Original Research Paper

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General Medicine

RARE CAUSE OF END STAGE RENAL DISEASE- LCAT DEFICIENCY

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ABSTRACT LCAT deficiency is a disorder of lipoprotein metabolism occurring due to mutation of LCAT gene located on 16q22.1. It is a very rare disorder with only 70 reported cases of familial LCAT deficiency and only 30 cases of partial LCAT deficiency. This is a rare case of LCAT deficiency, which presented as ESRD.A 28-year-old female diagnosed with ESRD 2 years earlier and already on treatment, referred for renal transplantation. On examination B/L corneal opacities, pallor and pedal edema were present. Patient had proteinuria and HDL <10mg/dl and resistant anemia. Renal biopsy showed deposit glomerulopathy with foam cells. Genetic analysis was done which showed LCAT deficiency. Supportive and symptomatic treatment initiated. She was enrolled for cadaver transplantation in view of recurrence.

KEYWORDS : LCAT Deficiency, ESRD, HDL cholesterol, Lipoprotein metabolism disorder

INTRODUCTION:

LCAT deficiency is a disorder of lipoprotein metabolism occurring due to mutation of LCAT gene located on 16q22.1[1]. It is a very rare disorder with only 70 reported cases of familial LCAT deficiency and only 30 cases of partial LCAT deficiency (Fish-eye disease)[2]. Around 90 mutations are seen in LCAT gene which presents with varying clinical manifestations. Renal involvement is major cause of morbidity and mortality.

CASE REPORT:

A 28-year-old female presented to OPD for further evaluation regarding renal Transplantation with mother as donor. She was diagnosed 2 years back as having Chronic kidney disease and is on Haemodialysis. At the age of 15 years she had swelling of both lower limbs, diagnosed to have renal disease by a local practitioner. She discontinued all the medication for 10 yrs. She gives history of intermittent pedal edema during this period but it was never evaluated. 2 years after marriage, during routine evaluation for infertility found to have renal insufficiency and proteinuria. Her Serum creatinine was 2.1mg/dl, Urinalysis showed 2+ albumin, RBCs 10-12/hpf and 24hr Urine Protein was 2.2 gm/day. Ultrasound abdomen done showed normal sized kidneys and so patient was subjected to renal biopsy outside.

Renal biopsy revealed enlarged glomeruli with significant mesangial widening, scattered foam cells within the mesangium with mild interstitial lymphocytic infiltration, suggestive of deposit glomerulopathy. Immunofluorescence showed peripheral and mesangial deposits of C3c.

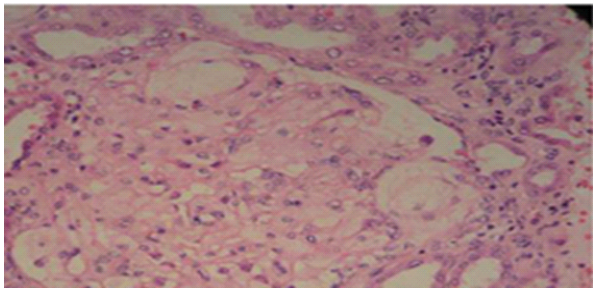

Fig 1: Renal biopsy showing mesangial expansion and foamy cell infiltration.

Electron microscopy of glomerulus showed few curvilinear deposits present in the capillary lumina which resemble cryoglobulins. Collagen profile was negative, C3 and C4 were normal, Cryocrit was negative, TSH was 7.8 µIU/ml and Anti TPO antibodies was negative. Patient was started on steroids, diuretics, anti-hypertensives, haematinics and other supportive measures. She received multiple blood transfusions for resistant anaemia. In spite of all these measures, patient slowly progressed to End Stage Renal Disease and initiated on maintenance haemodialysis. She came to us for further evaluation for renal transplantation.

On examination in the OPD, patient was pale and had bilateral pedal edema. There were corneal opacities in both eyes. Ocular Examination revealed Visual Acuity of 6/6 in both eyes with bilateral focal hazy cornea. Fundus examination revealed hazy media in both eyes due to corneal haziness with bilateral Arteriolar narrowing with AV crossing changes-Bilateral Grade II Hypertensive Retinopathy with Sclerocornea.Investigations revealed Creatinine- 4.6 mg/dl,Total cholesterol -73mg/d, *HDL- 10 mg/dl*, LDL- 23 mg/dl, Triglycerides - 199 mg/dl, VLDL- 40 mg/dl, LDL/HDL Ratio 2.3.

Differential Diagnosis: Familial LCAT deficiency, Apo A-I deficiency, Combined apo A-I/ apo-III deficiency, Familial Hypoalphalipoproteinemia, Tangier disease

Genetic Analysis:

She was diagnosed as Chronic Kidney Disease Stage V Secondary to familial LCAT Deficiency. Patient started on supportive and symptomatic treatment, continued hemodialysis. Deferred mother as donor and patient was enrolled for cadaver transplant as there will be definite recurrence.

Test purpose:

Testing for the presence/absence of specific variants in the *LCAT* gene.

RESULT:

We identified the following variants in the *LCAT* gene in this individual.

Gene Genomic Coordinate, hg19	Exon	HGVSc Nomenclature, Zygosity	Inheritance[a]	HGVSp Nomenclature	Variant Category[b]
LCAT, chr16:67974176C>T	6	NM_000229.1:c.954G>A, Homozygous	AR	NP_000220.1:p.Trp318*	VUS

[a]AD - Autosomal Dominant, AR-Autosomal Recessive, XL-X-Linked,
[b] As per Richards, Sue et al; Genet Med 2015/05/print 17- 5 pg 405-423. ACMG

Fig 2: Genetic analysis report

DISCUSSION:

LCAT enzyme is a monomeric glycoprotein. Gene is located on chromosome 16 (q21 – q22). It is synthesized in liver and is responsible for the production of cholesteryl esters and the maturation of HDL cholesterol. It plays a key role in reverse cholesterol transport[3]. It has role in adrenal steroidogenesis, platelet activation, insulin sensitivity and metabolism of oxidized phospholipids. Transfer of cholesteryl esters leads to conversion of nascent HDL to mature α LCAT. β LCAT also facilitates esterification of LDL cholesterol. Accumulation of pre β HDL and triglyceride rich LDL, in association with phosphatidylcholine form abnormal lipoprotein X which gets deposited in tissues such as cornea, spleen, bone marrow and kidney[4]. Corneal opacities as minute greyish dots in the entire corneal stroma.Anaemia due to decreased red cell span due to altered phospholipid content of the RBC membrane , impaired membrane stability and reduced production due to foamy cell infiltration. Renal failure Presents as nephrotic or non nephrotic proteinuria and slowly progresses to End Stage Renal Disease[5].

Familial apo A-I structural mutations	Abnormal apo A-I	Autosomal dominant	Rapid apo A-1 catabolism	HDL 15-30 mg/dL; TGs increased	Often none; sometimes corneal opacities	
Familial LCAT	LCAT deficiency (complete)	Autosomal recessive	Rapid HDL catabolism	HDL < 10 mg/dL; TGs increased	Corneal opacities, anemia, proteinuria, renal insufficiency	No
Fish-eye disease	LCAT deficiency (partial)	Autosomal recessive	Rapid HDL catabolism	HDL < 10 mg/dL; TGs increased	Corneal opacities	No
Tangier disease	Unknown	Autosomal codominant	Very rapid HDL catabolism	HDL < 5 mg/dL; TGs usually increased	Corneal opacities, enlarged orange tonsils, hepatosplenomegaly, peripheral neuropathy	No to yes
Familial HA	Unknown	Autosomal dominant	Usually rapid HDL catabolism	HDL 15-35 mg/dL; TGs normal	Often none; sometimes corneal opacities	No to yes

Fig 3: Differential Diagnosis

There is no definitive therapy. Symptomatic treatment with lipid lowering drugs, steroids, ACEI and anti-hypertensives should be considered. Patients who develop ESRD require haemodialysis or kidney transplantation. However, it recurs in the graft following renal transplantation with reasonable graft survival.

CONCLUSION:

LCAT deficiency is a rare genetic disorder, which may present with varying clinical manifestations, of which chronic kidney disease is common causing morbidity. Though patients present with low HDL levels and high triglycerides, there is no significant evidence of increase in incidence of coronary heart disease. Diagnosing a genetic disorder can be challenging. Physical examination still remains the cornerstone in its diagnosis even in this modern era.

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