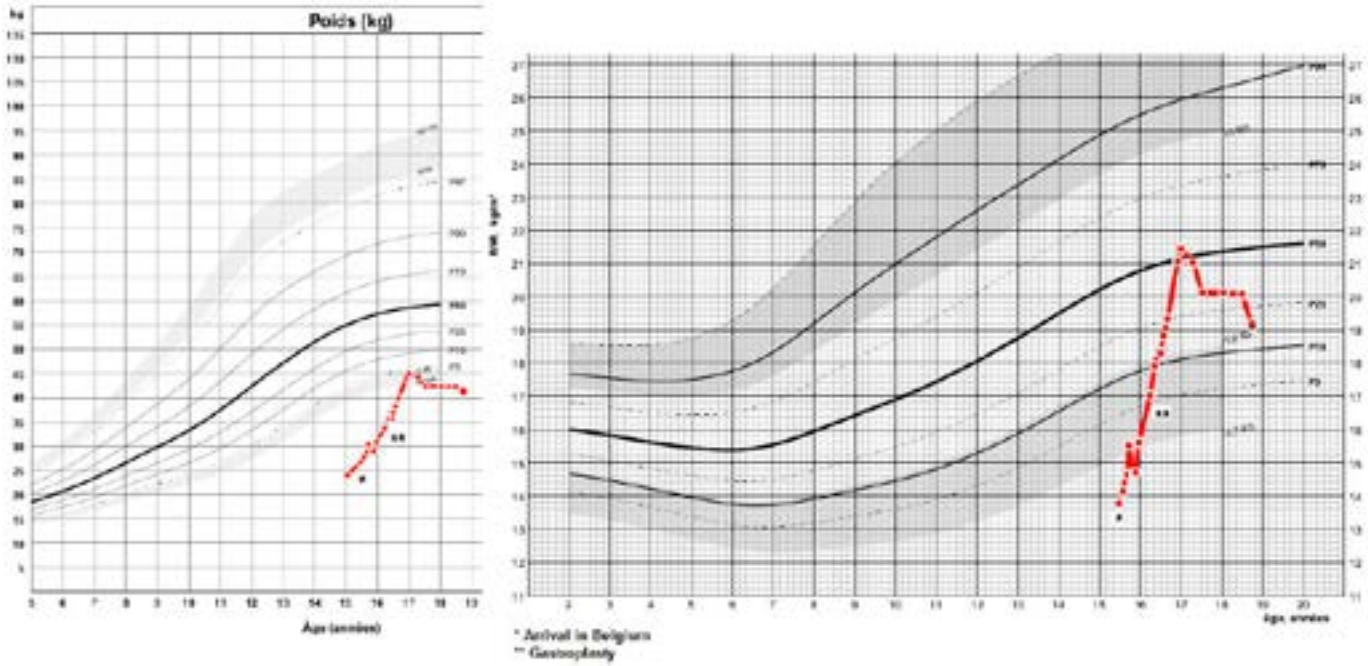


Figure 3: Growth and BMI curve with arrival in Belgium and gastroplasty.



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