Liver Damage in a Patient with Gaucher’s Disease Type 1 and Alpha-1 Antitrypsin Deficiency: a Potential Epigenetic Effect?

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INTRODUCTION

Gaucher’s disease (GD) is the most common autosomal recessive lysosomal storage disease. It is caused by mutations in the gene that encodes the glucocerebrosidase enzyme (GCase), present on chromosome 1q21 [1, 2]. This results in enzyme deficiency and decreased lysosomal degradation of the glicosilceramide (GC) protein, leading to its accumulation within the reticuloendothelial system, especially in the liver, spleen and bone marrow [1]. This enzyme deficiency also triggers the complement system, especially C5a and C5aR1, leading to the production of IgG autoantibodies against the GC protein. While this helps regulate the balance between production and degradation of GC, it also induces a chronic inflammatory state [3]. The clinical presentation of the disease is widely variable [4, 5]. Hepatomegaly is the most common liver alteration in patients with GD. Other findings, such as chronic hepatitis, fibrosis, cirrhosis and hepatocarcinoma are uncommon, and reports of an association between GD and other chronic liver diseases are rare [4, 6-8].

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive genetic disorder. The molecular defect is the result of a specific mutation of the Serpina1 gene, leading to the synthesis of an abnormal protein (alpha-1 antitrypsin Z) which cannot be secreted, and consequently polymerizes in the endoplasmic reticulum of hepatocytes [9, 10]. The disease affects the liver, where the abnormal protein is synthesized, and the lung, which is its place of action [10]. Liver involvement is recognized in homozygous patients with the ZZ phenotype. In these patients, the presentation of the disease may vary, ranging from cholestasis to cirrhosis or hepatocellular carcinoma [11]. The presentation of the liver disease and its course can be affected by other diseases and environmental factors, and cirrhosis and liver failure generally present in patients about 50 years of age [10-12]. Until now, an association between GD and AATD was not described.

CASE REPORT

A 47-year-old Caucasian female patient diagnosed with type I GD in 2003 (at the age of 35) presented for the first time in our service in 2004 with anemia (hemoglobin level of 10.4g/dl), thrombocytopenia (88,000/mm³), hepatomegaly (twice the upper normal size), splenomegaly (three times the upper normal size) and radiological aspect of osteonecrosis of the left hip. Diagnostic examinations included measurement...
of the beta glicosidase (leukocytes) level, which was 0.15 nmol/h/mg (reference 10–45 nmol/h/mg), in addition to the genetic profile, which revealed pathogenic variants (exon 9, p. N435T, homozygous Asn435Thr), no common variants, and one variant of unknown effect (intron 8, homozygous C1225 34c>a). The patient’s parents were blood related, and she had a sister with GD. She denied drinking alcohol.

In 2004, the patient started enzymatic replacement therapy (imiglucerase at a dose of 60 u/kg). One year later, hemoglobin and platelet levels were normal (12.6g/dl and 181,000/mm³, respectively) and the liver and spleen sizes were in normal ranges. The imiglucerase dosage was reduced to 30 u/kg according to the national treatment protocol at that time. Five years later, a persistent increase in transaminase levels was observed, three times above the reference levels. She was checked for all possible causes of liver disease, viral B and C hepatitis (HbsAg, anti-Hbc IgG and anti-HCV), hemochromatosis (ferritin and transferrin saturation), autoimmune hepatitis (gama-globulin levels, ANA, AMA, ASMA and anti-LKM1 antibodies), Wilson’s disease (ceruloplasmin), drug-induced liver dysfunction (history of ingested hepatotoxic drugs or herbs), alcoholic liver disease (history or not of alcohol abuse and evaluation of liver steatosis by ultrasonography). The only alteration found was the low level of alpha-1 antitrypsin in the peripheral blood, i.e. 0.91 mg/dL (normal reference levels higher than 2.64 mg/dL, measured by the immunonephelometric method). The patient was then submitted to genetic study for AATD, which revealed a heterozygous Z mutation in the Serpina1 gene, but absence of the S mutation (real-time PCR of peripheral blood). Pulmonary involvement was not found.

In the same year, the patient was submitted to a liver biopsy (Fig. 1), which revealed cirrhosis and the presence of histiocytes with fibrillar cytoplasm consistent with Gaucher cells, and preserved ducts. There were no characteristic signs of AATD, including the presence of positive PAS granules in the cytoplasm and signs of portal or lobular inflammation. At that time, she did not show anemia or worsening of platelet levels, liver or spleen sizes, or changes in radiological examinations. Digestive endoscopy did not show any signs of esophageal varices.

The patient remained clinically stable with normal laboratory test results until 2010, when she received 3 months of irregular doses of imiglucerase, followed by 6 months without treatment due to a global shortage of the medication. The patient only returned to the required dosage in 2011. Since then, a gradual, progressive decrease in albumin levels and prolonged prothrombin activity time were observed, at which point we opted to increase the imiglucerase dosage to 60 u/kg. Even so, the disease continued to evolve, with signs of liver failure and portal hypertension, presenting with esophageal varices. The patient was classified as Child-Pugh score B and MELD score of 20, and was stated on the waiting list for liver transplant. However, she suffered an acute infection with worsening of the liver failure and subsequently passed away in 2015, at the age of 47, after 12 years of follow-up.

**DISCUSSION**

It is not common for patients with GD to develop cirrhosis and liver failure, but some do this, especially patients with long-term disease, those who are splenectomized and those with significant bone disease [4, 13, 14]. In addition, patients with AATD with a heterozygous Z mutation in the Serpina1 gene, as this patient, do not usually present with liver injury [11]. The possible role of the Z allele in the pathogenesis of chronic liver disease in heterozygous AATD patients is still controversial. Some studies provide evidence of an association between the heterozygous Z allele alpha-1-antitrypsin phenotype and end-stage liver disease of different etiologies [15-18]. The heterozygous Z mutation, however, has been identified two to five times in patients with cryptogenic cirrhosis, or in patients with cirrhosis associated with other causes of chronic liver disease, such as viral hepatitis [15]. It is important to note that phenotypical variety cannot always be explained by the mutation, and it has been suggested that other environmental and genetic factors may be involved in the clinical course and evolution of the disease [19]. The presence of this mutation in a patient with an additional genetic disturbance may present with liver injury, driven by an epigenetic factor, which might not have occurred with the mutation alone. This raises the hypothesis that the liver injury observed in our patient might
have resulted from the combination of two genetic diseases, GD and AATD, which have previously been described to be associated with other chronic liver diseases [15, 20]. It is possible that liver failure in this patient occurred due to the difficulties experienced in the treatment of GD.

CONCLUSION

This case report raises the possibility of an epigenetic contribution to the development of cirrhosis in a patient with GD and AATD, who was heterozygous for the Z mutation.

Conflicts of interest: None to declare.

Authors’ contribution: C.N.D.F. performed data statistical analysis, literature review, manuscript composition, discussion and provided patient information. V.R. participated in data statistical analysis, methodology, research design, performed data collection and systematization. J.A. B. was responsible for the genetic analysis, literature review and pulmonary data of the patient. M.L.A.P. is the head of current research, provided manuscript organization and corrections, as well as discussion. All authors read and approved the final version of the manuscript.

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