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CASE REPORT

A Rare Cause of Elevated Chitotriosidase Activity: Glycogen Storage Disease Type IV

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Abstract Human chitinolytic enzyme named "chitotriosidase" takes part in the defense mechanism against pathogens and the homeostasis of innate immunity. Chitotriosidase was firstly reported to be markedly high in plasma of patients with Gaucher disease. Abnormal lipid laden macrophages are thought to be responsible for stimulating the secretion of chitotriosidase in Gaucher disease. Subsequently, various disorders have also been found to be associated with elevated levels of chitotriosidase. Chronic liver diseases that are also related with macrophage activation may have elevated chitotriosidase activity. We report the second case of the literature with glycogen storage disease (GSD) type IV that presented with high chitotriosidase levels. GSD type IV should be taken into consideration in case of elevated chitotriosidase levels, stigmas of chronic liver disease, and inconsistency of lysosomal storage diseases.

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Abbreviations

GSD	Glycogen storage disease
LSD	Lysosomal storage disease
NPD	Niemann-Pick disease
PAS	Periodic acid-Schiff

Introduction

Chitin is an abundant polysaccharide molecule that consists of homopolymers of β-1,4-linked *N*-acetylglucosamine units and appears in the cell walls of fungi, exoskeleton of arthropods, and structures of parasites (Eide et al. 2013). Chitinases, the enzymes that are responsible for hydrolyzing chitins, were previously identified in bacteria, fungi, insects, plants, and nematods. Humans were thought to be incapable of processing chitin due to absence of chitinases. However, in 1994, Hollak et al. reported the first discovered mammalian chitinase – chitotriosidase – that was found to be significantly elevated in the serum of patients with Gaucher disease (Hollak et al. 1994; Gorzelanny et al. 2010). Chitotriosidase is mainly produced, stored, and secreted by activated macrophages and neutrophils (Kanneganti et al. 2012). Primary indication for studying chitotriosidase activity is screening for lysosomal storage diseases (LSD), especially Gaucher and Niemann-Pick disease (NPD) A/B (Sheth et al. 2010).

Elevated chitotriosidase activities have also been reported in various diseases related with macrophage activation (Michelakakis et al. 2004; Kanneganti et al. 2012; Tumer et al. 2013).

Previously, a patient with glycogen storage disease (GSD) type IV was reported with high chitotriosidase activity (Michelakakis et al. 2004). Herein, we also present

a patient with elevated chitotriosidase activity who had been investigated for LSD and finally was diagnosed with GSD type IV.

Case Report

A 3.5-year-old girl presented to the emergency department with complaints of pallor, malaise, and abdominal distension. Abdominal distension had initially been recognized at 7 months of age. She was investigated for hepatosplenomegaly and anemia in another hospital 2 years ago. On admission to our hospital paleness, fatigue, doll's face appearance, telangiectasia on the face, tachycardia with cardiac murmur (II/VI), severe abdominal distention due to ascites, enlarged firm liver (6 cm below costal margin), and spleen (8 cm below costal margin) were determined. Neurologic examination and development stages were appropriate for her age. Initial laboratory evaluation revealed hemoglobin: 4.2 g/dL, white blood cell: 7.3×10^3/ μL platelet: 113×10^3/ μL, alanine aminotransferase (ALT): 124 U/L (<39), aspartate aminotransferase (AST): 381 U/L (<52), gamma-glutamyl transferase: 92 U/L (<23), alkaline phosphatase: 301 U/L (<269), direct bilirubin: 0.4 mg/dL, total bilirubin: 1.2 mg/dL, albumin: 4.3 g/dL, total protein: 6.8 g/dL, glucose: 200 mg/dL. International normalized ratio (INR) was 1.9 and was unresponsive to parenteral vitamin K. Hematological tests for hemolysis were normal and occult blood in stool was negative. Triglyceride, cholesterol, creatine kinase, alpha1 antitrypsin, ceruloplasmin levels, and metabolic investigations (tandem mass spectrometry and urine organic acid profile) were normal. Serology of hepatitis B, hepatitis C, and parvovirus PCR was negative. Abdominal ultrasonography showed hepatosplenomegaly and coarse echo pattern of the liver. She was also investigated for lysosomal storage disease. Despite elevation of plasma chitotriosidase (1,209 nmol/h/mL, reference range: 0–90 nmol/h/mL) and two foamy cells on bone marrow aspiration, enzyme levels in white blood cells for Gaucher disease [beta glucosidase: 206 (200–2,000 pmol/spot*20 h)] and NPD A/B [acid sphingomyelinase: 454 (200–3,500 pmol/spot*20 h)] were normal. Mutation analysis for NPD type C was negative. Echocardiography was normal.

Due to bleeding diathesis, a transjugular liver biopsy was performed. Diastase-resistant periodic acid-Schiff (PAS) positive-stained intracytoplasmic material in hepatocytes and extensive periportal and parenchymal fibrosis with nodule formation revealed the diagnosis of GSD type IV with micronodular cirrhosis. Appropriate size biopsy sample for enzymatic study could not be obtained due to liver stiffness. Finally, a homozygous mutation in the GBE1 gene [p.K521E (c.1561A>G)] confirmed GSD type IV.

Discussion

Under normal conditions, chitinases in human are presumed to take part in degrading the structure of chitin in pathogens as well as organizing the homeostasis of innate immunity. Besides this, chitotriosidase activity is also known to be directly associated with acute or chronic inflammatory conditions (Kanneganti et al. 2012). In Gaucher disease, storage of glucocerebroside in macrophages causes proinflammatory activation and finally elevation of chitotriosidase. Similar mechanism is also observed in NPD. Massive increased activity of chitotriosidase is a hallmark of Gaucher disease (10–1,000-fold), while other conditions have less elevated levels (Sheth et al. 2010; Kanneganti et al. 2012). Limited reports are available about chitotriosidase levels in other LSD (Michelakakis et al. 2004; Sheth et al. 2010). Sheth et al. (2010) indicated that 76.8% of the patients with LSD such as Gaucher disease, NPD type A/B, Morquio, mucopolysaccharidosis type VI, Tay-Sachs and Sandhoff diseases, metachromatic leukodystrophy, and GM2 gangliosidosis had statistically significant elevated levels of plasma chitotriosidase. NPD type C, Krabbe disease, GM1 gangliosidosis, Wolman and cholesterol ester storage disease, fucosidosis, and galactosialidosis were also reported to have elevated chitotriosidase levels (Michelakakis et al. 2004).

Some original articles and case reports have stated that various inherited or acquired conditions related with inflammation and macrophage activation may also be associated with high chitotriosidase levels. Fungal and granulomatous infections like tuberculosis and leishmaniasis, malaria, β-thalassemia, sarcoidosis, Wegener's granulomatosis, cerebral adrenoleukodystrophy, atherosclerosis, nonalcoholic liver disease, diabetes mellitus, multiple sclerosis, Alagille syndrome, GSD type I and IV, lung and prostate cancer are the diseases in the literature that have been related with elevated plasma chitotriosidase activity and inflammation (Hollak et al. 1994; Altarescu et al. 2002; Michelakakis et al. 2004; Malaguarnera 2006; Orchard et al. 2011; Kanneganti et al. 2012; Tumer et al. 2013).

In our case, NPD was thought to be a provisional diagnosis due to the following findings: hepatosplenomegaly, early onset chronic liver disease, a few foamy cells in bone marrow aspiration, and elevated chitotriosidase level. However, normal sphingomyelinase level and negative mutation analysis for NPD type C helped us to exclude NPD type A/B and C. The second provisional diagnosis was GSD type IV. Diastase-resistant PAS positive-stained intracytoplasmic material in hepatocytes with micronodular cirrhosis and homozygous mutation in the GBE1 gene [p.K521E (c.1561 A > G)] confirmed the exact diagnosis. Despite being a novel mutation, SIFT score (0, damaging), mutation taster score (disease causing, prob: 0.999985371153983), and PolyPhen2 score (0.998- probably damaging) supported its capability about disease formation.

This mutation is placed on a conserved area in different species and there have also been other reported mutations around the position of the mutation. For example, Arg515Cys and Arg524Gln mutations were referred to as disease-causing variations in HGMD-public (Human Genome Mutation Database). This finding strongly suggests that this variation is placed on a critical region for enzyme activity.

GSD type IV (Andersen disease) is characterized by deficiency of glycogen-branching enzyme (amylo-1, 4 to 1, 6-transglucosidase) that results in accumulation of unbranched and abnormal glycogen in the liver, heart, muscle, nervous system, and skin (Ozen 2007; Escobar et al. 2012). The most common form that is named "classical hepatic form" rapidly progresses to cirrhosis in the first 18 months of age and results in hepatosplenomegaly, end-stage liver disease, and finally death due to liver failure between 3 and 5 years of life. Besides histological examination of the liver, enzyme deficiency and the result of mutation analysis of GBE1 gene confirm the exact diagnosis (Ozen 2007).

Elevated chitotriosidase activity in GSD type IV was previously stated in only one study (Michelakakis et al. 2004). In two chronic liver diseases, nonalcoholic steatohepatitis and GSD type I, lipid accumulation, and peroxidation in hepatocytes trigger activation of resident macrophages of the liver (Kupffer cells). As a consequence, this activation induces proinflammatory cytokines and results in secretion of chitotriosidase (Malaguarnera 2006; Tumer et al. 2013). Besides this, Kupffer cells also activate hepatic stellate cells that synthesize several extracellular matrix components and also induce hepatic fibrosis and ultimately liver cirrhosis. In GSD type IV, similar mechanisms may act in the elevation of chitotriosidase and fibrosis (Malaguarnera 2006; Kanneganti et al. 2012).

In conclusion, the diagnosis of GSD type IV should be taken into consideration in patients with chronic liver disease and elevated chitotriosidase activity, once Gaucher disease and NPD have been ruled out.

Take Home Message

Elevation of chitotriosidase activity is not only determined in lysosomal storage diseases but also in other macrophage activation-related conditions such as glycogen storage diseases.

Compliance with Ethics Guidelines

Conflict of Interest

Hayriye Hizarcioglu-Gulsen, Aysel Yuce, Zuhal Akcoren, Burcu Berberoglu-Ates, Yusuf Aydemir, Erdal Sag, and Serdar Ceylaner declare that they have no conflict of interest.

Informed Consent

An informed consent was obtained from the parents of the patient.

Animal Rights

This article does not contain any studies with animal subjects performed by the any of the authors.

Details of the Contributions of Individual Authors

Hayriye Hizarcioglu-Gulsen is the corresponding author. The draft of the manuscript was prepared and written by her and she is the guarantor for this report.

Aysel Yuce also participated in designation of the case report and revised it critically.

Zuhal Akcoren was responsible for histological assessment.

Burcu Berberoglu-Ates, Yusuf Aydemir, and Erdal Sag were responsible for clinical follow-up of the patient and they also participated in the drafting the manuscript.

Serdar Ceylaner performed the genetic analysis of the GBE1 gene.

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