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Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency as a Rare Cause of Bilateral Corneal Opacities: A Case Report of a Novel Frameshift Mutation

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TITLE: Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency as a Rare Cause of Bilateral Corneal Opacities: A Case Report of a Novel Frameshift Mutation

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ABSTRACT

Introduction: Lecithin–cholesterol acyltransferase (LCAT) deficiency is a rare autosomal recessive disorder of lipid metabolism characterized by corneal opacification, hemolytic anemia, and chronic kidney disease. We describe the ophthalmic, systemic, and genetic findings of a patient with LCAT deficiency and report a novel frameshift mutation in the LCAT gene.

Case Presentation: Ophthalmic findings may represent the first clinical sign and guide the diagnosis. A 50-year-old white male with end-stage renal disease on hemodialysis and a history of recurrent hemolytic anemia was referred for bilateral corneal opacities. Despite diffuse opacification involving all corneal layers, his best-corrected visual acuity remained 20/20 in both eyes with normal color vision, although contrast sensitivity was reduced. Laboratory testing revealed normocytic, normochromic anemia, low HDL cholesterol, and reduced apolipoprotein A levels. Genetic analysis identified compound heterozygosity in the LCAT gene: a novel frameshift variant c.580_598del p.(Ala194Serfs*64), classified as likely pathogenic, and the previously described missense variant c.619G>A p.(Gly207Ser), also classified as likely pathogenic.

Conclusion: This case highlights the importance of considering metabolic disorders in the differential diagnosis of bilateral corneal opacities and expands the genetic spectrum of LCAT deficiency by reporting a novel frameshift mutation.

Keywords: Corneal opacities; Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency; Norum disease; Fish-eye disease.

INTRODUCTION

Bilateral corneal opacifications are significant ophthalmic findings that may indicate underlying systemic disease. One such condition is LCAT deficiency, a very rare autosomal recessive disorder caused by mutations in the LCAT gene located on chromosome 16q22.1. The enzyme catalyzes the esterification of cholesterol and its transfer to lipoproteins such as HDL, LDL, and VLDL [1].

Mutations impairing enzyme activity result in reduced cholesterol esterification, markedly low HDL cholesterol levels, accumulation of unesterified cholesterol, and lipid deposition in multiple tissues, including the cornea, erythrocytes, and kidneys.

The clinical presentation varies according to the degree of enzyme dysfunction. Complete deficiency, sometimes referred to as Norum disease, is characterized by a triad of corneal opacification, hemolytic anemia, and progressive chronic kidney disease that may evolve to end-stage renal disease.
A milder variant, known as fish-eye disease, presents primarily with corneal involvement without systemic manifestations such as anemia or renal failure [2]. Fish-eye disease is rare, and its diagnosis can be challenging due to its similarity to primary corneal dystrophies.

CASE REPORT

A 50-year-old white male with end-stage chronic kidney disease, maintained on hemodialysis after two failed renal transplants (1998 and 2013), was referred to the Ophthalmology Department for evaluation of bilateral corneal opacities. He did not report visual symptoms.
His past medical history included membranous glomerulonephritis diagnosed at the age of 21, complicated by secondary hyperparathyroidism. He also had a long-standing history of recurrent hemolytic anemia of uncertain etiology. During his first transplant admission, he experienced episodes of unconjugated hyperbilirubinemia that were initially attributed to tacrolimus-induced hepatotoxicity, although liver function tests, coagulation parameters, and imaging studies showed no evidence of hepatic or biliary disease. He was also followed by Cardiology for hypertension.
His current medications included everolimus, mycophenolate mofetil, prednisolone, a calcimimetic agent, and perindopril
Family history was notable for a father who died at age 72 due to cerebrovascular disease, with no history of renal or ophthalmologic disease, and a mother who died at age 82 due to respiratory disease. He has two healthy brothers with no renal or ocular disease and one healthy 20-year-old daughter.
On ophthalmologic examination, best-corrected visual acuity was 20/20 in both eyes (OU). Ishihara colour plates were normal OU. No RAPD was present. Ocular motility was full and symmetric, and no nystagmus was noted. Slit-lamp examination revealed diffuse corneal opacities involving all layers of the cornea OU (figure 1). The anterior chamber was quiet, intraocular pressure was normal, and fundoscopic evaluation showed healthy optic discs with a cup-to-disc ratio of 0.3 in both eyes.
Contrast sensitivity was evaluated monocularly using the Contrast Sensitivity Function (CSF) test on the Metrovision MonPack One system (model MON-2008A, Metrovision, Pérenchies, France) under photopic conditions.
Testing revealed a peak sensitivity of approximately 19 dB in the right eye at 2–5 cycles per degree (cpd) and 18 dB in the left eye at 2 cpd, with a mild, generalized reduction across all spatial frequencies in both eyes compared to normative values.
Laboratory studies revealed normocytic, normochromic anemia with a hemoglobin of 9.7 g/dL, leukocytes of 4.4 × 10^3/µL, and platelets of 102 × 10^3/µL. Urea was 112 mg/dL, and creatinine was 1.94 mg/dL. The lipid profile showed total cholesterol of 139 mg/dL, HDL cholesterol of 34 mg/dL, LDL cholesterol of 88 mg/dL, and triglycerides of 83 mg/dL. Apolipoprotein A was markedly reduced at 52 mg/dL, while apolipoprotein E was within the normal range. Haptoglobin was 54.2 mg/dL, and lactate dehydrogenase was 147 U/L.
Central corneal thickness (pachymetry) measured 600 µm in both eyes (OU).
In the genetic test, the following likely pathogenic variants were detected, in compound heterozygosity, in the LCAT gene: c.580_598del p.(Ala194Serfs*64) and c.619G>A p.(Gly207Ser).
The c.580_598del p.(Ala194Serfs*64) variant in the LCAT gene has not been described in the literature, nor in the gnomAD population database. It is a frameshift variant that occurs in exon 5 (of 6), which introduces a premature stop codon and is predicted to lead to the creation of a truncated protein and/or its loss of expression due to mRNA degradation. With the available information, this variant should be classified as likely pathogenic.
The c.619G>A p.(Gly207Ser) variant in the LCAT gene has been described in the literature in a patient with cholesterol acyltransferase deficiency [3], as well as in the gnomAD population database (0.0016%, with 4 heterozygous individuals reported). It is located in a highly conserved residue, and bioinformatic analysis predicts that this variant is deleterious. With the available information, this variant should be classified as likely pathogenic.
Pathogenic variants in the LCAT gene cause Fish-eye disease (MIM 136120) and Norum disease (MIM 245900), both with autosomal recessive inheritance.

DISCUSSION

LCAT deficiency is among the rarest genetic lipid disorders, with fewer than 150 cases reported worldwide [4,5]. It may present in two clinical forms: complete deficiency, associated with the classical triad of corneal opacities, hemolytic anemia, and renal disease, and the partial form known as fish-eye disease, characterized by isolated corneal involvement. The corneal opacities result from deposition of unesterified cholesterol and phospholipids in the stroma and may significantly alter contrast sensitivity while sparing high-contrast visual acuity, as demonstrated in this patient.

The systemic features of LCAT deficiency are of major clinical significance. Anemia is typically normocytic and normochromic and arises from altered erythrocyte membranes and reduced red cell survival. Renal involvement is related to the accumulation of lipoprotein-X and may progress to end-stage renal disease, as occurred in our patient.

Differential diagnosis includes other rare disorders of HDL metabolism such as Tangier disease and apolipoprotein A-I deficiency. Tangier disease, however, is usually associated with hepatosplenomegaly, neuropathy, and pathognomonic orange tonsils, which were not present in this case.

Therapeutic options are limited. Recombinant human LCAT enzyme replacement has shown promising results in preliminary studies, including improvement of anemia, normalization of HDL cholesterol, and slowing of renal disease progression. However, this therapy remains experimental, and current management is primarily supportive, with renal replacement therapy for kidney failure and corneal transplantation considered in cases of significant visual impairment.

This case is noteworthy for the identification of a novel LCAT frameshift mutation.

LCAT deficiency should be considered in the differential diagnosis of bilateral corneal opacities, particularly when associated with unexplained anemia and renal dysfunction. Our report describes a novel frameshift mutation in the LCAT gene in a patient with the classical systemic phenotype, thereby contributing to the understanding of the genetic basis of this rare disorder.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Data Availability Statement: The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author committee upon reasonable request.

Author Contributions:

João Mendes - Conceptualization; Writing - original draft; Writing - review & editing.
Francisco Mendes - Conceptualization; Writing - original draft; Writing - review & editing.
Diogo Valente Fortunato - Writing - review & editing
João Vasco Garrido - Writing - review & editing
Rita Condesso - Conceptualization; Supervision; Validation; Visualization; Writing - review & editing
Augusto Candeias - Conceptualization; Supervision; Validation; Visualization; Writing - review & editing

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Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Figure 1. Slit-lamp examination of the left eye revealed diffuse corneal opacities involving all layers of the cornea.