Lipoprotein Lipase Deficiency in an Infant

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Patients with isolated hypertriglyceridemia usually present with recurrent abdominal pain, pancreatitis, eruptive xanthomas, lipemia retinalis and hepatosplenomegaly. We describe the diagnosis and treatment of an infant with severe hypertriglyceridemia. The child was found to be heterozygous for two novel mutations in the lipoprotein lipase gene.

Key words: *Hypertriglyceridemia, Lipoprotein lipase deficiency, Lipemia retinalis, Medium chain triglyceride oil, Mutation analysis.*

Lipoprotein lipase (LPL) is the rate-limiting enzyme for the hydrolysis of triglycerides in chylomicrons and very-low-density lipoproteins (VLDL). LPL is active as a homodimer; for full enzymatic activity, the presence of apolipoprotein (apo) CII is required as a cofactor. The LPL gene is located on chromosome 8p22 and as a result of mutations in this gene, the enzyme is either not produced or becomes catalytically inactive [1].

Genetic deficiency of LPL or its cofactor apo CII causes type I hyperlipoproteinemia syndrome, which is characterized by the presence of chylomicrons (CM) in fasting plasma and a marked increase in plasma triglyceride levels. The estimated prevalence for Western countries is 1 in $1:10^6$ [1].

CASE REPORT

A 38-day old male baby was referred for evaluation in genetic clinic following the observation of lipemic (milky) serum during the evaluation for fever. Baby was the first child born to non consanguineous parents with a birthweight of 3.5 kg and was exclusively breastfed. He had hepatomegaly of 4 cm below right costal margin. Fundus examination revealed lipemia retinalis. There were no eruptive xanthomas. Laboratory studies showed serum triglycerides of 8874 mg% and cholesterol 659 mg%. Lipoprotein electrophoresis showed very high levels of pre β lipoproteins and presence of chylomicronemia, thyroid function tests were normal, and SGOT was 480 IU/L, SGPT 120 IU/L and alkaline phosphate was 1150 1U/L. Total serum protein was 11.3 g/dL and albumin was 5.1 g/dL and globulin was 8.1 g/dL. Ultrasound study of abdomen was normal. Hemoglobin was 19.9 g/dL, whereas the RBC count was only 3.07 m/uL. In presence of extremely elevated triglyceridemia with moderate elevation of cholesterol, lipemic serum and lipemia retinalis, possibility of familial LPL deficiency or apolipoprotein C II deficiency were considered. LPL mass measurement could not be performed due to non availability of this test in India.

To analyze the underlying molecular defect, complete apoC II gene, the promoter, and all 10 exons of the LPL gene were sequenced. The apo CII gene showed no change, whereas two novel mutations were detected in the LPL gene: +3insT in intron 1, which was transmitted together with the Ser447Stop variant by the mother. The possibility that the insertion in intron 1 disturbs the splicing of the LPL mRNA is very high because in the consensus sequence for splicing the nucleotide T at position +3 has the lowest probability [2]. The second mutation is a C/T exchange in exon 5 leading to the change of proline 214 into serine and it was transmitted by the father. Exon 5 codes for a portion of a hydrophobic pocket in which the proposed catalytic triad is located. It is very likely that the exchange of proline by the hydrophilic serine will lead to an inactive enzyme. This is supported by the very strong conservation of the protein sequence of this area in mammals.

Baby was started on a fat restricted diet from 40th day of life. There was a dramatic decrement in the serum triglycerides (TG) and cholesterol levels after 2 weeks of introduction of completely skimmed milk and medium

chain triglycerides (MCT) oil. 10% of the caloric need was provided by MCT oil. Baby was also given multivitamin drops and vitamin E supplementation. Four weeks after starting this modified diet there was significant improvement in biochemical parameters.

40 days after initiation of therapy, the fundus evaluation showed near normal level vessels and retina. Semisolids were introduced at 4th month and he was entirely switched to skimmed milk. Baby was monitored once monthly and now the baby is 24 months old and has normal growth and development and is on normal diet, skimmed milk, MCT oil and multivitamins.

DISCUSSION

Familial hyperchylomicronemia syndrome is an autosomal recessive disorder which results from LPL deficiency, apolipoprotein CII deficiency or familial inhibitors to LPL. Patients with this disorder have increased risk of pancreatitis and they present with hepatosplenomegaly, lipemia retinalis and eruptive xanthomas. Recurrent pancreatitis ultimately leads to pancreatic insufficiency, which is the major threat of this disease [3]. About 25% of patients with familial chylomicronemia manifest complications before the age of one year and majority develop before 10 years and the most common symptoms include severe recurrent colicky abdominal pain, failure to thrive and acute pancreatitis [4]. TG levels above 2000 mg/dL predisposes to pancreatitis. High TG values lead to false low value for sodium, hemoglobin and bilirubin [5].

Detection of LPL mass and activity in the plasma of affected patients after heparin administration is one way to search for the underlying defect of LPL deficiency but these assays are not freely available and therefore the genetic analysis is becoming the most readily applied diagnostic method [6].

The parents, heterozygote for one LPL mutation, did not show any abnormalities in their lipids. Heterozygous carriers of LPL deficiency have moderate elevation of TG and decrease of HDL and they are predisposed to development of ischemic heart disease [5].

The mainstay of management is strict adherence to fat restriction which should be continued throughout life. MCT is recommended for patients with chylomicronemia as it is directly absorbed into the portal circulation [5]. Addition of coconut oil for cooking helps to provide MCT. The ultimate aim is to maintain TG values < 2000mg/dL so that it decreases the risk of pancreatitis.

Lipid lowering drugs are not very effective in familial LPL deficiency and gene therapy is in its infancy [5,7]. Once the chylomicronemia is cleared, the patient is advised to consume a non-fat rice based diet, fruits with small portions of fish and meat. Life style management includes physical activity which also helps to decrease TG [8]. Diet modification should start as early as possible and therefore detailed evaluations of those infants are strongly recommended when lipemic serum is detected during routine evaluation.

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