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Case Report (Pages: 5839-5842)

Lipoprotein Lipase (LPL) Gene Mutation: A First Report in Children

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Abstract

Genetic hyperchylomicronemia is a rare autosomal recessive disorder of lipoprotein metabolism estimated to affect approximately one per million individuals. We report a case with a rare mutation identified. It's a genetic chylomicronemia in a Moroccan newborn baby, with massive hypertriglyceridemia and clinical signs of acute pancreatitis. She was a newborn female, first-degree of consanguineous parents. She was hospitalized for hypertriglyceridemia, complicated by acute pancreatitis; serum was noted to be milky. The genetic study found a mutation of the Lipoprotein Lipase (LPL) gene: homozygous pathogenic variant c.1019-3C > A.

She enjoyed good health, developed well and the triglyceride was maintained at a concentration of <12 g/l, after a digestive rest of five days. This mutation is the second case discovered in the world and the first case in children. The identification of the molecular etiology of these dyslipidemias explain the wide variety of phenotypes observed, some of which are accessible to targeted therapies.

***Key words*:** Children, Hyperchylomicronemia, LPL gene, Mutation, Pancreatitis.

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1- INTRODUCTION

Familial hyperchylomicronemia is a rare autosomal recessive disorder of lipoprotein metabolism, estimated to affect approximately one per million individuals (1). This disorder characterized by extremely high triglyceride (TG) levels in fasting serum due to the accumulation of chylomicrons.

Major hypertriglyceridaemia is the only emergency in lipidology. Its severity is linked to risk of acute pancreatitis, which is life-threatening. In the LPL gene, many mutations responsible for LPL deficiency have been identified. We report a very rare mutation of the LPL gene, the second in the world and the first identified in a newborn.

2- CASE REPORT

We report the case of a Moroccan newborn, was incidentally found to have hypertriglyceridemia. He was hospitalized in the neonatal intensive care unit, Mohamed VI University Hospital. The mutation in her LPL was a very rare one. A Moroccan baby girl was born at term, from a primipara mother. Both parents were healthy and the marriage was first degree consanguineous. She was admitted in neonatology for fever with persistent crying. Clinical examination revealed hepatomegaly and the rest was normal.

An infectious etiology was suspected at the beginning, blood count, C-reactive protein, lumbar puncture and blood culture were normal. Serum was noted to be milky. Further investigations showed elevated triglyceride concentration (92.02 g/L). Her liver and renal function, hemoglobin, glucose and amylase concentrations were all normal. The diagnosis of acute pancreatitis developed from hypertriglyceridemia was confirmed: Lipase levels at 6.6-fold normal and abdominal CT scan showed acute pancreatitis stage C. The creaming test showed the exclusive presence of chylomicrons (exogenous lipids) suggestive of Hyperlipoproteinemia type 1. No familial history of premature atherosclerosis, pancreatitis or lipid disorders. The diagnosis of lipoprotein lipase deficiency was made when subsequent mutational analysis of the LPL gene showed a mutation: homozygous pathogenic variant c.1019-3C > A.

The development was favorable after a digestive rest of five days, feeding was resumed with specialized soy milk. No medium chain triglyceride (MCT) was prescribed (Non available in Morocco). The evolution was marked by the normalization of the pancreatic function at 5^{th} day and its lipid profile showed a decrease in triglyceride (TG) level to 12 g/l, after 15 days.

The outcome was good, with normal clinical development and an important decrease of TG to 5 g/L. We summoned her parents for genetic counseling, sibling and relatives to check their lipid profiles and LPL genotypes.

3- DISCUSSION

Familial chylomicronemia syndrome (FCS) or Primary hyperchylomicronemia is a rare inherited metabolic disorder with autosomal recessive transmission, characterized by extremely high triglyceride levels due to the accumulation of chylomicrons in the blood. The pathophysiology of FCS relies on the lack of a functional LPL enzyme that affects the catabolism of triglyceride-rich lipoproteins, in particular CM and very low density lipoproteins (VLDL), after fat intake (2).

Family hyperchylomicronemia syndrome may also be consequent to other rare genetic disorders like Apolipoprotein CII (apoC-II), Apolipoprotein A5 (ApoA5), Lipase Maturation Factor 1 (LMF1) and Glycosylphosphatidylinositol anchored

high density lipoprotein binding protein 1 (GPI-HBP1) deficiency (2). Currently, full gene sequencing of LPL and the four cofactor genes is the preferred method in establishing the diagnosis in patients with suspected FCS (3). Mutations in the LPL gene is responsible of for more than 95% of the cases of Familial chylomicronemia syndrome FCS reported in literature (4).

In patients with Primary hyperchylomicronemia, lipoprotein lipase activity can be absent or markedly decreased (5). Gene encoding LPL is located at position 8p22 and comprise 10 exons (6). The first mutation of the LPL gene was reported in 1989 (7). More than 200 different mutations have been described with variable phenotypes depending on the nature of the mutations. The most frequent are missense mutations in exon 5 and 6 affecting the catalytic site of the enzyme (AA 120-216) (8).

In this study, we describe a 3-day-old newborn that incidentally was found to have severe Hypertriglyceridemia (HTG) while taking his blood sangles. Primary hyperchylomicronaemia by homozygous mutation of LPL was diagnosed. Its expression is an important and complex post-transcriptional regulation. This mutation of the LPL gene was a "homozygous pathogenic variant c.1019-3C> A", the second time described in the literature. In 1994, in an adult patient with primary hyperchylomicronaemia, a mutation of cytosine (C) to adenine (A) mutation at position 3 was reported. On the same allele they detected, there were four polymorphic variations in the LPL gene (9). This case is a report of the first same LPL mutation in children, diagnosed during the neonatal life.

Patients with two defective LPL alleles have no or markedly reduced LPL activity. They typically present in early childhood with recurrent colicky abdominal pain, acute pancreatitis, hepatosplenomegaly, eruptive xanthomatosis and lipemia retinalis. This neonate didn't have any xanthomatosis or lipemia retinalis, however the HTG was complicated with acute pancreatitis, resolved after dietary restriction of fat. Heterozygous carriers with one defective LPL allele may have normal to moderately increased fasting triglyceride concentrations (10).

The management of this disease, is base on nutritional support: fat restriction which should be continued throughout life. Medium Chain Triglycerides (MCTs) is recommended for patients with chylomicronemia. No data for newborns are available concerning the medical management. Thus, genetic diagnosis, oriented by the clinical and biochemical parameters, allows, in addition to the possibilities of family screening, to start a dietetic and/or medical treatment to decrease or even to suppress the possible consequences of the metabolic disorder induced by the molecular anomaly causal relationship.

4- CONCLUSION

The diagnosis of familial hyperchylomicronemia, due to its low frequency, is not always considered. Identification of the molecular etiology of these dyslipidemias explains the wide variety of phenotypes observed, some of which are accessible to targeted therapies.

5- CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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