

Primary hyperchylomicronemia syndrome treated with ciprofibrate in childhood[☆]



Síndrome de hiperquilomicronemia primaria tratado con ciprofibrato en la infancia

Primary hyperchylomicronemia syndrome or hyperlipoproteinemia type 1 (HLP-1) of the Fredrickson classification is a genetic disorder characterized by markedly increased triglyceride and chylomicron levels in blood which causes a high risk of pancreatitis and other complications.¹ The syndrome is caused by mutations in the gene that encodes the enzyme lipoprotein lipase (LPL) or, less commonly, by mutations in genes encoding other proteins required for LPL function.² The condition is usually diagnosed in childhood,¹ an age for which the use of lipid lowering drugs is controversial.

We report the case of a three-year-old girl with no family history of consanguinity or primary hyperlipidemia who was referred for severe hypertriglyceridemia (8492 mg/dL) and hypercholesterolemia (584 mg/dL) measured at two years and 10 months of age. A physical examination revealed 17 kg of weight, a height of 98 cm, and a body mass index of 17.7 kg/m² (between the 90th and 97th percentiles). Eruptive xanthomas were found on the face, shoulders, buttocks, and upper and lower limbs. Eye fundus examination found *lipemia retinalis*, and abdominal palpation revealed hepatomegaly with no splenomegaly. Repeat lipid profile tests showed a lactescent plasma which contained 475 mg/dL of total cholesterol, 4727 mg/dL of triglycerides, and 32 mg/dL of HDL cholesterol. Lipoprotein electrophoresis showed a marked elevation of chylomicrons only. A complete blood count disclosed normochromic, normocytic anemia (10.2 g/dL). An abdominal ultrasound examination confirmed hepatomegaly.

Based on the clinical signs and symptoms of the patient and on data from supplemental tests, the patient was diagnosed HLP-1 and prescribed a low-fat diet (18 g/day) and the addition of medium-chain triglycerides (30 mL daily in salads). Despite this, the patient was seen again after two months of treatment for abdominal pain, and testing revealed a triglyceride level of 3273 mg/dL. There was no elevation of liver enzymes or amylase. In view of the persistence of hypertriglyceridemia, the patient was prescribed ciprofibrate, 50 mg daily after supper, which achieved a significant clinical improvement at four months of treatment. Lipid levels were as follows: 191 mg/dL of total cholesterol, 169 mg/dL of triglycerides, 44 mg/dL of HDL cholesterol, and 112 mg/dL of LDL cholesterol. Transaminase and creatine phosphokinase levels were not increased.

A genetic analysis found no changes in the gene sequence of apolipoprotein C-II (*APOC2*), apolipoprotein A-V (*APOA5*), and *GPIHBP1* (the protein transporting LPL to capillaries, which serves as a platform for chylomicron hydrolysis

mediated by this enzyme). Analysis of the LPL gene (*LPL*) showed a variant of the promoter 1-281C>T which was not associated with any mutation.

After two years of treatment with ciprofibrate, the patient had not experienced new episodes of abdominal pain or new eruptive xanthomas. Lipid levels in the last assessment included 212 mg/dL of total cholesterol, 307 mg/dL of triglycerides, 112 mg/dL of LDL, and 37 mg/dL of HDL.

In children, hypertriglyceridemia is defined as plasma triglyceride levels above the 95th percentile for age and sex, and HLP-1 is the best example of severe hypertriglyceridemia.³ HLP-1 is a disorder of autosomal recessive inheritance, and the screening of first-degree relatives is therefore required. Our patient, however, had no siblings, and her parents had no lipid profile changes. It should be noted that the variant of the promoter 1-281C>T in the *LPL* gene has not been reported in the literature, but it could not have caused the hypertriglyceridemia found in the patient because it causes no changes in the amino acid sequence and does not therefore impair LPL function. In this regard, Surendran et al.² showed in 86 subjects with severe forms of hypertriglyceridemia that common variants were found in *LPL* and *APOA5* in 26% of cases, and that no mutation was found in 21%. These data open up new avenues for the study of novel candidate genes regulating triglyceride metabolism. No relationship exists between genotype and phenotype, but women with HLP-1 often experience anemia,⁴ which was also found in our patient.

The basic treatment consists of dietary fat restriction to no more than 20 g/day⁵; in this pediatric patient, however, diet adherence was poor because of its low palatability. The use of medium-chain triglycerides is also recommended, because they enter the bloodstream without being incorporated into chylomicrons.⁵

Fibric acid derivatives (fibrates) are recommended for the treatment of hypertriglyceridemia. These are agonists of the peroxisome proliferator-activated receptor alpha, and decrease extracellular triglyceride levels by inducing transcription of the *LPL* gene and reducing the expression of the apolipoprotein C-III gene, an LPL inhibitor.⁶ To our knowledge, no other case of HLP-1 treated with ciprofibrate has been reported in the literature. However, there is evidence of the effective and safe use of gemfibrozil 300 mg in two children with HLP-1 aged seven and four years.⁷ Genotyping was not performed in these cases, but there is evidence that patients with a heterozygous mutation in *APOA5* respond adequately to medical treatment.⁴ It may thus be that the response to fibrates in patients with HLP-1 is dependent on the existence of significant residual LPL activity.

The main adverse effects derived from the use of fibrates are gastrointestinal. Wheeler et al.⁸ conducted a prospective, randomized study in 14 children with familial hypercholesterolemia treated with bezafibrate and found good tolerability and no adverse effects on both growth and pubertal development.

There is now evidence favoring the use of gene therapy in patients with HLP-1. Access to these new agents is limited, and the use of gene therapy requires the detection of the causative mutation in the *LPL* gene and the absence of LPL mass, so that our patient would have been discarded as a suitable candidate. Nutritional management combined with the use of fibrates may therefore be an effective and

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safe option in children with primary hyperchylomicronemia syndrome.

Conflicts of interest

The authors have no conflicts of interest related to this manuscript.

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Marcos M. Lima-Martínez^{a,b,*}, Martha Piñango^a, Miguel Lima-Ostos^{a,c}

^a *Departamento de Ciencias Fisiológicas, Escuela de Ciencias de la Salud, Universidad de Oriente, Ciudad Bolívar, Venezuela*

^b *Unidad de Endocrinología, Diabetes, Metabolismo y Nutrición, Anexo A, Centro Médico Orinoco, Ciudad Bolívar, Venezuela*

^c *Consultorio Dermatológico «Lima-Ostos», Ciudad Bolívar, Venezuela*

* Corresponding author.

E-mail address: marcoslimamedical@hotmail.com (M.M. Lima-Martínez).