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CASE REPORT

Familial chylomicronemia syndrome: case report

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Abstract

Objective: To report a case of familial chylomicronemia syndrome diagnosed in an infant after admission to the intensive care unit for acute pancreatitis and to conduct a brief review of the literature on the subject. **Case Description:** Male infant with a history of irritability, low weight gain and regurgitations since 15 days of life, with progressive worsening. At 3 months of age, developed bilious vomiting and dehydration, requiring hospitalization. Metabolic acidosis and hypertriglyceridemia were evidenced, in addition to the lipemic aspect of the serum. Strict venous hydration was instituted, zero diet and antibiotic therapy, with clinical improvement and drastic reduction of serum triglycerides. After suspected familial chylomicronemia syndrome, skimmed-milk diet was started and specific molecular test was collected, which later confirmed the diagnosis. After hospital discharge, he was referred to the pediatric endocrinology clinic for follow-up. **Comments:** The description of a rare case of severe dyslipidemia is an essential tool for clinical suspicion, allowing for proper management and reduction of complications and risk of death.

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INTRODUCTION

Familial chylomicronemia syndrome (FCS) is an extremely rare autosomal recessive disorder, with an estimated incidence of one case in 1,000,000 people[1]. It is characterized by severe hypertriglyceridemia and originates from mutations in genes associated with lipoprotein lipase (LPL) activity, the enzyme responsible for lipolysis and clearance of chylomicrons in plasma. Mutations in the LPL gene account for more than 90% of the cases of FCS[2].

Clinical manifestations may present in early childhood or in young adults, and include eruptive xanthomas, serum lipemia, lipemia retinalis, hepatosplenomegaly, abdominal pain, among others. The main complication is acute pancreatitis, which can be recurrent and progress to pancreatic necrosis or chronic pancreatitis[3,4]. The diagnosis of FCS is based on clinical, laboratory and genetic findings[5].

This report describes a case of familial chylomicronemia syndrome diagnosed in a three-month-old infant.

CASE REPORT

SBM, aged three months, born in Patu, RN, Brazil, presented with irritability, regurgitation and low weight gain from 15 days of birth, and gradually worsening symptoms. At the age of three months, he was taken to the emergency unit with bilious vomiting and dehydration. Serum lipemia was observed in a blood sample (Figure 1). Laboratory tests revealed anemia, thrombocytopenia, severe hypertriglyceridemia, and changes in liver and kidney function. He was referred to the pediatric ICU for clinical stabilization.

He was the first child of healthy, distantly related parents. Prenatal care was uneventful. He was born from a cesarean section due to placental abruption at 35 weeks of gestation and was described as AGA. He was exclusively breastfed until one month of age, and has been given the formula since. Three days after admission, the formula was replaced with whole milk. His parents said he had not been hospitalized yet and did not have a history of disease.

During hospitalization in the ICU, familial chylomicronemia syndrome complicated with acute pancreatitis was considered (Balthazar A) upon confirmation of severe hypertriglyceridemia. The patient was maintained on a zero diet for six days and on rigorous intravenous hydration and antibiotic therapy. After this period, he was started on a skimmed milk-based diet. The patient progressed satisfactorily, with a significant drop in triglyceride levels (Table 1), without the need for plasmapheresis. Genetic material was collected using a buccal swab for a familial chylomicronemia syndrome panel, showing a homozygous mutation in the LPL gene, which confirmed the diagnosis.

After 10 days of hospitalization, he was discharged and referred to the pediatric endocrinology and nutrition outpatient clinic for follow-up.

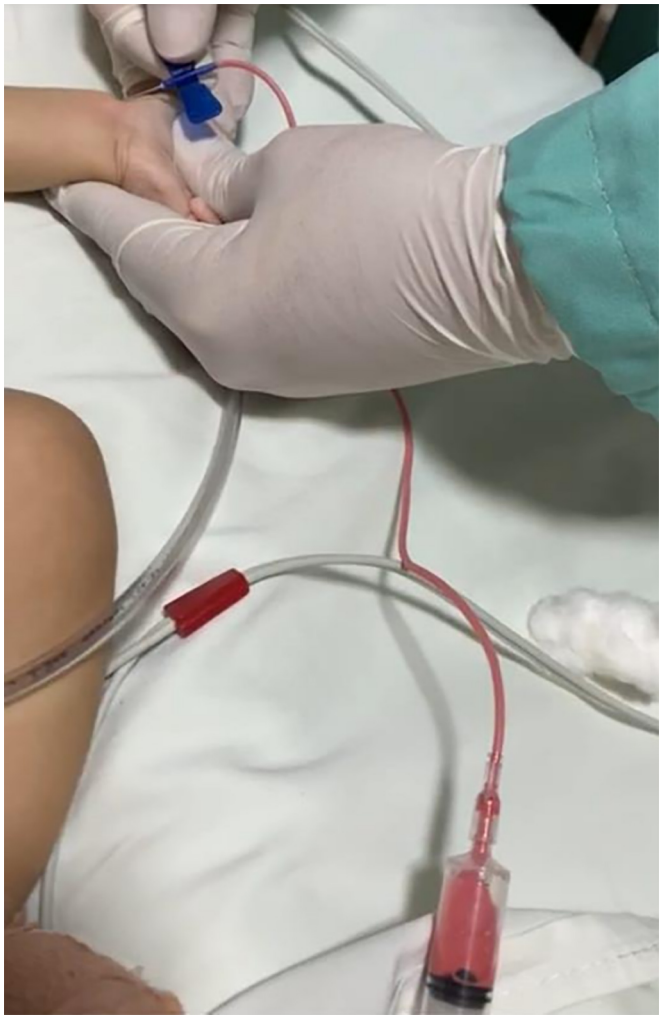


Figure 1. Serum lipemia seen during blood sample collection.

DISCUSSION

Lipid disorders in children and adolescents may result from defects in the production, transport or degradation of lipoproteins. Genetic mutations may cause some of these disorders, which have been described as primary dyslipidemias. These, in turn, may present as disorders of cholesterol metabolism, VLDL overproduction disorder and severe hypertriglyceridemia, with familial chylomicronemia syndrome as one of the conditions in the latter group[6].

Familial chylomicronemia syndrome, traditionally known as hyperlipoproteinemia type 1 (Fredrickson Classification)[7,8], is a rare autosomal recessive disease characterized by the accumulation of chylomicrons in blood. These are large triglyceride-rich lipoprotein particles produced by the enterocytes after a meal. Under physiological conditions, chylomicrons are rapidly cleared from plasma by lipoprotein lipase (LPL), an enzyme located on the endothelial surface of adipose and muscle tissue. In patients with FCS, due to biallelic

Table 1. Laboratory test results during ICU stay in 2019.

	Oct. 6	Oct. 7	Oct. 8	Oct. 9	Oct. 10	Oct. 11	Oct. 12	Oct. 15
Triglycerides (mg/dL)	5661.6	2720	1426.8	1689.5	1186.61	590.63	401.56	217.72
Total Cholesterol (mg/dL)	1202.5	736.5	-	608	463.71	384.89	353.66	378.5
Blood glucose (mg/dL)	582.43	389.92	237.2	-	-	104.04	106.74	81.88
Creatinine (mg/dL)	No reading		0.19				0.42	
Urea (mg/dL)	48.3		7.39				15.66	
AST (U/L)		860.2	19.3		23.85		36.36	
ALT (U/L)		210.4	40.6		97.61		13.82	
Lipase (UI/L)	304.1	107.2	148.5	216.2	116.9	69.4		
Amylase (UI/L)						16.25		

mutations in the genes associated with LPL, clearance of chylomicrons from plasma is impaired[9]. The LPL gene accounts for 90% of the cases of FCS, although four other genes are also involved in LPL function, namely APOC2, APOA5, LMF1 and GPIHBP1[10].

FCS is characterized in laboratory tests by very high plasma triglyceride levels (> 10 mmol/L or 880 mg/dL). A tell-tale sign is a plasma with a viscous, creamy appearance, due to the presence of a large number of chylomicron particles[6,9].

Affected individuals may be asymptomatic or present different symptoms, which usually appear during childhood or adolescence[4]. Recurrent abdominal pain is one of the main symptoms, with intensity ranging from mild to disabling. Patients with FCS are at high risk of developing acute pancreatitis (50 to 80%), a more serious complication, with a mortality rate ranging between 5 to 30% in adults and 5% in children[3]. Episodes of acute pancreatitis may recur, predisposing patients to developing chronic pancreatitis, permanent damage to pancreatic tissue, pancreatic insufficiency and type 3 diabetes. The risk of developing pancreatitis increases when triglyceride levels are > 885 mg/dL and increases dramatically when levels are > 1800 mg/dL, although most cases develop in individuals with levels > 3000 mg/dL[2,9,11].

Other symptoms include transient eruptive xanthomas, present in <50% of patients, often appearing on the trunk and extremities, and lipemia retinalis, a creamy white discoloration of the retinal vessels. Hepatosplenomegaly can also result from triglyceride uptake by macrophages. Neurological symptoms such as irritability, memory disorders, dementia and depression have also been documented. Patients with FCS tend to be thin due to dietary restrictions to control abdominal pain. The impact of the disease is such that quality of life and activities of daily living, including work, can be adversely affected[9].

Patients suspected with FCS must be tested for severe and refractory hypertriglyceridemia, with triglyceride levels > 880 mg/dL in three consecutive blood tests, with little or no benefit observed with standard lipid-lowering therapies[3]. Furthermore, any secondary causes of hypertriglyceridemia must be excluded, such as alcoholism, obesity, insulin resistance, severe hypothyroidism, uncontrolled diabetes, chronic kidney disease, nephrotic syndrome, inadequate diet and use of lipid-lowering medications, such as beta blockers, oral estrogens, retinoids, atypical antipsychotics, bile acid binding resins, protease inhibitors, corticosteroids, and tamoxifen[2].

Although described in the literature, post-heparin LPL activity measurement for confirmatory diagnosis is not widely available and produces variable results[3]. Complete sequencing of the LPL gene and of the four other associated genes is the gold standard method for accurately determining the basis of the metabolic disorder[4]. A molecular diagnosis can help in early identification of at-risk family members and finding the best candidates for emerging therapies, particularly young patients[2].

In the acute treatment and management of pancreatitis, food intake is interrupted to stop lipoprotein production and decrease triglyceride levels by half every 48 hours. Supportive measures must be implemented, such as intravenous hydration, pain management and frequent monitoring of complications, such as pancreatic necrosis or pancreatic abscesses. In very severe cases, plasmapheresis or hemodialysis may be required[2,11].

Long-term treatment requires regular multidisciplinary monitoring to maintain triglyceride levels below the threshold for risk of pancreatitis[3]. Currently, nutritional therapy is an essential element in the management of patients with FCS. It includes offering them a very low-fat diet (20 g of fat per day, corresponding to 15% of daily calories), limited to simple and refined carbohydrates. Infants diagnosed with FCS require a special low-fat formula (but high in medium-chain triglycerides) or fortified skimmed breast milk[12].

Standard lipid-lowering drugs (fibrates, statins, niacin, omega 3) are minimally effective, since their mode of action relies on a functional LPL lipolytic pathway[3]. Increased understanding of molecular characteristics has allowed the development of improved gene therapies. Volanesorsen, an antisense oligonucleotide inhibitor of APOC3, has been released and prescribed in Europe as an adjuvant to diet in adult patients at high risk of pancreatitis with genetically confirmed FCS, in whom response to diet and therapy to decrease triglyceride levels was poor[13]. There are currently no Food and Drug Administration (FDA)-approved treatments for FCS[12].

CONCLUSION

FCS is a rare genetic lipid metabolism disorder that, in addition to compromising one's quality of life, has been associated with serious complications, such as pancreatitis. A common trait among patients with FCS is late diagnosis due to lack of knowledge about the disease among health care workers[3]. Clinical suspicion, based on symptoms, medical history and laboratory data, allows for a better approach to optimize treatment and management of all aspects of patient care.

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