

# Alpha 1 antitrypsin deficiency: case report

## *Deficiência de alfa1antitripsina: relato de caso*

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### ABSTRACT

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This report draws attention to the alpha 1 antitrypsin deficiency in newborns presented as a cholestatic syndrome. Its sub-diagnosis constitutes a major constraint for recognition and appropriate treatment. Good outcomes occur in approximately 50% of patients. It is associated in most cases, to extra and intra-hepatic involvement and the absence of clinical signs that indicate its diagnosis. The alpha 1 antitrypsin deficiency is among the diseases that need to be excluded when facing neonatal cholestasis.

**Key words:** alpha 1-Antitrypsin Deficiency; alpha 1-Antitrypsin; Cholestasis; Infant, Newborn.

### RESUMO

*Este relato alerta para a deficiência de alfa1antitripsina em neonato, que se apresentou como síndrome colestática. Seu subdiagnóstico constitui-se em importante limitação para o seu reconhecimento e tratamento adequado. A boa evolução ocorre em cerca de 50% dos pacientes. Associa-se, na maioria das vezes, a acometimento extra e intra-hepático e ausência de manifestações clínicas que indiquem o seu diagnóstico. A deficiência de alfa1antitripsina está entre as doenças que precisam ser excluídas frente à colestase neonatal.*

**Palavras-chave:** Deficiência de alfa 1-Antitripsina; alfa 1-Antitripsina; Colestase; Recém-Nascido.

### INTRODUCTION

The cholestatic syndrome in infants is one of the major diagnostic challenges in pediatric hepatology; there are various clinical and surgical conditions under this denomination. Alpha 1 antitrypsin deficiency (A1AT) is the most frequent genetic disease of childhood. It is an autosomal recessive disorder that occurs in one in every 2,000-3,000 live births.<sup>1,2</sup> The first case was described in 1963 by Laurell and Eriksson.<sup>3-5</sup>

Only 10 to 15% of affected individuals develop liver disease, which is the primary genetic cause of liver disease requiring hepatic transplantation.<sup>2,6</sup> In most cases, liver lesion is associated with the PiZZ genotype; occasionally to the PISZ, and rarely to the PiMZ.<sup>6</sup>

This report presents the alpha 1 antitrypsin deficiency observed in neonates admitted to the University Hospital (HU/CAS-UFJF) and describes its clinical manifestations with the aim of raising awareness of the associated alterations and approaches.

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## CASE REPORT

METAS, female, was born on 11/01/2011 by cesarean section indicated by fetal distress, at 41 weeks of intrauterine life. Birth weight was 2,925 g and with uneventful prenatal. Normal newborn screening.

The mother noticed fecal acholic and dark urine from the first days of life, and jaundice 15 days after birth. At one-month-old, cholestasis (bilirubin dosages in Table 1) was identified in the first newborn consultation; prophaedutics was initiated for clarification. Serology for toxoplasmosis, rubella, cytomegalovirus, herpes I and II, and hepatitis A, B, and C were negative (Table 2). Abdominal ultrasound showed no gallbladder suggesting atresia of extrahepatic bile ducts. The dosage of proteins was also performed (Table 3).

On 2011/12/08, she was admitted for cholestatic syndrome investigation in the João Penido Regional Hospital (HRJP/FHEMIG) in Juiz de Fora. Because of technical difficulties and urgency in diagnosis clarification, the intraoperative evaluation was chosen when cholangiography and liver biopsy were performed. Cholangiography was normal, ruling out the possibility of biliary atresia. Liver biopsy showed: degenerative and regenerative alterations of rare transformation in giant cells, predominantly moderate intracytoplasmic and in periportal hepatocytes, cholestasis, and absence of biliary obstruction featuring neonatal hepatitis.

On 2012/01/17, 40 days after surgery, the value of serum alpha 1 antitrypsin was 60 mg/dL (VR: 140-320) and the PiZZ phenotype was identified.

The patient remains under monitoring in the Pediatric Gastroenterology Clinic. This description was preceded by the signing of the Voluntary Informed Consent Form.

**Table 2** - Values of several serologies identified in the first year of life of the METAS patient admitted to the João Penido Regional Hospital (HRJP/FHEMIG) in Juiz de Fora, Minas Gerais between 2011 and 2012

Markers of	Serologies
Hepatitis A	Anti HAV IgG negative, Anti HAV IgM negative
Hepatitis B	Hbs Ag negative, AntiHbs-positive Anti Hbc IgM negative, Anti Hbc total-negative Ag Hbe-negative, Anti Hbe-negative
Hepatitis C	HCV Ac negative
Rubella	IgG indeterminate, IgM-negative
Toxoplasmosis	IgG negative, IgM negative
Cytomegalovirus	IgG positive, IgM negative
Herpes 1 and 2	IgG negative, IgM negative

**Table 3** - Dosage of serum proteins identified in the METAS patient at about 30 and 60 days after birth. Admitted to the João Penido Regional Hospital (HRJP/FHEMIG) in Juiz de Fora, Minas Gerais between 2011 and 2012

Protein Serum	Identification after Birth (month)	
	1	2
Total	5.85	5.6
Albumin (A)	3.7	3.1
Globulin (G)	2.15	—
A/G ratio	1.72	—

## DISCUSSION

Alpha 1 antitrypsin deficiency (A1AT) is the most common congenital disorders in Caucasians and whites; the Z variant is practically absent in Eastern individuals and those from black ethnicity.<sup>5</sup>

A1AT is encoded by *serpina1*, a gene located on the long arm of chromosome 14 where many polymorphisms have been identified.<sup>7</sup> Its main function is antiprotease activity while that of A1AT is inhibition of neutrophil elastase, proteinase 3, and cathepsin G (proteases released by neutrophils during the infectious process).<sup>2,5</sup>

**Table 1** - Values of serum bilirubins identified from the first and followed up to the fifth month of life in the METAS patient admitted to the João Penido Regional Hospital (HRJP/FHEMIG) in Juiz de Fora, Minas Gerais between 2011 and 2012

Bilirubins	Dates					
	2011/12/06	2011/12/18	2012/1/17	2012/1/19	2012/1/31	2012/4/16
Total	8.38	14.2	10.38	5.65	3.9	0.58
Direct	6.35	9.7	6.99	3.62	3.2	0.3
Indirect	2.03	4.5	3.39	2.03	0.7	0.28

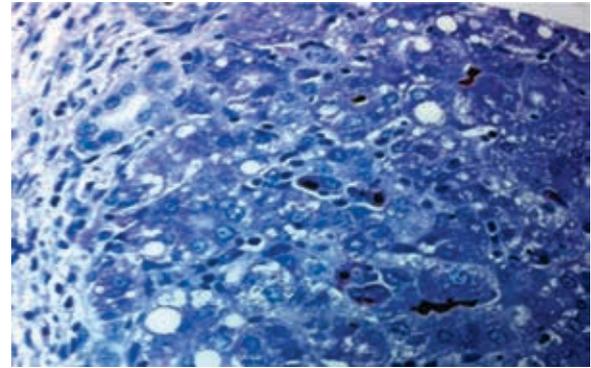
The M allele is the normal allele for forming alpha 1 antitrypsin; there are over 80 variant mutations for this gene.<sup>8,9</sup> The Z allele results from the glutamate to lysine mutation, while the S allele produces the glutamate to valine mutation. The serum levels of A1AT are reduced to 40 to 60% of normal levels in individuals with the SS, MZ, and SZ genotypes. Among non-smokers, this A1AT concentration is often sufficient to protect lungs from the effects of elastase.<sup>8</sup> Conversely, among individuals with the ZZ genotype, A1AT levels are generally less than 15% of the normal value, and these patients may develop lung disease at a young age. In addition, individuals with the ZZ genotype may develop liver disease associated with decreased secretion of A1AT and its consequent accumulation in the liver observed in the first 20 years of life.<sup>10</sup> Thus, alpha 1 antitrypsin deficient patients may present with chronic obstructive pulmonary disease (DPOC), pneumothorax, bronchiectasis, asthma, panacinar emphysema, and various liver diseases such as hepatitis, cirrhosis, and hepatocellular carcinoma.<sup>8</sup>

Prolonged jaundice is observed in approximately 10% of children with the protein Z phenotype, and about 2% of these children develop hepatic failure and require liver transplantation. With increasing age, there is a high risk of hepatopathologies.<sup>11</sup> The A1AT deficiency-associated liver disease can also be discovered in late childhood or early adolescence when abdominal distension is observed due to hepatosplenomegaly or ascites, splenomegaly, or presence of upper gastrointestinal bleeding caused by esophagus varicose veins.<sup>10</sup>

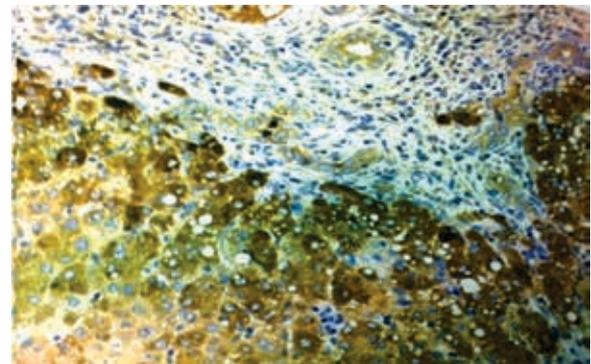
Several hypotheses are considered to justify the pathogenesis of liver damage caused by A1AT deficiency, highlighting:

- **immunity related:** wherein the liver lesion is caused by an abnormal immune response to liver antigens;
- **accumulation related (most accepted):** liver damage is justified by the accumulation of alpha 1 antitrypsin mutant molecules in liver cells.<sup>1</sup>

The mutation occurs in the substitution of lysine for glutamic acid at position 342, which results in abnormal molecule folding. The mutant protein, named ATZ, has an increased tendency to polymerization and A1AT retention in hepatocytes forming insoluble aggregates in the rough endoplasmic reticulum.<sup>1,12</sup> Deficiency is also associated with Schiff diastase-resistant globules in some hepatocytes. It is not clear why many hepatocytes do not have these globules and are called globular-less hepatocytes.<sup>12</sup>



**Figure 1** - Hepatic histopathological study: Enlargement of porta spaces, proliferation of bile ducts, biliary plugs in canaliculi, disruption of hepatic architecture, and mild steatosis.<sup>5</sup>



**Figure 2** - Immunohistochemistry: A1AT globules are observed primarily in hepatocytes close to the porta space.<sup>5</sup>

About 80% of patients are identified from the investigation of respiratory symptoms while the diagnosis is due to hepatic disease in 3% of cases.<sup>3</sup>

The diagnosis is established by determining the A1AT genotype in the serum in focus isoelectric electrophoresis or agar and acidic pH. The genotype should be determined in cases of neonatal hepatitis or unexplained chronic liver disease in older children, adolescents, and adults. This is particularly important in the neonatal period because it can be very difficult to distinguish this deficiency compared to those with biliary atresia.<sup>10</sup> The protein electrophoresis, however, has limitations because it is an acute protein phase, it may be normal or near normal.<sup>6</sup>

In the clinical suspicion of A1AT deficiency, the dosage of serum levels is recommended. The deficiency of alpha 1 antitrypsin activity (A1AT) is defined by blood levels lower than 11 mmol/L (50-80 mg/dL) associated with AAT severe genotype in the most common deficient alleles, i.e., s and z (genes related to A1AT).<sup>13,14</sup> The genotyping is performed

on a blood sample using the polymerase chain reaction (PCR) technology or analysis of the melting curve. In serum levels above 20 mmol/L (reference value as 80 mg/dL), it is unlikely that there is clinically significant deficiency.<sup>13,14</sup>

Positive/diastase-resistant eosinophilic PAS granules are detected in the histology of periportal hepatocytes, hepatocellular lesion with or without giant cell transformation, normal bile ducts with mild inflammation, varying degrees of fibrosis, ductular proliferation, and hypoplasia of intra-hepatic ducts.<sup>6</sup>

There is no specific treatment for liver disease associated with alpha 1 antitrypsin deficiency. The clinical monitoring involves, in large part, treatment of symptoms and prevention of complications. Although ursodeoxycholic acid and colchicine are mentioned in the literature, there is no evidence of the biochemical efficacy for any of these drugs.<sup>10</sup> The individual approach to the nutritional, vitamin and bile flow stimulation aspects are indicated. In cases of progressive cirrhosis, it is necessary to keep the patient in the best possible clinical conditions because he will be a candidate for hepatic transplantation.<sup>2</sup>

Carbamazepine, an anticonvulsant, and a mood stabilizer, is able to reduce the hepatic load of the A1AT mutant and hepatic fibrosis in rats improving the autophagic elimination of this mutant protein. These results demonstrate that the pharmacological manipulation of endogenous proteostasis mechanisms can be a chemoprevention strategy for these disorders.<sup>1</sup> Currently, transplantation is the only cure for the patient, correcting the metabolic defect in those undergoing this procedure. The receiver acquires the donor's phenotype, and his A1AT levels are normalized.<sup>2</sup>

The most important principle in the treatment of alpha 1 antitrypsin deficiency is to avoid smoking, which significantly accelerates the destruction caused by lung disease associated with A1AT deficiency providing significant reduction in the quality of life and shortening the longevity of affected individuals.<sup>2</sup>

## CONCLUSION

The prognosis of A1AT deficiency is variable, about 50% of patients have a good outcome, of which, half have normal aminotransferases and half have altered enzymes, however, without developing

chronic liver failure. Around 25% of cases progress to persistent cholestasis and progressive liver decompensation. In the PiZZ genotype, there seems to be an association between the severity and duration of hepatic dysfunction.<sup>6</sup> The under-diagnosis has been a significant limitation to the study of this disease and its adequate treatment.<sup>3</sup>

The approach of newborns and infants with cholestatic syndrome constitutes a major clinical challenge. It is associated with extra and intrahepatic involvement, in most cases without clinical evidence indicating a definitive diagnosis. The alpha 1 antitrypsin deficiency is among the diseases that need to be excluded when considering neonatal cholestasis.<sup>15</sup>

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