Lipoprotein glomerulopathy: a case report of a rare disease in a brazilian child

Glomerulopatia por lipoproteínas: relato de caso de uma doença rara em criança brasileira

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Abstract

Lipoprotein glomerulopathy (LPG) is a rare autosomal recessive glomerulopathy associated with the deposition of lipoprotein thrombi in the capillary lumina due to apoE gene mutations. Abnormal plasma lipoprotein profile and marked increase in serum apolipoprotein E (apoE) are characteristic clinical data. The compromised patients can present nephrotic syndrome, hematuria, and progressive renal failure. Herein, the authors present the first described case of LPG in a Brazilian male patient, 11 years, who presented with a steroid-resistant nephrotic syndrome. Renal function was normal. Kidney biopsy showed markedly enlarged glomerulus, with dilated capillary loops and weak eosinophilic lipoprotein thrombi in the capillary lumina. Interstitium, tubules, arteries, and veins showed normal histologic aspect. Genotypic study for the apoE gene showed the presence of the alleles E3 and E4. The diagnosis of LPG was then performed. The patient received lipid-lowering treatment. After 2 years of follow-up, renal function is gradually decreasing, with persisting heavy proteinuria, despite a marked decrease in serum cholesterol and triglycerides levels.

Keywords: apolipoproteins E; kidney; lipoproteins; nephrotic syndrome; pathology.

Resumo

A Glomerulopatia por Lipoproteínas (GLP) é uma glomerulopatia autossômica recessiva rara associada à deposição de trombos de lipoproteína nos lúmens capilares devido a mutações do gene de ApoE. Perfil anormal das lipoproteínas do plasma e aumento acentuado no soro de apolipoproteína E (apoE) são dados clínicos característicos. Os pacientes acometidos podem apresentar síndrome nefrótica, hematúria e insuficiência renal progressiva. Aqui, os autores apresentam o primeiro caso descrito de GLP em um paciente brasileiro do sexo masculino, 11 anos, que se apresentou com uma síndrome nefrótica corticoide resistente. A função renal era normal. A biópsia renal mostrou glomérulos marcadamente aumentados, com capilares dilatados e lúmens ocupados por trombos de lipoproteínas fracamente eosinofílicos. Interstício, túbulos, artérias e veias mostraram aspecto histológico normal. O estudo genotípico para o gene apoE mostrou a presença dos alelos E3 e E4. O diagnóstico de GLP foi então realizado. A paciente recebeu tratamento hipolipemiante. Depois de 2 anos de seguimento, a função renal está diminuindo gradualmente, com a persistência de marcada proteinúria, apesar de uma diminuição acentuada dos níveis séricos de colesterol e triglicerídios.

Palavras-chave: apolipoproteínas E; lipoproteínas; patologia; rim; síndrome nefrótica.

Introduction

Lipoprotein glomerulopathy (LPG) is a rare hereditary renal disease that is related to mutations in apoE gene. Abnormal plasma lipoprotein profile and marked increase in serum apoliprotein E (ApoE) are characteristic laboratory findings. Clinical manifestations include proteinuria, nephrotic syndrome, hematuria, and progressive renal failure. The most important histopathologic finding is the presence of eosinophilic lipoprotein thrombi within dilated glomerular capillary lumina.[1-3] Herein, the authors report the first case of LPG in a brazilian child, presenting with nephrotic syndrome.

Data de submissão: 07/23/2013.
Data de aprovação: 09/26/2013.

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DOI: 10.5935/0101-2800.20140015

Case report

Male Brazilian child, 11 years, was admitted to hospital service presenting marked edema of the lower limbs and face. Prior history did not reveal significant disorders, familial history of kidney disease, or parental consanguinity. The other organs and systems showed no changes on physical examination. Laboratory workup showed the features of a nephrotic syndrome, with normal urine sediment and oval fat bodies (detailed data on Table 1). Workup for underlying infectious disease was negative. The patient underwent steroid therapy (prednisone 2 mg/kg) for 6 weeks, with no response. At this time, a kidney biopsy revealed markedly enlarged glomerulus, with dilated capillary loops, and the presence of weak eosinophilic lipoprotein thrombi in the capillary lumina (Figure 1), which exhibited weakly positive reaction on periodic acid-Schiff (PAS) and Masson's Trichrome stains (Figure 2). Interstitium, tubules, and vascular vessels showed normal histologic aspect. Genotypic study (performed by polymerase chain reaction) for the apolipoprotein E (ApoE) gene showed the presence of the alleles E3 and E4. The diagnosis of LPG was then performed. The patient was submitted to clinical therapy with enalapril, simvastatin and losartan. After 6 months of treatment, serum cholesterol and triglyceride levels decreased significantly and a moderate reduction of proteinuria was identified. Albumin levels remained below normal, and serum creatinine levels remained stable (details on Table 1). Around twelve months of diagnosis, the patient received cyclosporin (6 mg/Kg) for thirty days, without clinical improvement, and then this therapy was interrupted. After 2 years of the diagnosis, serum cholesterol and triglyceride levels remain at near normal values, but proteinuria remains massive (13.3 g/24 hours in the last analysis), and renal function is declining (serum creatinine 2,4 mg/dl, estimated GFR 50 ml/min/1.73 m^2). The patient remains free of edema, despite hypoalbuminemia. Urinary sediment analysis at this point revealed a nephrotic and nephritic profile presenting mild hematuria (5-6 erythrocytes per high power field) including dismorphic erythrocytes, oval fat bodies and 5-6 casts (hialin, hialin-granular, granular and fatty) per low power field.

Table 1 Laboratory data

	At presentation	After 6 months*
Total Cholesterol	534 mg/dl	186 mg/dl
Triglycerides	637 mg/dl	197 mg/dl
VLDL	53 mg/dl	------
Albumin	2.6 g/dl	3.0 g/dl
Creatinine	0.7 mg/dl	0.7 mg/dl
Lactate dehydrogenase	174 u/l	-----
Proteinuria	10.7 g/24 hours	5.45 g/24 hours

* After therapy with enalapril, simvastatin and losartan.

Figure 1. Lipoprotein glomerulopathy: enlarged glomerulus showing eosinophilic lipoprotein thrombi in the capillary lumina, hematoxylin-eosin, 200x.

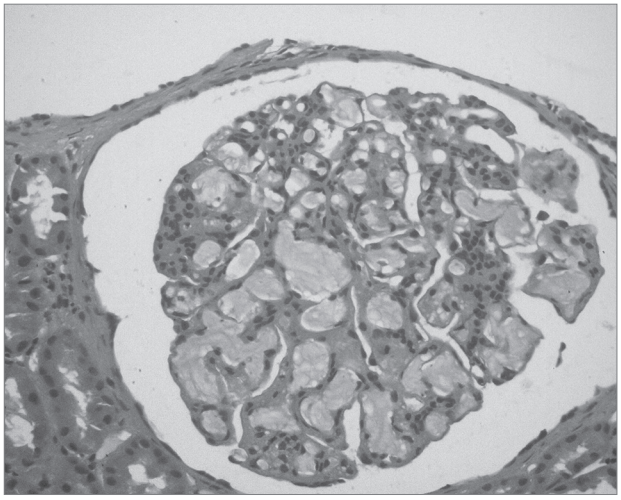
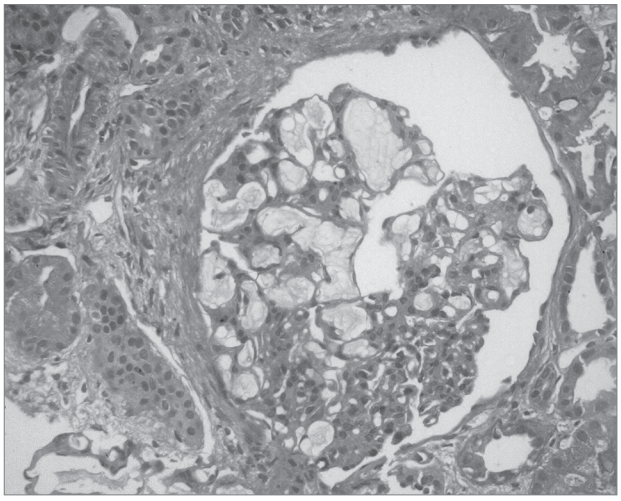


Figure 2. Lipoprotein glomerulopathy: lipoprotein thrombi were weakly positive on Masson's Trichrome stain, 200x.



Discussion

ApoE is an essential class of apolipoproteins related to the lipoprotein metabolism. ApoE mutations result in type III hyperlipoproteinemia in which increased serum cholesterol and triglyceride levels are the consequence of a decreased clearance of chylomicron, VLDL, and LDL. ApoE gene is located on chromosome

19q13.2, and has three common alleles E2, E3, and E4 that encode three isoforms: $_E2$, $_E3$, and $_E4$. These isoforms differ in one amino acid substitution. Several mutations in the ApoE gene have been described in patients with LPG, including ApoE Sendai, ApoE Kyoto, ApoE Tokyo, ApoE1, ApoE Chicago, ApoE Okayama, and ApoE Tsukuba. While the E3 isoform protein is present in most of the population and is considered a "neutral" phenotype, E2 and E4 may be dysfunctional and can be associated with atherosclerosis. E4 isoform also appears to be associated with an increased risk of Alzheimer's disease and impaired cognitive function.[2,4-9] Our institution does not have qualified tests to establish serum levels of apoE, but the characteristic histopathologic findings allowed us to establish the diagnosis of LPG.

LPG is an uncommon autosomal recessive glomerulopathy that predominantly affects Chinese, Japanese, and Taiwanese. Rare cases have been described in Caucasians/Europeans. There are no previous reports of LPG in Brazilian people in the international literature. The disease may present in childhood, and males are more commonly affected (2:1). Abnormal apoE proteins favor basement membrane and mesangial alterations that lead to increased glomerular permeability and nephrotic syndrome with higher levels of LDL, VLDL and apolipoproteins B, C-II, and C-III. Increase in LDL and VLDL is associated with decreased catabolism secondary to decreased binding of lipoprotein lipase to endothelial cells, and to a decrease in the VLDL receptor. In LPG, hyperlipidemia is also related to decreased clearance of chylomicron, VLDL, and LDL.[1-3,9]

Classic histologic features include the presence of weak eosinophilic lipoprotein thrombi in glomerular capillary loops, which are markedly dilated. The lipoprotein thrombi stains weakly on periodic acid-Schiff (PAS), Masson's Trichrome and Oil Red O stains, the latter in unfixed tissue sections. Mild glomerulomegalia, focal reduplication of capillary basement membrane with mesangial interposition, mesangiolysis, mesangial proliferation, and focal segmental sclerosis may occur in some cases. No foam cells are identified in glomeruli or interstitium.[1,2,4,5] Conventional immunofluorescence shows no deposits of immunoglobulins or complement. IgA deposition can be identified in rare cases. Glomerular thrombi can show positive immunoexpression for apolipoproteins B and E antibody. Electron microscopy shows dilation of glomerular capillary loops, which contain thrombi with granules and vacuoles of various sizes forming concentric lamellated structures.[1,2,4,5]

Differential diagnosis include fat emboli (round globules of fat, with scant or absence of apolipoprotein component, and without laminated appearance by electron microscopy), and deficiency of lecithin-cholesterol acetyltransferase (that is characterized by "bullous" capillaries, an expanded, vacuolated mesangium, and foam cells in capillaries and mesangium). There is no effective treatment for LPG. About 50% of patients progress to chronic renal failure. Intensive lipid-lowering therapy (statins) has been associated to clinical remission, and in some cases disappearance or reduction of thrombi in glomerular capillary loops has been described. Recurrence of disease after renal transplantation has been documented in some cases.[2,5,7,8,10]

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