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A Familial Infantile Renal Failure

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INTRODUCTION

The majority of cases of congenital nephrotic syndrome have mutations in components of glomerular filtration barrier especially nephrin and podocin. Mutations in genes highly expressed in podocytes have been found in two-thirds of patients presenting with steroid-resistant nephrotic syndrome in the first year of life.[1–4] Mutations in 7 genes (*NPHS1*, *NPHS2*, *CD2AP*, *PLCE1*, *ACTN4*, *TRPC6,* and *INF2*) are implicated in different forms of nonsyndromic steroid-resistant nephrotic syndrome.[2] We report a rare family with multiple cases of congenital nephrotic syndrome, with all of them progressing to end-stage renal disease during infancy.

CASE PRESENTATION

A 4-month-old boy presented at our clinic with acute gastroenteritis and anasarca, with the latter beginning at 2.5 months of age, and worsening progressively due to nephrotic range proteinuria. The child was born full term to an Indian family. He had a family history of anasarca that progressed to renal failure and death of 2 siblings at the age of 2 years and 9 months, respectively (Figure 1). Both siblings had early onset at around 2 months of life with anasarca. Laboratory parameters are shown in Table 1.

Kidney biopsy was done to underpin the etiology of his congenital nephrotic state. Light microscopy revealed 12 glomeruli, of which 8 were completely sclerosed with podocytic hyperplasia. Examination of the tubulointerstitial compartment showed patchy tubular atrophy, interstitial inflammation, and fibrosis involving 20%–25% of the cortex sampled. There was marked microcystic dilation of the tubules with occasional broad hyaline cast (Figure 2). Immunofluorescence was negative for Igs and complement. Electron microscopy revealed diffuse podocyte foot process effacement with focal areas of podocytic detachment and glomerular basement membrane wrinkling. Mild mesangial matrix expansion was also noted.

The diagnosis of familial congenital nephrotic syndrome was considered in this patient because of a positive family history of renal failure with an autosomal recessive inheritance pattern and early onset of nephrotic syndrome. Mutation analysis by Sanger sequencing was done for *NPHS1* (29 exons), *WT1* (for exons 8 and 9), and *PLCE1* (31 exons). We identified a novel homozygous nonsense mutation located in exon 7 (c.2290G>T, p.Glu764*) of the *PLCE1* gene. This is consistent with the diagnosis of autosomal recessive steroid-resistant congenital nephrotic syndrome type 3 (NPHS3) (Figure 3). The affected child developed early onset disease and inherited the mutation from his asymptomatic parents who were both heterozygous carriers.

The child received oral indomethacin and oral enalapril till 9 months of life. His indomethacin was stopped when his serum creatinine started increasing. He progressed to chronic kidney disease-stage V at 1 year of life, and he succumbed to his illness at home.

DISCUSSION

NPHS3 is a severe form of isolated congenital nephrotic syndrome with rapid progression to terminal renal failure. It is caused by a developmental rather than structural podocyte dysfunction, as *PLCE1* has been implicated in glomerulogenesis. It is a major cause of isolated diffuse mesangial sclerosis. Apart from *NPHS2*

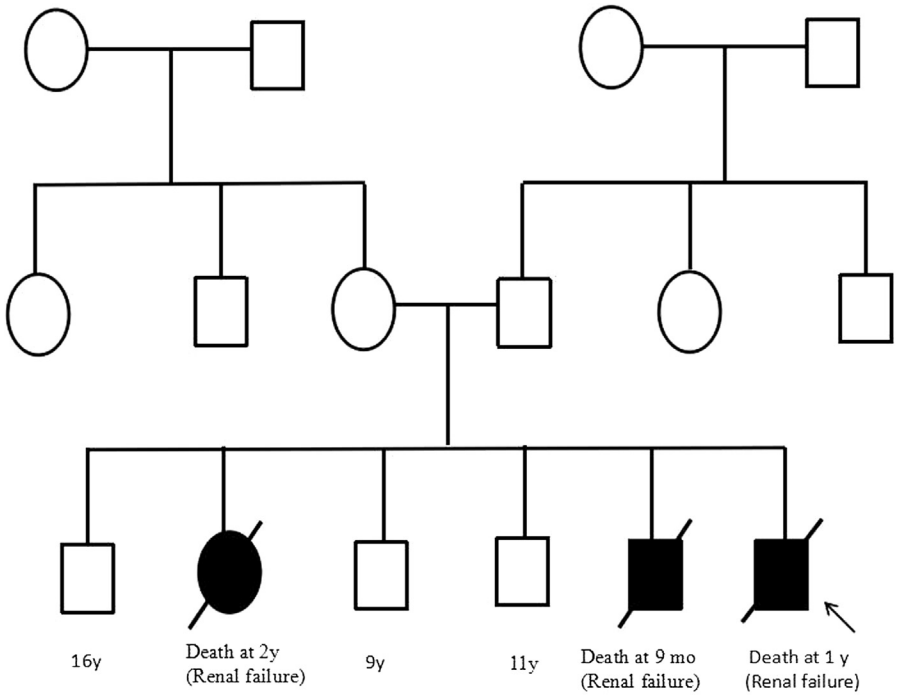

Figure 1. Pedigree of the family.

and *NPHS1*, *PLCE1* is involved in some cases of infantile and childhood-onset steroid-resistant nephrotic syndrome.[1–3] Causes of congenital nephrotic syndrome are summarized in Table 2.

Mutations in *PLCE1*, *WT1*, and *LAMB2* genes can cause isolated diffuse mesangial sclerosis, with *PLCE1* being the most common cause.[3,4] It is proposed that renal histopathologic patterns corroborate with the kidney developmental stages at which *PLCE1* activity is required. Accordingly, diffuse mesangial sclerosis occurs from a developmental arrest due to truncating *PLCE1* mutations, whereas focal segmental glomerulosclerosis arises from low-level or dysfunctional *PLCE1* in the less severe molecular defects.[1–3]

Therapy response in NPHS3 cases has been documented in a few cases, opening insights into genomic and nongenomic effects of glucocorticoids on podocytes.[2,4] Positional cloning has uncovered mutations in PLCE1 responsible for nephrotic syndrome that may be reversible with immunosuppressants.[2]

Most intriguing aspects with *PLCE1* mutations are the genotype-phenotype variability and response to immunosuppressants that have been documented in various studies, reiterating the importance of performing mutation analysis for all implicated genes in congenital nephrotic syndrome. We however did not use any immunosuppression in the case, in view of rapid deterioration of renal function during

Table 1. Laboratory investigations (4 mo of age)

Blood	
BUN (mg/dl)	27 (7–20)
Creatinine (mg/dl)	0.5 (0.1–0.4)
Cholesterol (mg/dl)	264 (<200)
Albumin (g/dl)	2 (3.5–5.5)
Hb (g/dl)	12.2 (10–14)
TLC ($\times 10^9$/l)	18.2 (5–15)
Platelet ($\times 10^9$/l)	302 (150–400)
Urine	
Protein/creatinine (mg/mg)	39.08 (<0.20)
Protein	3+
Radiology	
USG abdomen	Bilateral renal parenchymal disease, enhanced echogenicity, mild ascites

Data in parentheses represent normal range/values.
BUN, blood urea nitrogen; Hb, hemoglobin; TLC, total leukocyte count; USG, ultrasonography.

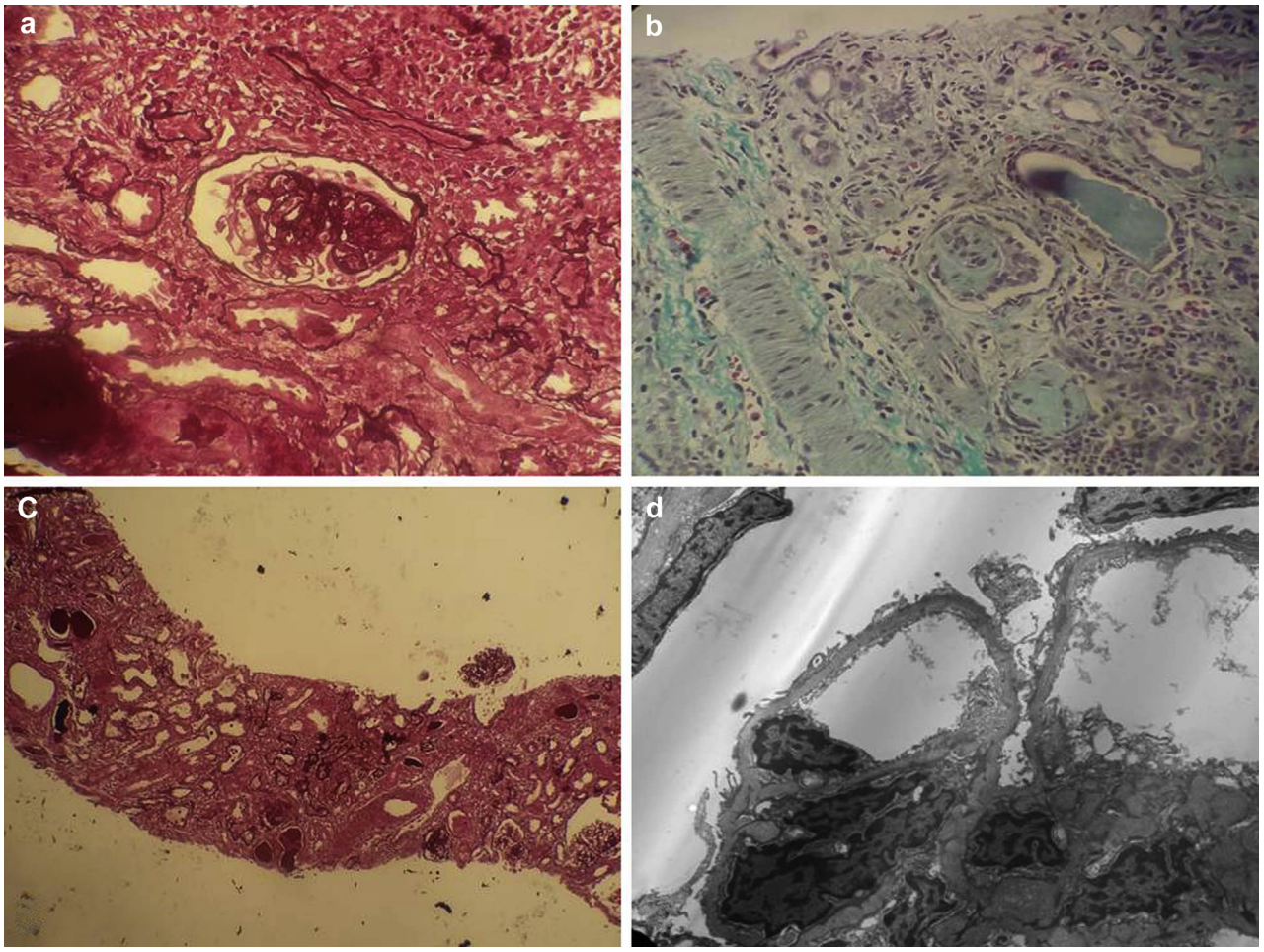

Figure 2. Light microscopy (with special stains) and electron microscopy of the kidney biopsy. (a) Glomerulus with mesangial matrix expansion and segmental sclerosis with proliferation of overlying podocytes is noted (hematoxylin and eosin [H&E] Ag, original magnification ×400). (b) Masson's trichrome stain highlights the area of mesangial expansion along with proliferation of overlying podocytes (MT, original magnification ×400). (c) Silver-stained section reveals single linear core of renal biopsy with a small patch of tubular atrophy occupying 15% of the sampled cortex (H&E Ag, original magnification ×100). (d) Electron microscopic examination reveals diffuse foot process effacement. No immune complex deposits noted (direct magnification ×10,000).

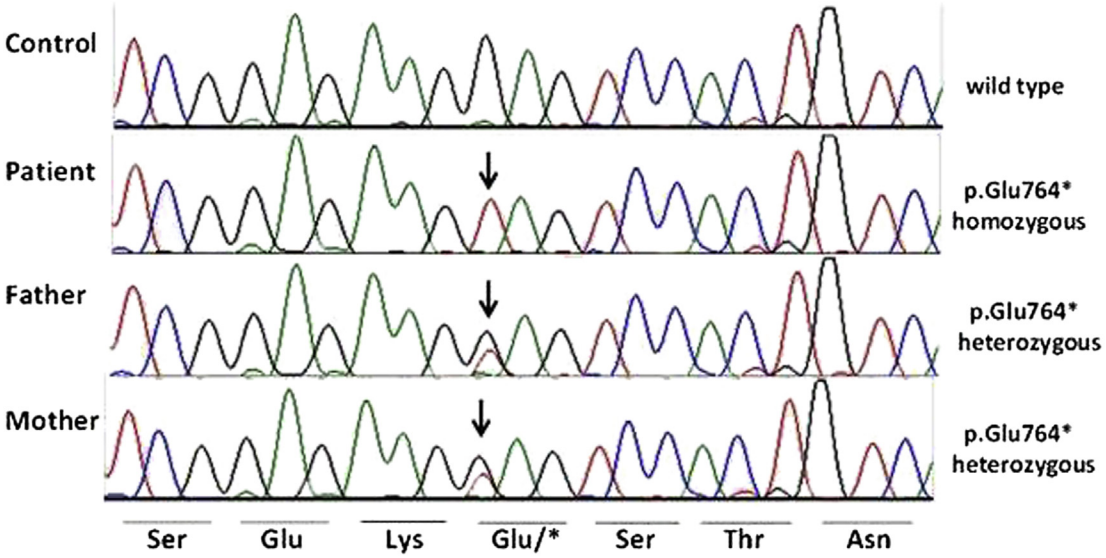

Figure 3. Electropherogram showing a novel homozygous nonsense mutation (c.2290G>T, p.Glu764*) in exon 7 of the *PLCE1* gene (phospholipase C, epsilon1) in the index patient. Note that both parents are heterozygous carriers of the mutation (arrows). Nucleotide and protein numbering are based on the *PLCE1* isoform with the Genbank accession number NM_016341.3.

Table 2. Causes of congenital nephrotic syndrome

Known mutations
• Nephrin (*NPHS1*) gene: classic "Finnish" type
• Podocin (*NPHS2*) gene
• Phospholipase C epsilon 1 (*PLCE1*) or *NPHS3* gene
• Wilms tumor suppressor 1 (*WT1*) gene: Denys-Drash syndrome; isolated nephrotic syndrome
• Laminin β2 (*LAMB2*) mutation: Pierson syndrome; isolated nephrotic syndrome
• Laminin β3 (*LAMB3*) mutation: Herlitz junctional epidermolysis bullosa
• Lim transcription factor 1β (*LMXB1*) mutation: nail-patella syndrome
Rare causes
• Galloway-Mowat syndrome
• Mitochondrial disorders
• Primary focal segmental glomerulosclerosis
• Congenital infections: syphilis, toxoplasma, malaria, cytomegalovirus, rubella, hepatitis B, HIV
• Maternal systemic lupus erythematosus

infancy. This report further highlights the idea that both clinical course and histology in NPHS3 are subject to genotypic variability and that mutational analysis is the most reliable diagnostic tool. Future studies are needed to determine the clinical implications of NPHS3.

DISCLOSURE

All the authors declared no competing interests.

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