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PREEMPTIVE KIDNEY TRANSPLANTATION IN A PATIENT WITH COMPOUND HETEROZYGOSITY IN THE LCAT (LECITHIN-CHOLESTEROL ACYLTRANSFERASE) GENE: CASE REPORT OF FAMILIAL LCAT DEFICIENCY IN PIAUÍ – BRAZIL

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ABSTRACT

Familial LCAT (Lecithin-Cholesterol Acyltransferase) deficiency is a rare disease caused by mutations in the LCAT gene. The deficiency of this enzyme promotes the deposition of lipids in organs, such as the cornea and kidneys, triggering the emergence of systemic morbidities of adverse prognosis. The authors report a male patient who, at 42 years of age, was diagnosed with nephrotic syndrome due to generalized edema and massive proteinuria. The patient's clinical picture associated with severe bilateral corneal opacity suggested a diagnostic hypothesis of familial LCAT deficiency (FLD), confirmed by genetic testing that detected compound heterozygosity in the LCAT gene (c.803G>A p.R268H and c.304A>T p.N102Y). After 12 years of conservative treatment, the patient underwent preemptive kidney transplantation from a deceased donor. At the 5-year follow-up after kidney transplantation, we documented that this was a favorable therapeutic intervention, with regression of proteinuria, control of arterial hypertension, anemia, and metabolic alterations.

Keywords: Lecithin-Cholesterol, Acyltransferase. LCAT Family Disability. Chronic Kidney Disease. Transplantation. Mutation. HDL-Cholesterol. Rare Disease.

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INTRODUCTION

Lecithin-Cholesterol Acyltransferase (LCAT) is an essential enzyme for the esterification of cholesterol and the formation of high-density lipoproteins (HDL). Initially described by Glomset (1962), LCAT catalyzes the cholesterol esterification reaction that occurs by the transfer of a fatty acid from lecithin (a phospholipid) to free cholesterol, forming esterified cholesterol, which becomes less soluble, being incorporated into the lipid nucleus of HDL particles, being ready to be transported back to the liver. where it is finally degraded and eliminated from the body through bile. Thus, the activity of LCAT, removing excess cholesterol from cells and circulation, is crucial for the maintenance of healthy HDL levels in the blood, playing a protective role in cardiovascular health (Glomset, 1968; Kunnen; Van Eck, 2012).

The deficiency or malfunction of the LCAT causes significant disturbances in lipid metabolism, resulting in the accumulation of free cholesterol and pathogenic lipid deposition in various tissues, the consequences of which are potentially serious. The gene responsible for encoding this enzyme is located on chromosome 16 (region 16q22.1), composed of 6 exons and with an approximate genomic size of 4.5 kb, plays a fundamental role in lipid metabolism, and LCAT deficiency is a hereditary disease, transmitted by an autosomal recessive pattern. Pathogenic variants of the *LCAT* gene can cause rare genetic diseases that share common biochemical characteristics, but have important differences in relation to circulating lipoproteins and clinical outcomes: (1) Fish-eye disease (FED; OMIM# 136120) and (2) Familial LCAT deficiency (FLD; OMIM# 245900) (Jonas, 2000).

In EDF, mutations in the *LCAT* gene lead to a partial loss of enzyme activity, specifically abolishing the activity of α-LCAT, preserving the action of β-LCAT (Santamarina-Fojo *et al*., 2019). This alteration causes in patients with fisheye disease an intermediate clinical phenotype with corneal opacity, which may course with anemia, but without severe renal involvement. (Vitali *et al*., 2022) Low HDL levels associated with hypertriglyceridemia are characteristic of this condition. In FLD, on the other hand, genetic mutations promote a complete loss of activity of both α-LCAT and β-LCAT. In this situation, the clinical manifestations are more severe, presenting corneal opacity, low HDL levels, increased triglycerides, associated with anemia of greater severity, and also progressing with chronic nephropathy, which is the main cause of morbidity and mortality in these patients. Renal involvement is characterized by proteinuria of varying degrees and the

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development of progressive chronic kidney disease, leading to the need for renal replacement therapies in the advanced stage (Calabresi, 2012).

Brandão *et al*. (2022) previously reported 6 patients with a clinical and genetic phenotype of FLD with a mutation (c.803G > A p.R268H) located in exon 6 of the *LCAT* gene. Genetic investigation in the family resulted in more than 100% increase in the number of diagnosed cases, totaling 13 individuals with FLD, all from the state of Piauí, Brazil.

The present case report presents the follow-up of a new patient from the same geographic region, without direct kinship with the known cases, without a family history of nephropathies or genetic diseases. He had metabolic alterations, with low levels of HDL cholesterol, bilateral corneal opacity, anemia and severe progressive proteinuric nephropathy. The genetic study revealed an unusual situation, due to the presence of two mutant alleles of the *LCAT gene*, characterizing a compound heterozygosity, with one of the alleles being the same variant previously described in the other families of the state.

CASE REPORT

A 59-year-old white male patient with Chronic Kidney Disease (CKD), secondary to familial LCAT deficiency diagnosed 18 years ago, under conservative clinical treatment for 12 years and submitted, in 2019, to preemptive kidney transplantation, with a deceased donor.

He was referred to a nephrologist at the age of 42 years to investigate anasarca (generalized edema), massive proteinuria (6.9 g/24 h), hypoalbuminemia and dyslipidemia, and the diagnosis of nephrotic syndrome was established, with the institution of treatment with enalapril (20 mg/day), furosemide (80 mg/day), prednisone (60 mg/day) and simvastatin (20 mg/day). The physical examination of the patient, in addition to generalized edema and arterial hypertension, stood out for the presence of symmetrical ocular opacification (fish-eye appearance). An extensive investigation of secondary causes of nephrotic syndrome was carried out at the time, and associated infections, autoimmune diseases and neoplasms were ruled out. In addition, renal biopsy was performed revealing mesangial proliferative glomerulonephritis without etiological identification, with glomerular sclerosis (present in 30% of the glomeruli), of pauci-immune nature.

Due to the presence of persistently reduced HDL cholesterol levels, without response to lipid-lowering therapy (statins), associated with the intense bilateral corneal

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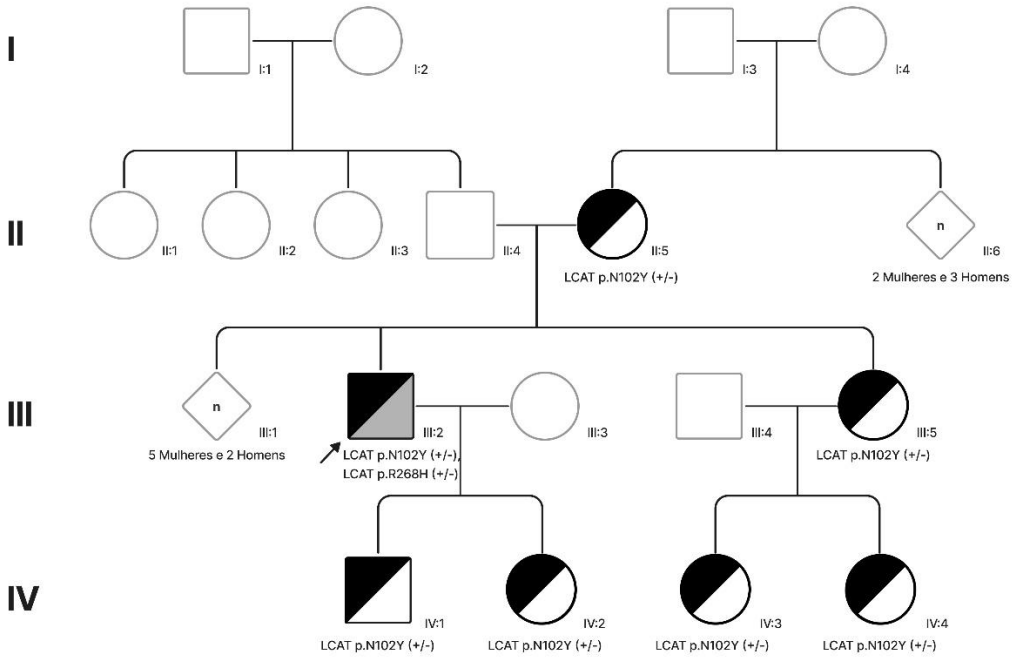
opacity observed in the clinical examination, the clinical suspicion of familial LCAT deficiency was raised, and the patient was referred to genetic analysis. Genotyping was performed by the Centogene laboratory (www.centogene.com), and the entire coding region of both DNA strands of the LCAT gene was sequenced, in addition to the splicing regions, revealing a rare case of compound heterozygosity, with a mutation in exon 6 (c.803G>A p.R268H) and another in exon 2 (c.304A>T p.N102Y).

With the confirmation of mutations in the *LCAT* gene, a genetic investigation was carried out in the family. None of the relatives tested showed clinical evidence of FLD, however all relatives tested showed heterozygosity in exon 2 (c.304A>T p.N102Y). Figure 1 shows the pedigree of the family.

Figure 1. Family pedigree indicating compound heterozygosity in the index case and heterozygosity of the relatives tested.



Squares indicate men; circles indicate women, rhombus indicates unspecified gender; half-black, half-gray symbol indicates compound heterozygosity; half-filled symbols indicate heterozygous carriers; Symbols with gray borders indicate untested individuals.

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DISCUSSION

In the present study, we describe the evolution of an adult male with chronic nephropathy secondary to FLD, whose etiological diagnosis was established by clinical, laboratory and molecular test criteria, with the identification of two mutations in the *LCAT* gene (c.803G>A p.R268H and c.304A>T p.N102Y) characterizing a compound heterozygosity.

During clinical follow-up, the patient developed progressive worsening of renal function, monitored by the glomerular filtration rate (GFR) estimated by creatinine clearance. In addition, she had persistent massive proteinuria, hypoalbuminemia, erythropoietin-resistant anemia, and statin-unresponsive dyslipidemia. After 12 years of conservative nephrological treatment, having reached stage G5A3 of CKD (with GFR less than 15ml/min/1.73m2), the patient was referred for renal replacement therapy through preemptive kidney transplantation from a deceased donor, performed in November 2019.

During the five years of post-transplant follow-up, the patient maintained the use of immunosuppressive treatment with prednisone, tacrolimus, and mycophenolate mofetil. Despite the chronic graft dysfunction, the clinical evolution has been favorable. Notably, there was a significant regression of proteinuria, anemia and dyslipidemia, with an increase in HDL levels, in addition to better control of arterial hypertension (Table 1).

Table 01. Clinical and biochemical data of the FLD patient in the evaluation before and after 5 years of preemptive kidney transplantation from deceased donor.

Parameters analyzed	Reference values	Pre-transplant	Post-transplant (5 years)
Age (years)		54	59
Weight		78.8 kg	76.5 kg
Blood pressure	<130x90 mmHg	177x90 mmHg	130x80 mmHg
Hemoglobin	13-16.9 g/dL	10.3 g/dL	14.3 g/dL
Haematocrit	40-50 %	32 %	43 %
Glucose	70 - 99 mg/dL	75 mg/dL	98 mg/dL
Total Cholesterol	< 190 mg/dL	240 mg/dL	93 mg/dL
HDL	> 40 mg/dL	12 mg/dL	25 mg/dL
Triglycerides	< 150 mg/dL	188 mg/dL	115 mg/dL
Urea	10 - 50 mg/dL	197 mg/dL	62 mg/dL
Creatinine	0.7 - 1.3 mg/dL	7.0 mg/dL	1.7 mg/dL
eGFR (CKD-EPI)	>90 mL/min/1.73m2	9 ml/min/1.73m2	48 ml/min/1.73m2
Creatinine clearance	85 - 125 mL/min/1.73 m2	11 mL/min/1.73 m2	---
24-hour proteinuria	< 0.3 g/24h	6900 mg/24h	< 300 mg/24h

The clinical picture and the biochemical and metabolic alterations of the patient corroborated the molecular diagnosis and the *in silico prediction* of the mutations found.

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The patient presents a clinical phenotype of familial LCAT disease, maintaining persistently reduced HDL cholesterol levels with altered lipid profiles, in addition to anemia, corneal opacity, and proteinuric nephropathy that evolves with progressive loss of renal function (Santamarina-Fojo *et al*., 2000). Renal dysfunction in this disease is usually variable and unpredictable, and may manifest early in childhood, but advanced renal failure usually appears between the fourth and fifth decades of life, which converges with the finding of this study (Santamarina-Fojo *et al*., 2019; Panescu *et al*., 1997).

Recently, Vitali and his collaborators (2022) in a systematic review documented a number of 89 mutations of homozygous and heterozygous composite patients with clinical classification for FLD and FED, with 61 mutations associated with FLD and 28 mutations that cause FED, in addition to a few other variants (04) that could not be clearly classified. This study also brought a dozen mutations in heterozygous individuals with no FLD or EDF phenotypes.

Familial disease of LCAT is an autosomal recessive disease. Although this condition is often associated with patients homozygous for mutations in the *LCAT* gene, it can also occur in compound heterozygous individuals, who inherit different mutations of each parent's gene. These patients have a clinical form of the disease with characteristics similar to those observed in homozygotes, including dyslipidemia with reduced high-density lipoproteins (HDL), lipid deposits in organs such as the cornea and kidneys, and an increased risk of cardiovascular complications (Strom *et al*., 2011; Norum *et al*., 2020).

The proband of this family has heterozygosity for two mutations in the *LCAT* gene, the mutation in exon 2 (c.304A>T p.N102Y) and exon 6 (c.803G>A p.R268H). The genetic investigation revealed that the mother has and transmitted the mutation (c.304A>T p.N102Y) to the proband, as well as transmitted it to the tested daughter and they transmitted it to their descendants, but none of them has the mutation (c.803G>A p.R268H) of exon 6. Thus, all the relatives tested in this family nucleus are heterozygous for the c.304A>T p.N102Y mutation (Figure 1).

The mutation (c.803G>A p.R268H) was first described by Calabresi *et al*. (2005). Subsequently, Norwegian researchers (Strom *et al*., 2011) described a case of compound heterozygosity and Brandão *et al*. (2022) reported the presence of this mutation in six families living in nearby municipalities in the interior of northeastern Brazil, who apparently do not have family relations.

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According to the genetic analysis of the family, it cannot be ruled out that it is a point mutation, since only the proband has it. The mutation present in exon 2 (c.304A>T p.N102Y) has not yet been described in the literature and all other relatives tested are carriers of this mutation. From the identification, this mutation was tested in the PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) program to predict whether it may be pathogenic or not. This software uses 11 predictive traits, 8 sequence-based and 3 structure-based, most of which involve comparing a wild-allele property with the corresponding mutated allele property. As a result, the program also brings a qualitative analysis, where it evaluates the mutation as benign, possibly harmful or probably harmful. Both the c.803G>A p.R268H mutation, with a known clinical character, and the c.304A>T p.N102Y mutation totaled the algorithm score (1.0), both being considered probably harmful (Adzhubei *et al*., 2010).

The identification of another family with the R268H mutation in such a restricted region in the interior of northeastern Brazil reinforces the idea that all these families come from a common ancestral branch that branched out and perpetuated over the years, thus reinforcing the idea of the need for a study of the founding effect of this mutation found in the interior of Piauí-Brazil.

To date, there is no specific treatment for LCAT activity deficiency. Studies with different approaches have been carried out using LCAT as a therapeutic target, among them: gene and cell therapies, peptides and small molecules activating LCAT and recombinant human LCAT (rhLCAT) for enzyme replacement therapy, the latter being the most advanced therapy in clinical studies (Freeman; Karathanasis; Remaley, 2020). Thus, the follow-up of affected patients requires an early assertive diagnosis, with in-depth genetic investigation in the family, support for the alterations presented, and monitoring of renal function to delay the progression of the disease as much as possible (Althaf *et al*., 2015; Aranda *et al*., 2008; Miarka *et al*., 2011; Naito *et al*., 2013).

Patients with FLD are candidates for kidney transplantation restoring kidney function. Although the literature indicates the presence of early histological findings compatible with FLD, graft survival persists in the long term (Panescu *et al*., 1997; Strom *et al*., 2011; Najafian *et al*., 2017). Pavanello and collaborators (2020) in an Italian cohort study following patients with FLD for a mean period of 12 years, showed a mean time of 10 years for a second recurrence (dialysis, kidney transplantation, or death from kidney complications).

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In the context of rare genetic diseases, such as familial LCAT deficiency, despite the current unavailability of specific treatments, early diagnosis and conservative treatment of CKD have allowed to delay the progression of nephropathy for about 12 years. Understanding the interaction between lipid metabolism defect and renal dysfunction was essential to improve patient care and minimize clinical complications. The preemptive kidney transplantation successfully performed in the case in a timely manner prevented the onset of uremia and life-threatening complications, avoiding the need for dialysis, significantly improving the quality of life of the patient, who has satisfactory control of clinical, metabolic and hematological parameters in the first 5 years of post-transplant follow-up.

CONCLUSION

In conclusion, this report highlights that the presence of nephropathy in familial LCAT deficiency is a complex condition, with progressive evolution, which requires a comprehensive and early approach to improve the clinical prognosis and quality of life, aiming to delay the progression of chronic kidney disease and associated complications. A particularity of this case was the identification of compound heterozygosity in *the LCAT gene* with a potential deleterious effect on the prognosis, reinforcing the medical interventions adopted and the rigorous clinical monitoring. In addition, preemptive kidney transplantation from deceased donors, adopted in a timely manner, proved to be a favorable therapeutic intervention in the clinical stabilization of the patient during the initial 5 years of follow-up.

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