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Familial chylomicronemia syndrome and response to medium-chain triglyceride therapy in an infant with novel mutations in *GPIHBP1*

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GPIHBP1

BACKGROUND: Severe hypertriglyceridemia predisposes to attacks of acute pancreatitis, a serious condition complicated by multiorgan failure, pancreatic necrosis, and mortality rates up to 20% in adults and 6.5% in children.

OVERVIEW: We describe an infant who suffered from an episode of acute pancreatitis from severe hypertriglyceridemia. Two major challenges complicate the case: identifying the etiology of severe hypertriglyceridemia and finding an efficacious treatment. A thorough history, physical examination, and laboratory workup failed to identify a clear etiology, prompting a genetic workup that identified compound heterozygous mutations in the glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) gene. This patient's hypertriglyceridemia responded to an infant formula rich in medium chain triglycerides (MCTs), and she remained free of pancreatitis 6 months later.

CONCLUSIONS: This case highlights the need to pursue a genetic evaluation in the absence of secondary causes of severe hypertriglyceridemia in infants. Patients with mutations in *GPIHBP1* fail to respond to currently available lipid-lowering agents so dietary management—specifically, an extremely low-fat diet and supplementation with MCT—remains the cornerstone of therapy. Treatment in infants should focus on dietary measures rather than pharmacologic agents.

Severe hypertriglyceridemia, defined as a serum triglyceride concentration of greater than 1000 mg/dL, predisposes to attacks of acute pancreatitis,[1,2] a serious condition complicated by multiorgan failure, pancreatic necrosis, and mortality rates as high as 20% in adults[3,4] and 6.5% in children.[5,6] Most cases of severe hypertriglyceridemia are multifactorial with risk factors such as obesity, ethanol intake, lipodystrophy, uncontrolled type 2 diabetes, or drugs such as estrogens, corticosteroids, HIV-1 protease inhibitors, sirolimus, and retinoic acid derivatives.

A subset of hypertriglyceridemic patients lack any secondary causes and develop severe hypertriglyceridemia because of inherited deficiencies in the proteins or enzymes involved in the clearance of triglycerides from the circulation. Such patients have familial chylomicronemia syndrome (FCS) (also called type 1 hyperlipoproteinemia, OMIM# 238600) and typically present with lipemic serum and characteristic physical findings such as eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. FCS results from autosomal recessive inheritance of rare

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mutations in lipoprotein lipase (*LPL*), apolipoprotein C2 (*APOC2*),[7] apolipoprotein A5 (*APOA5*)[8,9] lipase maturation factor 1 (*LMF1*),[10] or glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*).[11]

GPIHBP1 is the most recently discovered of these genes. The GPIHBP1 protein serves 2 major functions: to shuttle LPL across endothelial cells to the capillary lumen and to bind LPL on endothelial cells so it can catalyze lipolytic processing of chylomicrons and very low-density lipoproteins.[12] *GPIHBP1* mutations thus interfere with the transport and binding of LPL, resulting in elevations in circulating chylomicrons and severe hypertriglyceridemia.

GPIBHP1 mutations have been reported in only 12 FCS families,[11,13–16] including 3 patients we previously reported with severe elevations in triglycerides that fail to drop <1000 mg/dL. Other than an extremely low-fat diet, we lack an effective means to lower their circulating triglyceride levels and reduce the risk of pancreatitis. Here, we describe an infant who presented with pancreatitis and was identified to have novel biallelic *GPIHBP1* mutations; her hypertriglyceridemia seemed to respond to an infant formula rich in medium-chain triglycerides (MCTs).

Case presentation

The patient is a Caucasian female who was born to nonconsanguineous parents after an uncomplicated pregnancy, labor, and delivery. She was of average size with a birth weight of 3.6 kg (50th to 75th percentile) and length of 49.5 cm (50th percentile). She was first noted to have lipemic serum at 2 months of age when blood drawn for a complete blood count, done by her general pediatrician for fever and congestion, could not be analyzed because of the turbidity of the serum. Plasma triglycerides were measured to be >2000 mg/dL and confirmed upon repeat testing. She was started on 5 mL flaxseed orally twice daily and continued on exclusive breastfeeding.

The patient's mother, 27 years old, reported that her own triglycerides had been transiently elevated during the pregnancy, but returned to normal after delivery. At the time of our evaluation, her fasting triglycerides were measures to be 90 mg/dL. The patient's father, 30 years old, was healthy with normal serum lipid and lipoprotein levels. His triglycerides were 101 mg/dL. There was no known family history of pancreatitis.

At 6 months of age, the patient presented to an emergency department after 24 hours of refusing feedings, irritability, low-grade fever, and 2 episodes of nonbilious vomiting. On physical examination, she appeared well-developed but anxious. Her length was 65 cm (43th percentile); weight 7.4 kg (56th percentile). Her pulse rate was 156 beats per minute, respiratory rate 38 per minute, blood pressure 73/29 mmHg, and temperature 99.7°F. Her abdomen was distended and tender to palpation. The liver and spleen were not enlarged. Eruptive xanthomas were noted over the buttocks. Body fat distribution was normal. Laboratory testing revealed plasma triglycerides to be 2663 mg/dL, total cholesterol 107 mg/dL, and high-density lipoprotein cholesterol 20 mg/dL. The serum lipase was 692 U/L (normal 22 to 51); amylase 39 U/L (normal 39 to 214). Thyroid, liver, and kidney function tests were all within normal limits. Serum glucose was not elevated. The child was diagnosed with acute pancreatitis and admitted to the inpatient service. Oral feedings were discontinued, and she was given intravenous fluids and medications for pain. She responded well to treatment and was able to resume oral intake within 48 to 72 hours without further abdominal pain or vomiting.

At the time of hospital discharge, she was tolerating feedings of Monogen (Nutricia, Netherlands), a milk protein-based powder which is low in fat and high in MCTs. Monogen contains 25% of calories from fat, 80% of which is MCT with a 6:1 ratio of omega 6 to omega 3 essential fatty acids. After 3 months, her fasting triglycerides were 423 mg/dL. During the ensuing 6 months, she continued to tolerate the feedings well without further episodes of pancreatitis; growth and development remain normal.

Methods

All subjects gave informed consent and the study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. The exons of *LPL, APOC2,* and *GPIHBP1* were amplified from 50 ng of genomic DNA using the polymerase chain reaction and oppositely oriented oligonucleotides that flank the exons of these genes. Amplification products were sequenced using dye-terminator chemistry and an ABI 3730xl DNA analyzer. Sequence variants were verified by manually inspecting chromatograms.

Results

No disease-causing variants were identified in *LPL* or *APOC2*. In exon 2 of *GPHBP1*, the proband harbored a 4-base pair heterozygous deletion resulting in a stop codon at amino acid 79 (p.E28fs), and in exon 3 she harbored a heterozygous nonsense mutation at amino acid 89 (p.C89X). Neither of these mutations has been reported previously. Her father harbored the heterozygous C89X mutation and her mother harbored the heterozygous E28fs mutation (Fig. 1).

Discussion

We describe an infant who suffered from an attack of acute pancreatitis resulting from severe hypertriglyceridemia. She harbors previously unreported biallelic mutations in *GPIHBP1*, and treatment with MCT-rich formula