

## Type 1 Hyperlipoproteinemia and Recurrent Acute Pancreatitis due to Lipoprotein Lipase Antibody in a Young Girl with Sjögren's Syndrome

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**Context:** Type 1 hyperlipoproteinemia (T1HLP) in childhood is most often due to genetic deficiency of lipoprotein lipase (LPL) or other related proteins.

**Objective:** The aim was to report a case of marked hypertriglyceridemia and recurrent acute pancreatitis due to the presence of LPL autoantibody in a young girl who was subsequently diagnosed with Sjögren's syndrome.

**Subject and Methods:** A 9-yr-old African-American girl presented with acute pancreatitis and serum triglycerides of 4784 mg/dl. Strict restriction of dietary fat reduced serum triglycerides, but she continued to experience recurrent pancreatitis. Approximately 18 months thereafter, she developed transient pauciarticular arthritis with elevated serum antinuclear antibody (>1:1280). Minor salivary gland biopsy revealed chronic sialadenitis with a dense periductal lymphocytic aggregate suggestive of Sjögren's syndrome. Genomic DNA was analyzed for *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, and *LMF1*. Immunoblotting was performed to detect serum LPL autoantibody.

**Results:** The patient had no disease-causing variants in *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*. Immunoblotting revealed serum LPL antibody. The patient responded to immunosuppressive therapy for Sjögren's syndrome with resolution of hypertriglyceridemia.

**Conclusions:** Unexplained T1HLP in childhood could be secondary to LPL deficiency induced by autoantibodies. Therefore, diagnosis of autoimmune T1HLP should be entertained if clinical features are suggestive of an autoimmune process. (*J Clin Endocrinol Metab* 96: 3302–3307, 2011)

Type 1 hyperlipoproteinemia (T1HLP) presenting in childhood is in most cases due to genetic deficiency of lipoprotein lipase (LPL) or related proteins such as apolipoprotein (apo) C2, apo A5, lipase maturation factor 1 (LMF1), and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) (1–5). Absent or nonfunctional LPL due to mutations in LPL or other genes encoding the cofactors essential for its

activity results in decreased hydrolysis of triglycerides transported in chylomicrons and very low-density lipoproteins at the tissue capillary endothelial surface. These patients suffer from recurrent attacks of acute pancreatitis, eruptive xanthomas, and lipemia retinalis (6, 7).

Severe hypertriglyceridemia may also develop secondary to poorly controlled diabetes mellitus, heavy alcohol intake, nephrotic syndrome, obesity, drug therapy, or a

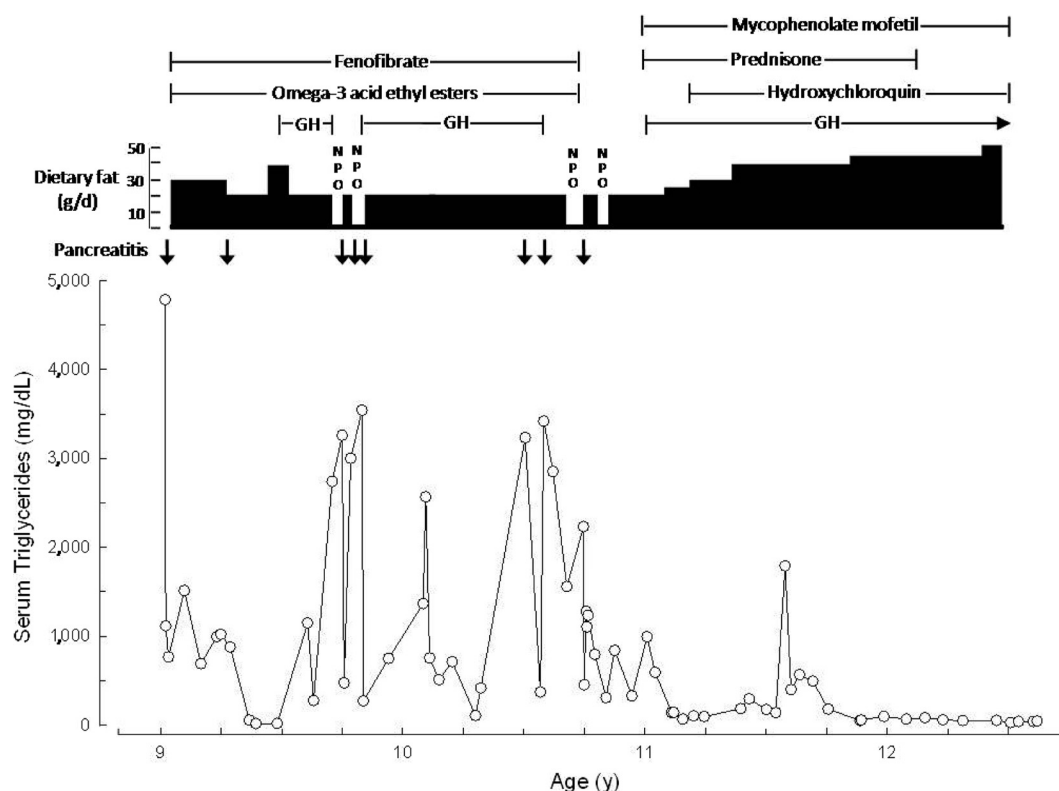


**FIG. 1.** Clinical course of the patient. Serum triglyceride levels during ages 9–12 yr are shown. Various therapies and dietary fat content are depicted above the data. Arrows indicate attacks of acute pancreatitis. NPO, Nil per os (nothing by mouth).

combination of these conditions (6–8). Rare cases of type 1/5 hyperlipoproteinemia-induced acute pancreatitis have been reported in four adults due to autoantibodies to LPL (9–12). We report the first case of T1HLP and recurrent attacks of acute pancreatitis secondary to an LPL inhibitory antibody in a young girl who developed Sjögren's syndrome.

## Case Reports

A 9-yr-old African-American female presented with abdominal and back pain and emesis for 1 d before admission. She had experienced similar episodes of abdominal pain and vomiting 6 wk before presentation, all of which resolved without any intervention. Otherwise, she was healthy before that. Physical examination revealed a thin (weight, 20 kg; <3rd percentile), small (height, 120 cm; <3rd percentile) girl with a body mass index of 13.7 kg/m<sup>2</sup>. She did not have hepatosplenomegaly, eruptive xanthomas, or lipemia retinalis. No clinical features of lipodystrophy were noted. There was no family history of hypertriglyceridemia, pancreatitis, or consanguinity. Her mother was diagnosed with systemic lupus erythematosus 4 yr previously, and the maternal grandmother had multiple sclerosis.

The initial laboratory evaluation revealed lipemic serum with total cholesterol of 209 mg/dl, triglycerides of

4784 mg/dl, and high-density lipoprotein cholesterol of 41 mg/dl. She did not have any evidence of glycogen storage disease (no hepatomegaly or hypoglycemic episodes), nephrotic syndrome, hypothyroidism, or diabetes. Given the severity of the hypertriglyceridemia, a provisional diagnosis of either LPL or apo C2 deficiency was considered. She was treated with omega-3 acid ethyl esters 2 g/d and fenofibrate, 48 mg initially and later 145 mg daily, both of which did not appear to affect her clinical or biochemical course (Fig. 1). She was instructed to adhere to a low-fat diet with 30 g of fat daily and subsequently to take only 20 g of dietary fat daily because she continued to develop acute pancreatitis. A magnetic resonance cholangiopancreatography was negative for peripancreatic edema and biliary duct abnormalities. At the time of one of her admissions for pancreatitis, the computed tomography scan showed evidence of edema of pancreas and fluid density in the peripancreatic tissue.

She underwent an endoscopic retrograde cholangiopancreatography and sphincterotomy with stent placement for management of sphincter of Oddi dysfunction because the pancreatic sphincter pressure measured greater than 200 mm Hg. Ultrasound examination of the abdomen did not reveal fatty liver. In addition to several hospital admissions with acute pancreatitis, she also had frequent minor abdominal pain. Serum triglycerides be-

low 500 mg/dl were found only with strict adherence to an extremely low-fat (20 g fat daily) diet.

She was also noted to have persistent microcytic anemia with hematocrit between 26 and 30% and mean corpuscular volume around 60 fl. Her white blood cell count was  $3500/\text{mm}^3$ , with an absolute neutrophil count of  $1500/\text{mm}^3$ . The platelet count was normal, but platelets were slightly large in size with accumulated lipid material in them. Hemoglobin electrophoresis, serum lead, copper, ferritin, and total iron binding capacity, and blood reticulocyte count were all normal. Peripheral blood smear showed hypochromic and microcytic red blood cells with some acanthocytes and very few spherocytes. She had an attenuated growth velocity, and height was below the third percentile, which prompted provocative GH testing with arginine and L-dopa. Baseline GH value was 5.5 ng/ml and the peak stimulated value was 6.4 ng/ml, consistent with GH deficiency. IGF binding protein 3 level was 4.3 mg/liter (normal, 1.6–7.1), somatomedin-C was 135 ng/ml (normal, 49–461), and GH binding protein was 614 pmol/liter (normal, 267–1638). She was started on human GH 0.3 mg/kg · wk, which she continues to receive at present.

She reported two isolated brief episodes of overt joint swelling of her ankle, knee, and wrist with associated pain several weeks apart. The joint swelling episodes occurred several weeks apart and resolved in 2–3 d without intervention. Rheumatological serological evaluation revealed a speckled antinuclear antibody pattern with a titer of more than 1:1280. Sjögren syndrome antigen B (SS-B) antibody was weakly positive at 1.2 (normal, <1.0), and anti-DNA, Smith, ribonucleoprotein, and SS-A antibodies were negative. She had positive anticardiolipin antibody. Rheumatoid factor was weakly positive at 15 IU/ml (normal, <14). A presumptive diagnosis of Sjögren's syndrome was established after a minor salivary gland biopsy revealed chronic sialadenitis with a dense periductal aggregate of lymphocytes (Fig. 2, A and B). She did not have dry mouth or dry eyes. Therapy was initiated with prednisone 20 mg/d and mycophenolate mofetil 500 mg twice daily. Subsequently, she reported a dry mouth and frequent arthralgia, at which time mycophenolate mofetil was increased to 750 mg every morning and 500 mg every evening. Hydroxychloroquine 100 mg/d was started as the prednisone dose was slowly decreased. Her serum triglyceride concentrations reduced drastically. No further episodes of marked hypertriglyceridemia or pancreatitis occurred while her dietary fat content was increased to 45 g/d. Prednisone was successfully discontinued approximately 15 months after initiation of treatment.

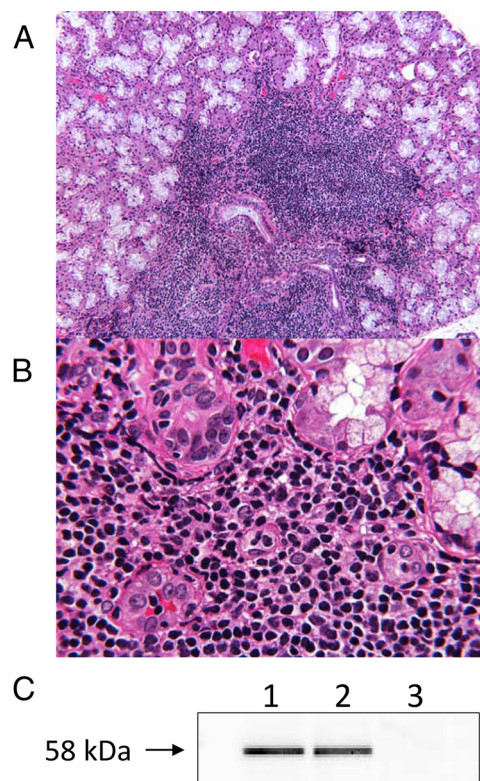


**FIG. 2.** Histopathology of lip biopsy and detection of LPL antibody in serum. A, Hematoxylin and eosin stain in low-power view (magnification,  $\times 33$ ) shows the intralobular duct surrounded by dense aggregate of lymphocytes, some plasma cells, and occasional immunoblasts. B, High-power view (magnification,  $\times 132$ ) demonstrates infiltration of glandular tissue with lymphocytes and immunoblasts. C, Detection of LPL autoantibodies in patient plasma by Western blot analysis. LPL purified from postheparin human plasma was subjected to SDS-PAGE, followed by transfer to nitrocellulose. The blots were incubated with positive control from a previous patient with autoimmune hyperchylomicronemia (lane 1), plasma from our patient (lane 2), or negative control plasma (lane 3) and then stained with a peroxidase-labeled goat antihuman antibody. Both the positive control and our patient revealed presence of anti-LPL antibody. The negative control plasma did not show a band.

## Patient and Methods

The patient was evaluated at the University of Alabama at Birmingham Pediatric Endocrinology Lipid Clinic. A written informed consent was obtained from the parents of the patient for genetic testing, and the study was approved by the Institutional Review Board (IRB) of the University of Texas (UT) Southwestern. Approval was also obtained from University of Alabama at Birmingham IRB for retrospective chart review.

Serum triglycerides and lipoproteins were measured enzymatically in commercial laboratories. Genomic DNA was isolated from blood using the Easy DNA kit from Invitrogen (Carlsbad, CA) according to the manufacturer's protocol. The coding regions and the adjacent splice sites of *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, and *LMF1* were amplified using gene-specific primers at UT Southwestern. The purified PCR products were sequenced to determine the nucleotide alternations.

Detection of circulating autoantibody directed against LPL was performed as previously described (11, 12). Briefly, human post-heparin LPL was electrophoresed using 10% SDS-PAGE

**TABLE 1.** SNP identified upon screening the candidate genes for T1HLP in our patient

| Genes          | Variant      |             | SNP no.    | Minor allele frequency (%) | Genotype |
|----------------|--------------|-------------|------------|----------------------------|----------|
|                | Nucleotide   | Protein     |            |                            |          |
| <i>LPL</i>     | c.541+74T>C  | NA          | rs249      | 17                         | CC       |
|                | c.1139+43T>C | NA          | rs301      | 37–40                      | CT       |
|                | c.1164C>A    | p.Thr388Thr | rs316      | 30                         | CA       |
|                | c.1437G>A    | NA          | rs4922115  | 15                         | GA       |
| <i>GPIHBP1</i> | c.295+27C>T  | NA          | rs56046179 | 16                         | CT       |
|                | c.295+83C>T  | NA          | rs78632667 | 3                          | CT       |
|                | c.12C>T      | p.Leu4Leu   | rs61747644 | 25                         | CT       |
|                | c.41G>T      | p.Cys14Phe  | rs11538389 | 14                         | GT       |
| <i>APOA5</i>   | c.-3A>G      | NA          | rs651821   | 20                         | AG       |
|                | c.49+55G>T   | NA          | rs41338746 | 8                          | GT       |
| <i>APOC2</i>   | c.-13-67T>G  | NA          | rs10422603 | 33                         | TG       |
| <i>LMF1</i>    | c.-4-21G>T   | NA          | rs13334376 | 21                         | GT       |
|                | c.194-28T>C  | NA          | rs3751666  | 22                         | CC       |
|                | c.306G>A     | p.Thr102Thr | rs3751667  | 42                         | GA       |
|                | c.514+131G>T | NA          | rs11248955 | 31                         | GT       |
|                | c.540G>A     | p.Thr180Thr | rs2277892  | 44                         | GA       |
|                | c.543G>A     | p.Gly181Gly | rs2277893  | 42                         | GA       |
|                | c.756G>A     | p.Ala252Ala | rs2076425  | 24                         | GA       |
|                | c.1232+54C>G | NA          | rs13329717 | 25                         | CG       |

NA, Not available.

and then transferred onto a nitrocellulose membrane. Membrane was cut into vertical strips, and each strip was incubated with plasma samples at 1:100 dilution from a previous patient with autoimmune T1HLP serving as a positive control, a negative control, or from our patient. All blots were then stained with a peroxidase-labeled goat antihuman IgG antibody (1:1000 dilution; Sigma-Aldrich, St. Louis, MO) and visualized with the ECL Advance Western Blotting Detection Kit (Amersham Biosciences, Piscataway, NJ).

## Results

The patient had no disease-causing variants in the *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*. Only a few heterozygous or homozygous single nucleotide polymorphisms (SNP) were noted upon sequencing these candidate genes (Table 1). None of the SNP linked to serum triglyceride concentrations in the genome-wide association studies, near the five T1HLP loci that we sequenced,

were intragenic (rs964184, which is ~11 kb downstream of *APOA5*; rs12678919, which is 20 kb downstream of *LPL*; and rs439401, which is 33 kb upstream of *APOC2*); therefore, we do not have data on those in our patient. Immunoblotting demonstrated the presence of LPL antibody in the serum of our patient (Fig. 2C).

## Discussion

Despite a high suspicion for a genetic form of T1HLP based on our patient's initial presentation, we were unable to find any disease-causing variants in the known candidate genes. We screened not only *LPL* and *APOC2*, the two most common loci for T1HLP (1, 2), but also *APOA5*, *LMF1*, and *GPIHBP1*, which have been associated with type 1 or 5 hyperlipoproteinemias in a few patients (3–5). Lack of consanguinity and presence of heterozygous in-

**TABLE 2.** Previously reported patients with T1HLP due to LPL antibody and our patient

| First author (Ref.)                             | Patient's age (yr)/gender | Highest serum TG (mg/dl) | Acute pancreatitis | Other conditions     | Autoantibody | Other autoantibodies                                       | Therapeutic response to immunosuppressive therapy         |
|-------------------------------------------------|---------------------------|--------------------------|--------------------|----------------------|--------------|------------------------------------------------------------|-----------------------------------------------------------|
| Kihara <i>et al.</i> (9)                        | 26/F                      | >2000                    | + Frequently       | ITP, Graves' disease | LPL + HTGL + | Antithyroglobulin, antimicrosomal, platelet-associated IgG | Not available                                             |
| Yoshimura <i>et al.</i> (10)                    | 27/F                      | 5420                     | +                  | ITP, pregnancy       | LPL + HTGL + | Antinuclear, anti-DNA, antiplatelet                        | Prednisolone                                              |
| Pruneta <i>et al.</i> (11)                      | 35/F                      | >4425                    | +                  | None                 | LPL +        | Thyroid peroxidase, antistriated muscle                    | Azathioprine and prednisolone                             |
| Pruneta-Deloché <i>et al.</i> (12) <sup>a</sup> | 50/M                      | >2477                    | + Multiple         | None                 | LPL + IgG    | None                                                       | Azathioprine                                              |
| Our patient                                     | 9/F                       | 4784                     | + Multiple         | Sjögren's syndrome   | LPL +        | Antinuclear, SS-B<br>Anticardiolipin<br>Rheumatoid factor  | Mycophenolate mofetil<br>Prednisone<br>Hydroxychloroquine |

M, Male; F, female; HTGL, hepatic triglyceride lipase; ITP, idiopathic thrombocytopenic purpura; TG, triglyceride; +, present.

<sup>a</sup> Also had heterozygous p.Ser172fsx179 mutation in *LPL*.

tragenic SNPs reduce the likelihood of large homozygous deletions in the screened genes. These negative genotyping data prompted investigations into other causes of T1HLP.

When the patient developed pauciarticular arthritis and antinuclear antibody was detected in high titer in her serum, the possibility of autoimmune T1HLP due to antibodies against LPL was entertained. Indeed, immunoblotting confirmed the presence of antibodies against LPL. Antibodies toward LPL function as circulating LPL inhibitors with resultant severe hypertriglyceridemia (9–12).

Previously, only four adults with severe hypertriglyceridemia secondary to autoantibody to LPL have been reported (Table 2). Two of them had associated immune thrombocytopenic purpura, and one of them also had Graves' disease. The other two did not have any underlying autoimmune disorder, but serum of one individual was positive for the presence of autoantibodies such as thyroid peroxidase and antistriated muscle. Initially, our patient did not demonstrate any manifestations of autoimmune disease, but she was later diagnosed with Sjögren's syndrome. Three of the previously reported patients had marked reduction in serum triglycerides in response to immunosuppressive therapy (10–12). Likewise, our patient also responded dramatically to immunosuppressive therapy with resolution of hypertriglyceridemia, an observation favoring the autoimmune nature of T1HLP. Interestingly, one of the previously reported patients was found to harbor a heterozygous p.Ser172fsx179 mutation in LPL (12). However, extensive genotyping in our patient did not reveal any mutations in LPL and other related proteins.

There are other reports of poor LPL activity in the setting of severe hypertriglyceridemia; however, there was no documentation of the presence of LPL autoantibody in the serum (13, 14). Garcia-Otin *et al.* (13) reported a 13-yr-old with severe hypertriglyceridemia in the setting of chronic idiopathic urticaria whose LPL activity increased with remission of urticaria. Nagasaka *et al.* (14) reported two infants with severe hypertriglyceridemia, but they had no evidence of autoimmune disease. Interestingly, detection of LPL antibodies in subjects with systemic lupus erythematosus has not uniformly resulted in marked hypertriglyceridemia (15, 16). Furthermore, compared with patients with systemic lupus erythematosus, the prevalence of significant titers of anti-LPL antibodies is much lower in patients with Sjögren's syndrome (15). In addition, the antihuman LPL IgG has been detected in patients with chylomicronemia as well as in control subjects (17). However, only those subjects with a high level anti-LPL IgG inhibited triglyceride hydrolysis, thus raising questions about specific immunogenicity of LPL (17).

To date, it has not been documented whether reduction in serum triglycerides in response to immunosuppressive therapy in patients with autoimmune T1HLP is associated with reduction in serum titers of anti-LPL antibody. Furthermore, no studies have addressed whether there are many different types of anti-LPL antibodies, some which may affect the binding or active site and thus hinder lipolysis.

We conclude that unexplained T1HLP in childhood could be secondary to impaired LPL activity induced by autoantibodies. The diagnosis of autoimmune T1HLP in children should be considered if clinical findings are suggestive of an autoimmune process. Demonstration of autoantibodies to LPL in such patients may be important therapeutically because these patients respond to immunosuppressive therapy.

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Disclosure Summary: All authors have nothing to declare.

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