Severe Hypertriglyceridemia in an Infant of Arab Descent

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For Editorial see page 43

Severe hypertriglyceridemia is a rarely occurring simple monogenic disorder resulting from loss of function mutations in the genes *LPL*, *APOC2*, *APOA5*, *LMF1* and *GPIHBP1*. Inheritance is typically autosomal recessive, often presenting in childhood, and the result of homozygosity (or compound heterozygosity) for large-effect genetic mutations [1]. Specifically, mutations in the *LPL* gene (OMIM 609708), encoding for lipoprotein lipase, were proved to be causative for type I hyperlipoproteinemia (OMIM 238600). Lipoprotein lipase plays a crucial role in lipid metabolism and transport by catalyzing the rate-limiting step in the hydrolysis of the triacylglycerol component present in the circulating chylomicrons and very low density lipoprotein with apolipoprotein C2 functioning as an essential cofactor/activator for its activity. We report the identification of the pathogenic missense mutation LPL, c.809G>A (p.AGR270HIS) in an infant presenting with severe hypertriglyceridemia.

PATIENT DESCRIPTION

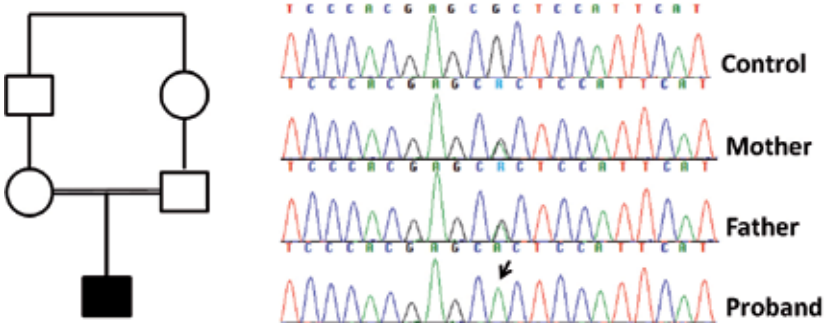
A 3 month old infant was referred for genetic counseling following the identification of severe fasting hypertriglyceridemia peaking at 24,550 mg/dl. The boy is the first child born to healthy consanguineous parents of Arab Muslim origin [Figure]. Obstetric history and developmental milestones were unremarkable. He was born at term with a birth weight of 3000 g. At age 2 months, during a general checkup because of earache, hepatomegaly was noted and he was referred for routine laboratory workup, which revealed extreme hypertriglyceridemia. Upon admission his height was 58 cm (14th percentile), weight 6060 g (47th percentile), and head circumference 40.5 cm (31th percentile). On physical examination, he had no dysmorphic features or physical abnormalities apart from slight hepatomegaly palpable 2 cm below the right costal margin and a few xanthomas on the trunk and limbs. Ophthalmoscopy was compatible with lipemia retinalis. Triglyceride and total cholesterol levels 3 hours postprandial were 24,550 mg/dl and 1700 mg/dl, respectively. An abdominal ultrasound confirmed the hepatomegaly.

Genomic DNA was extracted from peripheral leukocytes following standard protocols. DNA was amplified to obtain all *LPL* and *APOC2* genes coding exons and their flanking regions using conventional polymerase chain reaction techniques. PCR products were purified using magnetic particle technology (Seradyn Inc., IN, USA). After purification, all fragments were sequenced by forward and backward internal primers to determine the noted regions. Sequencing was performed on a 3730xl DNA Analyzer (Applied Biosystems, CA, USA), and the resulting sequences were analyzed with the Sequencher software (Gene Codes Corporation, MI, USA). Mutations were scored relative to the reference sequences deposited in NCBI [APOC2: (NM_000483); LPL: (NM_000237)].

A base alteration in exon 6 of the *LPL* gene (c.809G>A), resulting in a missense mutation substitution at amino acid position 270 (p.ARG270HIS), was detected in the proband [Figure]. His parents were het-

PCR = polymerase chain reaction

Identification of the *LPL*, c.809G>A (p.ARG270HIS) mutation by sequence analysis



erozygous for the mutation, as expected. No mutations were found within the boundaries of the coding exons and the splicing regions of the *APOC2* gene.

The patient was put on a medium-chain triglyceride-rich diet with fast response and reversion of the lipemia retinalis. Upon discharge, his fasting plasma values of triglycerides and cholesterol were 437 mg/dl and 428 mg/dl, respectively.

COMMENT

A few individuals with plasma triglyceride level surpassing the 95th percentile have rare monogenic disorders resulting from homozygous loss-of-function mutations in *LPL*, *APOC2*, *APOA5*, *LMF1* or *GPIHBP1* genes. The frequency of individuals with these elevated triglyceride syndromes is less than $1:10^5$ and they fit the definition of hyperlipoproteinemia type 1, with chylomicronemia, skin and eye abnormalities, and often pancreatitis [1]. We describe a family demonstrating an autosomal recessive pattern of inheritance for the missense mutation c.809G>A in the *LPL* gene. This mutation was previously labeled as *LPL*, ARG243HIS and was reported to be pathogenic in one Caucasian patient, one Japanese, one Italian, one Dutch and one Chinese [2]. Expression studies demonstrated that the p.ARG270HIS substitution not only abolishes lipoprotein lipase enzymatic activity but also decreases enzyme secretion [3]. The importance of early identification of LPL deleterious mutations seems to be critical since a highly effective and simple treatment that primarily relies on strict adherence to a medium-chain triglyceride-rich diet is available. In particular, the 34 year old female of Caucasian origin carrying the very same mutation in a compound heterozygote state was reported to have suffered throughout childhood from recurrent episodes of abdominal pain and pancreatitis and was noted to have eruptive xanthomas, lipemia retinalis, and splenomegaly [4]. Similarly, the Italian patient carrying the mutation also in a compound heterozygote state presented with recurrent vomiting at age 3 months. Following initiation of a low fat diet no additional episodes were recorded and at the age of 7 she was noted to have lipemia retinalis and splenomegaly, but no eruptive xanthoma or hepatomegaly [5].

To our knowledge, the present article is the first report of an *LPL* deleterious mutation in Israel. The reported mutation should be considered for testing in patients presenting with severe hypertriglyceridemia predominantly among Arab Muslims in central Israel. Precise estimation of the carrier frequency of this mutation and the contribution of common and rare variants of the *LPL* gene to hypertriglyceridemia in the Israeli population is the scope of future studies.

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References

1. Johansen CT, Hegele RA. Genetic bases of hypertriglyceridemic phenotypes. *Curr Opin Lipidol* 2011; 22: 247-53.
2. Gilbert B, Rouis M, Griglio S, de Lumley L, Laplaud P. Lipoprotein lipase (LPL) deficiency: a new patient homozygote for the preponderant mutation Gly188Glu in the human LPL gene and review of reported mutations: 75% are clustered in exons 5 and 6. *Ann Genet* 2001; 44: 25-32.
3. Gotoda T, Yamada N, Kawamura M, et al. Heterogeneous mutations in the human lipoprotein lipase gene in patients with familial lipoprotein lipase deficiency. *J Clin Invest* 1991; 88: 1856-64.
4. Dichek HL, Fojo SS, Beg OU, et al. Identification of two separate allelic mutations in the lipoprotein lipase gene of a patient with the familial hyperchylomicronemia syndrome. *J Biol Chem* 1991; 266: 473-7.
5. Ishimura-Oka K, Semenkovich CF, Faustinella F, et al. A missense (Asp250→Asn) mutation in the lipoprotein lipase gene in two unrelated families with familial lipoprotein lipase deficiency. *J Lipid Res* 1992; 33: 745-54.

Capsule

Generation of functional thyroid from embryonic stem cells

The primary function of the thyroid gland is to metabolize iodide by synthesizing thyroid hormones, which are critical regulators of growth, development and metabolism in almost all tissues. So far, research on thyroid morphogenesis has been missing an efficient stem cell model system that allows for the in vitro recapitulation of the molecular and morphogenic events regulating thyroid follicular-cell differentiation and subsequent assembly into functional thyroid follicles. Antonica et al. report that a transient overexpression of the transcription factors NKX2-1 and PAX8 is sufficient to direct mouse embryonic stem cell differentiation into thyroid follicular cells that organize into three-dimensional follicular structures when treated with thyrotropin. These in vitro-derived follicles showed appreciable iodide organification activity. Importantly, when grafted in vivo into athyroid mice, these follicles rescued thyroid hormone plasma levels and promoted subsequent symptomatic recovery. Thus, mouse embryonic stem cells can be induced to differentiate into thyroid follicular cells in vitro and generate functional thyroid tissue.

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Eitan Israeli

"No man, for any considerable period, can wear one face to himself and another to the multitude, without finally getting bewildered as to which may be true"

Nathaniel Hawthorne (1804-1864), American writer whose many works featuring moral allegories with a Puritan inspiration and deep psychological complexity, exemplified by his most famous work *The Scarlet Letter*