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Increased levels of chitotriosidase in a patient with Alagille syndrome: association or coincidence?

Aumento dos níveis de quitotriosidase em um paciente com síndrome de Alagille: associação ou coincidência?

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ABSTRACT

We describe a case of a patient with Alagille syndrome (AS) presenting an increased level of the enzyme chitotriosidase (ChT), evaluating factors that could justify the relationship between AS and ChT. He was a male patient with cholestatic jaundice, facial dysmorphia and congenital heart disease who presented a brief septicemia. He underwent liver biopsy and analyses for inborn errors of metabolism that respectively showed ductopenia and increased levels of ChT. This increase could be potentially explained by inflammatory and infectious processes, or even by AS itself.

Key words: chitinase; cholestasis; inflammation; Alagille syndrome; sepsis.

INTRODUTION

Alagille syndrome (AS; OMIM 118450), also known as Alagille-Watson syndrome or arteriohepatic dysplasia, is an autosomal dominant genetic disease with variable clinical manifestations that may involve different organs and systems[1, 2]. Its first description occurred in 1969, by Alagille *et al*.[3], and it was also subsequently reported by Watson and Miller, in 1973[4]. However, the diagnostic criteria were only established by Alagille *et al*. in 1975[2]. Originally, the prevalence of the syndrome was estimated at 1:70,000 live births, but considering individuals without hepatic involvement, this frequency increases to 1:30,000[1, 2]. This disease is mainly caused by mutations in JAG1 (AS type 1) (about 90% of cases) and NOTCH2 genes (AS type 2)[2]. The first prominent clinical feature in most patients is the presence of neonatal liver disease, with conjugated hyperbilirubinemia (cholestasis)[1, 2]. Our aim was to describe a patient with AS presenting an increased level of chitotriosidase (ChT), evaluating factors that could explain the relationship between AS and ChT.

CASE REPORT

The patient was a boy aged 1 month and 3 days, with a history of cholestatic jaundice. He was the first child of a young and non-consanguineous couple, with no family history of genetic diseases. The mother has a previous history of a stillbirth and two gestational losses. The gestation of the patient was uneventful. His prenatal serologies were negative. The mother reported smoking throughout pregnancy (mean of 10 cigarettes per day) and occasional alcohol intake. The patient was born prematurely, at 33 weeks and 3 days, by cesarean section due to fetal distress, weighing 1,460 grams, measuring 42 cm, with head circumference of 24.5 cm and Apgar scores of 5 and 7 at first and fifth minutes, respectively. At birth, septicemia and respiratory failure were verified. Cholestasis was also diagnosed soon. Septicemia was treated with antibiotic therapy during 10 days. The patient presented alterations in liver function tests, with an increase in the levels of aspartate aminotransferase (AST or GOT) (150 U/l – reference values: 14 to 42 U/l), glutamic pyruvic

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transaminase (GPT) (61 U/l – reference values: 10 to 43 U/l), direct bilirubin (10.8 mg/dl – reference values: 0.1 to 0.4 mg/dl) and total bilirubin (14.4 mg/dl – reference values: 0.3 to 1.2 mg/dl). Hepatic scintigraphy showed findings suggestive of biliary atresia. However, the cholangiography was normal, such as the total abdominal ultrasound. For serological tests, only cytomegalovirus and rubella IgG were positive. Alpha-1-antitrypsin dosage was normal (146 mg/dl – reference values: 103 to 202 mg/dl). Screening for inborn errors of metabolism performed at the 28th days showed an increase in the chitotriosidase levels: 1,355 nmol/h/ml (reference value: 8.8 to 132).

His liver biopsy revealed ductopenia. The patient was also diagnosed with hypothyroidism, starting treatment with levothyroxine at 1 month of age. Echocardiography disclosed pulmonary valve stenosis, valve dysplasia and patent foramen ovale. Ophthalmologic evaluation and the spine radiography did not identify alterations. The patient underwent a nasofibrolaryngoscopy that showed alterations suggestive of laryngomalacia. At 4 months and 19 days of age, the physical exam revealed growth retardation and several dysmorphisms that include triangular face, broad forehead, saddle nose with bulbous tip, high arched palate, prominent chin, increased intermammillary distance and right hydrocele. High-resolution GTG-Banding (G bands produced with trypsin and Giemsa) karyotype showed a normal male chromosome constitution (46,XY).The patient had follow-up with us up to 2 years and 3 months of age. He presented an adequate developmental progress, but had speech delay. Liver disease has not progressed until that moment for cirrhosis or hepatic insufficiency. The dosage of chitotriosidase was not repeated during this period.

Although the genetic cause of AS is already known, diagnosis is essentially clinical, especially due to the presence of biliary ductopenia and congenital heart disease. Currently, there are minimal clinical criteria for the diagnosis. The classical criteria involve the presence of ductopenia associated with three of five major criteria: cholestasis; ophthalmologic abnormalities; facial features (prominent forehead, hypertelorism, bulbous nose and protruding nose); congenital heart disease (pulmonary artery stenosis) and skeletal abnormalities (commonly butterfly vertebrae)[1, 2]. As our patient presented cholestasis secondary to ductopenia (evidenced by liver biopsy) associated with facial features and pulmonary stenosis, these clinical findings were compatible with the diagnosis of AS. The **Table** shows clinical findings and diagnostic criteria for AS according to the literature compared to those found in our patient.

ChT, a human chitinase, is an enzyme encoded by the *CHIT1* gene (1q31q32) secreted by activated macrophages that participate in the degradation of chitin containing pathogens in their composition or metabolism, such as bacteria, fungi and viruses[5]. Chitin degradation associated with ChT elevation has been described in infectious and inflammatory processes[6]. Increased plasma levels of this enzyme are also frequently found in patients with lysosomal storage diseases, such as Niemann-Pick disease and especially Gaucher disease[7].

TABLE – Overview of the clinical findings of AS compared with those found in our patient

Clinical findings	Our patient
Major criteria	
Cholestasis	+
Ophthalmologic abnormalities	-
Characteristic facial features	+
Cardiac defect	+
Skeletal abnormalities	-
Other findings	
Growth retardation	+
Hypothyroidism	+
Kidney anomalies	-
Neurovascular abnormalities	-
Pancreas alterations	-
Intellectual disability	-
Developmental delay	-
Positive family history for AS	-

AS: Alagille syndrome.

In our literature review, we found the description of only one patient with AS presenting high levels of ChT[8]. This increase was justified by a history of congenital herpes virus infection. As mentioned before, infection may be associated with increased levels of ChT. It is important to point out that our patient presented septicemia in his first month of life, and ChT analysis did not occur in the same period (18 days after). However, we cannot rule out the possibility that the ChT increased verified in our patient may be associated with this infectious event during the perinatal period, even because the half-life of the enzyme is not known.

Increased levels of ChT have also been described under conditions related to exacerbated inflammatory processes, such as inflammatory bowel disease, sarcoidosis, and atherosclerosis[9]. It is noteworthy that high levels of ChT have been described in patients with liver diseases, such as non-alcoholic steatohepatitis[10]. Ductopenia, which is the anatomopathological aspect evidenced in the present case and is a very common finding within the clinical spectrum of AS, can cause alterations in the transmembrane transport, intrahepatic bile production and mechanical obstruction by decreasing the biliary flow, leading to accumulation of biliary substances in the liver and, consequently, an inflammatory process[11]. Accordingly, liver biopsy of ductopenia cases usually reveals the typical portal inflammation, with presence of edema, inflammatory infiltrate and tissue fibrosis[12]. With that in mind, we cannot disregard that the increased ChT observed in our patient may be related to his liver finding of ductopenia.

Thus, the increase of ChT verified in our case could be potentially explained by other factors, different from the syndrome, as infectious and inflammatory processes. However, we cannot rule out that a direct relationship between ChT levels and AS could exist, because this enzyme is not usually measured in cases with suspicion or diagnosis of this disease. It is important to note that, in this case, the finding of increased ChT was accidentally verified due to the investigation for cholestasis.

RESUMO

Descrevemos o caso de um paciente do sexo masculino com síndrome de Alagille (SA), o qual manifestou aumento do nível da enzima quitotriosidase (ChT). Avaliamos os fatores que pudessem justificar a relação entre AS e ChT. O paciente apresentou icterícia colestática, tinha dismorfias faciais, cardiopatia congênita e manifestou um breve quadro de septicemia. Foi submetido à biópsia de fígado e análises para erros inatos do metabolismo que mostraram, respectivamente, ductopenia e aumento dos níveis de ChT. Esse aumento poderia ser potencialmente explicado por processos infecciosos e inflamatórios, ou mesmo pela própria SA.

Unitermos: *quitinase; colestase; inflamação; síndrome de Alagille; sepse.*

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