A NEW CASE OF LIPOPROTEIN LIPASE DEFICIENCY

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ABSTRACT

We describe a new case of lipoprotein lipase (LPL) deficiency in a 33 year old man with a history of milky serum, severe hypertriglyceridemia with hyperchylomicronemia and recurrent episodes of acute pancreatitis.

Analysis of the complete coding sequence, with intronic boundaries, and the promoter region of the LPL gene of the propositus revealed a G-->C transversion at the 5' donor splice site of intron 1. We suggest that this mutation is not compatible with normal mRNA processing and it is responsible for the defect in our patient.

INTRODUCTION

Lipoprotein lipase (LPL-triacylglycerolprotein acylhydrolase) has a pivotal role in the metabolism of plasma lipoproteins.

Active LPL is a noncovalently linked homodimer of a glycoprotein of 448 amino acids, 54 KD m.w. (1,2). It is synthesized mainly by parenchimal cells of adipose tissue, heart and muscle. It is then transported to the luminal surface of capillary endothelial cells where it presumably binds to heparan sulfate.

To hydrolyze triglycerides to di- and monoglycerides and free fatty acids, LPL requires the binding of a specific co-factor, the apolipoprotein (apo) C-II.

The LPL gene has been mapped on the short arm of human chromosome 8 (3). It extends over 30 kb and consists of 10 exons interrupted by 9 introns (4-6).

Human LPL cDNA has been cloned and its sequence reported. It includes a region of 1425 nucleotides coding for a protein of 475 aminoacids which becomes a mature protein of 448 residues after cleavage of a 27 residue signal peptide (5,6).

LPL deficiency is a rare autosomal recessive disorder occurring with a carrier frequency of 1/500 in most parts of the world, one notable exception being Quebec (2,7). Fasting plasma from these patients reveals type I hyperlipoproteinemia with triglyceride concentration above 2000 mg/dl, normal or slightly elevated cholesterol in total plasma and in very low density
lipoproteins (VLDL), and markedly reduced cholesterol concentration in low and high density lipoproteins (LDL and HDL). LPL activity in post-heparin plasma is typically absent, in the presence of normal levels of apo C-II. Hepatic lipase (HL) is normal.

The clinical syndrome of LPL deficiency is characterized by severe hypertriglyceridemia with chylomicronemia, abdominal pain, recurrent acute pancreatitis, lipaemia retinalis, eruptive xantomata, hepato-splenomegaly and failure to thrive.

Several LPL gene mutations have been identified (7-23): 10 of them were missense mutations, 4 nonsense mutations, 1 frameshift, 2 splice site mutations (intron 2), 1 large deletion (6 kb) and 1 duplication (2 kb).

We describe a new case of LPL deficiency due to a point mutation in the 5' splice site of intron 1.

METHODS

Clinical Data

The proband is a 33 year old male. He presented at the age of 16 with a history of severe recurrent abdominal pain and milky serum. The first serum lipid analysis revealed a typical hyperlipoproteinemia phenotype I, with chylomicronemia and a triglyceride level of 2160 mg/dl. The electrophoresis of post-heparin plasma failed to show the typical increase in pre beta and beta electrophoretic mobility and measurement of post heparin lipolytic activity (PHLA) with radiolabeled triolein showed none or only trace amounts of LPL activity while HL activity was normal. Apo C-II, evaluated in native serum by radial immunodiffusion and in VLDL by isoelectric focusing, was normal.

Subsequently, the patient entered the hospital several times suffering from recurrent pancreatitis. In these circumstances, his serum triglyceride level was above 3000 mg/dl. A low fat diet (20 g/day) and substitution of fats with medium chain triglycerides (MCT) reduced the level of serum triglycerides below 1000 mg/dl.

On physical examination, using ecotomography and C.T.scan, the patient showed a normal physical growth, typical lipaemia retinalis, moderate hepatomegaly but no splenomegaly, Histological examination of liver biopsy showed the presence of steatosis, scattered foci of hepatocyte necrosis and slight fibrosis of portal areas. Cutaneous eruptive xantomata were never observed.

Recent fasting plasma lipoprotein values were: triglycerides 1910; cholesterol 269; LDL-cholesterol 39; HDL-cholesterol 11 (expressed in mg/dl).

Laboratory methods

Blood samples were obtained in the fasting state from the proband, parents and siblings. Post-heparin plasma was obtained from blood taken 10 mins after an intravenous bolus of heparin administered at 60 U/kg body mass. Protease inhibitor aprotinin (trasylol) was added to the samples at 25 IU/ml. Aliquots were either assayed immediately or stored at -80° C.

Lipoprotein fractionation (by preparative ultracentrifugation, delipidization and isoelectric focusing of apolipoproteins), cholesterol and triglyceride evaluation and serum apolipoproteins quantitation with specific antibodies, were all performed as previously reported (24). Plasma lipoprotein (a) level (Lp(a)) was evaluated by enzyme immuno-assay (IMMUNOZYM Lp(a)-Immuno AG A-1220 WIEN).