CLINICAL STUDY

Acquired lipoprotein lipase deficiency associated with chronic urticaria. A new etiology for type I hyperlipoproteinemia

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Abstract

Type I hyperlipoproteinemia (type I HLP) is a rare disorder of lipid metabolism characterized by fasting chylomicronemia and reduced postheparin plasma lipoprotein lipase (LPL) activity. Most cases of type I HLP are due to genetic defects in the LPL gene or in its activator, the apolipoprotein CII gene. Several cases of acquired type I HLP have also been described in the course of autoimmune diseases due to the presence of circulating inhibitors of LPL. Here we report a case of type I HLP due to a transient defect of LPL activity during puberty associated with chronic idiopathic urticaria (CIU). The absence of any circulating LPL inhibitor in plasma during the disease was demonstrated. The LPL genotype showed that the patient was heterozygous for the D9N variant. This mutation, previously described, can explain only minor defects in the LPL activity. The presence of HLP just after the onset of CIU, and the elevation of the LPL activity with remission of the HLP when the patient recovered from CIU, indicate that type I HLP was caused by CIU. In summary, we report a new etiology for type I HLP – a transient decrease in LPL activity associated with CIU and with absence of circulating inhibitors. This is the first description of this association, which suggests a new mechanism for type I HLP.

European Journal of Endocrinology 141 502–505

Introduction

Lipoprotein lipase (LPL) is the major enzyme responsible for the hydrolysis of triglycerides transported by chylomicrons and very low density lipoproteins (VLDL). LPL is present as an active dimer which is noncovalently linked to proteoglycans in the endothelial wall, where it can be transferred to chylomicrons and VLDL. Apolipoprotein (apo) CII, carried by the target lipoproteins for LPL, is the physiological activator of LPL in plasma.

Type I hyperlipoproteinemia (type I HLP) is a rare disorder of lipid metabolism characterized by fasting chylomicronemia, with subsequent hypertriglyceridemia, and reduced postheparin plasma LPL activity. This hyperlipoproteinemia is due to a decreased hydrolysis of triglycerides transported in chylomicrons and VLDL. Type I HLP is characterized clinically by repeated episodes of abdominal pain, with or without pancreatitis, eruptive cutaneous xanthomatosis and hepatosplenomegaly. Three inherited disorders have been described to be responsible for type I HLP, two of them being autosomal recessives (familial LPL deficiency and familial apo CII deficiency), and the third

showing an autosomal dominant mode of transmission (familial inhibitor of LPL) (1).

Several cases of acquired type I HLP have also been described in the course of autoimmune diseases, such as systemic lupus erythematosus (2, 3), idiopathic thrombocytopenic purpura and Graves' disease (4). The mechanism in these autoimmune disorders is probably related to the presence in plasma of a circulating autoantibody directed against LPL, as demonstrated by Pruneta *et al.* (5) in a case of autoimmune type I HLP.

We report one case of acquired type I HLP in a 13-year-old girl, associated with chronic idiopathic urticaria (CIU). This is, to our knowledge, the first description of this association, and the first acquired form of type I HLP not related to the presence of circulating inhibitors of LPL.

Case report

A 13-year-old girl was referred to Miguel Servet Hospital for evaluation of severe hypertriglyceridemia. No family history of hyperlipidemia, pancreatitis or coronary heart disease was present. Her aunt had

Table 1 Lipid, apolipoprotein, lipoprotein and lipolytic activities from the patient. All concentrations pre- and post-urticaria are means of two different determinations, except for LPL and HL activities. Lipid and apolipoprotein concentrations during urticaria phase are means[#] of at least 6 different determinations, except for LPL and HL activities (each from one determination).

	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-C (mg/dl)	Apo AI (mg/dl)	Apo B (mg/dl)	Chylomicrons (%) [#]	LPL (mU/ml)	HL (mU/ml)
Pre-urticaria	191	56	nd	nd	nd	nd	nd	nd
During urticaria	193	1352	15	86	65	64	8	78
Post-urticaria	168	58	40	115	57	0	21	82
Controls (n = 2)	196	98	48	138	77	0	47	109

HDL-C, high density lipoprotein cholesterol; nd, not determined.

[#] Percentage of total lipoproteins contained in chylomicron subfraction observed by cellulose acetate gel electrophoresis.

systemic lupus erythematosus and she was also normolipidemic.

Previous lipid analysis at 7 and 10 years of age were normal (Table 1). At the age of 11, three months before menarche, generalized skin lesions consisting of itchy edematous papules and wheals, frequently associated with angioedema, occurred. Skin lesions appeared in crises and after a few months urticaria episodes presented almost daily in spite of histamine antagonist treatment. After the appropriate diagnostic testing, she was diagnosed as having CIU. Four months after the onset of CIU, a blood test revealed the presence of severe hypertriglyceridemia (triglyceride concentration 2122 mg/dl). During the following three years her triglyceride levels remained elevated ranging from 375 to 2765 mg/dl (Table 1) in spite of various diet and drug treatments. The lowest triglyceride levels during this period were obtained after severe fat restriction (< 10% of total calories from fat) and 100 mg/day fenofibrate. Throughout this period, she presented with several acute episodes of abdominal pain with normal amylase (some of them required hospitalisation) and unexplained crises of blurred vision. During this three-year period no medication other than H1 receptor antagonists were prescribed for her urticaria.

At the age of 15, crises of urticaria became less frequent until they spontaneously disappeared. Her triglycerides returned to normal values (Table 1), fenofibrate treatment was stopped, and the diet was progressively less restricted in fat. After 6 months without any lipid lowering drug and with a standard free living diet (35% calories from fat) her triglycerides were 44 mg/dl. A new determination of her LPL activity showed an increase up to 21 mU/ml, an increment of 260% (Table 1).

Methods

Lipid plasma concentrations in the proband, her parents, sister and maternal grandparents were obtained after at least 10 h fasting. Measurements of total plasma cholesterol and triglycerides were determined by enzymatic methods, high density lipoprotein (HDL) cholesterol was assayed after precipitation with magnesium-phosphotungstate (Boehringer Mannheim,

Germany), and apolipoprotein AI and B concentrations were quantified by rate immunonephelometry (Beckman, USA). All lipid analyses were performed in a laboratory participating in a lipid standardization program. Plasma lipoproteins in the proband were visualized after electrophoretic separation on cellulose acetate and Sudan black staining.

Cholesterol and triglyceride levels were, respectively, 212 mg/dl and 74 mg/dl in the father, 250 mg/dl and 120 mg/dl in the mother and 155 mg/dl and 78 mg/dl in the sister, and triglyceride levels in the grandfather and grandmother were 191 mg/dl and 120 mg/dl respectively.

Fasting plasma LPL and hepatic lipase (HL) activities were measured in the proband and in normolipidemic controls before and 15 min after the intravenous injection of 100 units heparin/kg body weight. Samples were chilled to 4 °C, immediately centrifuged, aliquoted and stored at -80 °C until analysis. LPL and HL activities were measured by the methods described by Ramirez *et al.* (6) and Ehnholm and Kuusi (7) respectively. Plasma LPL activity in the proband was only 18% of control values. To avoid a possible interference in the LPL activity in the proband due to an excess of lipids, her plasma samples were also studied after ultracentrifugation (70 000 r.p.m./4 °C/24 h) and also after delipidation with cold acetone. No differences were obtained in her LPL activity after these procedures. LPL and HL activities in the proband and normolipidemic controls are shown in Table 1.

The ability of the proband's apo CII to activate LPL was studied by comparing it with control plasma. Fifteen microliters of pre- and postheparin plasma samples from a control subject were incubated with substrate in the presence of inactivated rat serum (as a source of apo CII) or in the presence of the patient's plasma. The incubations were carried out at 25 °C for 30 min. The addition of the patient's plasma induced the same LPL activity as the control serum, indicating that the LPL activating activity was normal. In order to investigate the presence of a circulating inhibitor of LPL activity in the proband's plasma, 15 µl from a control plasma were incubated for 30 min with the same amount of the proband's plasma. LPL activity in the proband was previously inactivated at 65 °C for 30 min.

Postheparin LPL activity was then measured as described above. The LPL activity showed similar values, indicating the absence of any LPL inhibitor in the proband's plasma.

The apo E genotype was determined as previously described (8) for the proband, her parents and for the normolipidemic controls. The genotype of the proband and her mother was E3/E4, while it was E3/E3 for the other subjects in the study.

All study subjects were checked for the presence of three common variants of the LPL gene: D9N, G188E and N291S. Specific regions of the LPL gene were amplified by PCR in each case and the material obtained was digested with restriction enzymes as previously described (9–11). The proband and her mother were identified as heterozygous carriers of the D9N mutation in the LPL gene, which causes a substitution of Asn for Asp at codon 9 of LPL.

Discussion

Chylomicronemia syndrome is a relatively common lipid disorder usually associated with a quite evident metabolic abnormality, such as diabetes mellitus, or alcohol consumption, especially in the presence of a genetic form of hyperlipidemia, i.e. familial hypertriglyceridemia or familial combined hyperlipidemia. Chait and Brunzell (12) studied a group of 54 patients with plasma triglycerides over 2000 mg/dl and they found that severe hypertriglyceridemia is often due to the coexistence of familial and secondary forms of hyperlipidemia. In their study, only 3 patients (5.6%) did not have any recognizable cause. Normal lipid values in the relatives of the patient can exclude both familial hypertriglyceridemia and familial combined hyperlipidemia. Secondary metabolic causes for the hyperlipidemia were excluded because of her normal plasma glucose levels and glucose tolerance test, thyrotropin and thyroid hormones, renal function, as well as the absence of alcohol consumption or any medication intake. Absence of the broad beta band in serum electrophoresis and the presence of apo E3/E4 genotype in the proband excluded type III hyperlipoproteinemia which in some cases can produce severe hypertriglyceridemia (13). The absence of compatible symptoms and a negative profile for organ-specific autoantibodies (rheumatoid factor, antiparietal cell, antithyroid peroxidase, antithyroid globulin, thyroid-stimulating antibody, anti smooth muscle cell) and organ-nonspecific autoantibodies (ANA, anti DNA, anti Sm, anti RNP, anti Ro) make the diagnosis of an autoimmune disease very unlikely.

The proband status as an LPL D9N heterozygous carrier can explain a partially diminished plasma LPL activity, as described by Mailly *et al.* (9), but it cannot account for the severe LPL deficiency observed in this case. The variant D9N has been associated with mild hypertriglyceridemia and it has a high prevalence in hyperlipidemic subjects.

Chylomicronemia in this case seems to be clearly associated with an acquired and transient defect in LPL plasma activity. The mechanism of this defect was not elucidated, as no plasma inhibitor could be detected in plasma, in contrast with previously described acquired defects. Since CIU and hyperlipidemia showed temporary coexistence, this probably reflects the fact that CIU triggered the hypertriglyceridemia.

Hide *et al.* (14) have recently identified the presence of an immunoglobulin (Ig) G autoantibody against the alpha subunit of the high-affinity IgE receptors (IgE-FcεRI) that cause the release of histamine from basophil of healthy donors. Mast cells activated through their IgE-FcεRI release different mediators as proteoglycans and proinflammatory cytokines that could modify the primary site of action of LPL – the luminal surface of endothelial cells where the enzyme is anchored to proteoglycans (15). The idea that CIU has an autoimmune mechanism is also supported by its association with autoimmune thyroid disease (16) and it could also be possible that the LPL deficiency in this case was due to the presence of a non-circulating autoantibody against the enzyme.

Another predisposing mechanism to chylomicronemia in this case is the temporary association of lipid and lipoprotein changes with puberty (17, 18). Physiological changes during puberty include an increase in plasma triglycerides, which is due to the higher levels of sexual hormones, especially estrogens. It has previously been shown that the phenotypic expression of type I hyperlipidemia is modified by estrogens, and some patients present their first symptoms during pregnancy (19). Bucher *et al.* (20) have recently described the case of a girl compound heterozygote for two missense mutations in the LPL gene with a severe increase in triglyceride plasma concentration during puberty due to a marked accumulation of chylomicrons, without modifications in the VLDL, LDL and HDL values, suggesting that the catabolism of chylomicrons in type I hyperlipoproteinemia is further affected by estrogens.

In summary, we report the first description of type I HLP due to an acquired LPL deficiency during puberty associated with CIU. The absence of a circulating LPL inhibitor in plasma during the disease, and the spontaneous remission of the HLP with recovery of the LPL activity with the cure of CIU suggest a new mechanism for type I HLP.

Acknowledgements

This work was supported by the FIS project 97/0010–02. We thank Dr A Cenarro for helpful comments on this manuscript.

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Received 8 February 1999

Accepted 30 June 1999