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Pierson Syndrome in an Infant With Congenital Nephrotic Syndrome and Unique Brain Pathology

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INTRODUCTION

Congenital nephrotic syndrome (CNS) typically results from mutations leading to abnormalities of the glomerular filtration barrier. Laminin β2, encoded for by *LAMB2*, is a major component of numerous structures throughout the body, including the glomerular basement membrane (GBM). Loss of laminin β2 results in CNS with ocular abnormalities, also known as Pierson syndrome. Although first described by Pierson *et al*. in 1963,[1] the underlying genetic defect was not identified until 2004.[2]

Here we present a case of Pierson syndrome in an infant with CNS and unique brain pathology. Although genetic testing is critical in the evaluation of all patients with CNS, increased recognition of the phenotypic spectrum of CNS-associated mutations is important to provide individualized treatment.

CASE PRESENTATION

Clinical Presentation

A 2600-g male infant was delivered by emergency cesarean section at 35 weeks secondary to oligohydramnios and poor physical profile to a 21-year-old gravida 1 para 0 mother. Prenatal ultrasound demonstrated hyperechoic kidneys, but laboratory testing was unremarkable, including negative rapid plasma reagin, HIV, and hepatitis B. Dysmorphic facial features and microphthalmia, worse on the right side, were noted at birth. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively, but the infant was noted to have generalized edema with abdominal distension and required suction due to meconium aspiration. Laboratory testing revealed elevated blood urea nitrogen (22 mg/dl) and creatinine (1.3 mg/dl) with hyponatremia (116 mEq/l). He developed respiratory issues in addition to worsening edema with oliguria and nephrotic syndrome and was subsequently intubated and transferred to the neonatal intensive care unit. He underwent renal biopsy on day 10.

Kidney Biopsy

The biopsy showed up to 50 glomeruli by light microscopy, none of which was globally sclerosed. There was marked podocyte hypertrophy and hyperplasia. Mesangial matrix and cellularity were increased with partial obliteration of capillary loops. There was moderate to severe interstitial fibrosis and tubular atrophy with focal tubular microcystic change and acute tubular injury (Figure 1). Immunofluorescence showed no significant staining for IgG, IgA, IgM, C3, C1q, kappa, lambda, and fibrinogen. Electron microscopy revealed segmental thickening of GBMs with areas of lamellation and scalloping. There were no electron-dense deposits. Podocytes displayed complete foot process effacement with microvillous transformation (Figure 2). The findings were consistent with CNS, and genetic testing was recommended.

Follow-Up

Genetic testing was performed following the biopsy. No sequence alterations were found for *NPHS1*, *WT1*, or *NPHS2*. Sequence alterations were found in *LAMB2* that were predicted positive for Pierson disease. Variant 1 in *LAMB2* was a 4-bp deletion at nucleotide position 2956_2959 (codon position 986_987). Variant 2

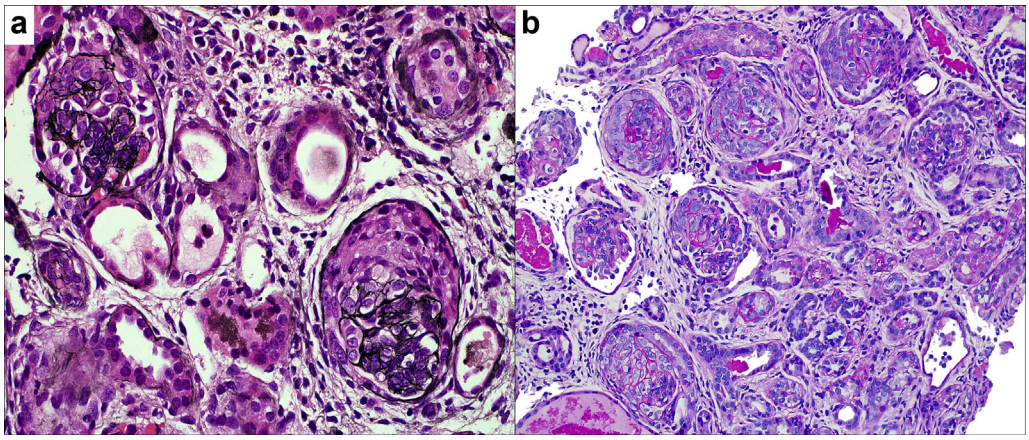

Figure 1. (a) Glomeruli show mesangial sclerosis with increased matrix and cellularity as well as epithelial cell proliferation without necrosis or glomerular basement membrane breaks (Jones methenamine silver, original magnification ×400). (b) Diffuse mesangial sclerosis with a background of severe interstitial fibrosis and tubular atrophy (periodic acid–Schiff, original magnification ×200).

was a 2-bp duplication of guanine-cytosine at nucleotide position 3646_3647 (codon position 1216). Both variants led to frameshift mutations.

The infant continued to have respiratory and electrolyte issues as well as nutritional difficulties because of protein loss from nephrotic syndrome. He underwent bilateral nephrectomy at 5 weeks that showed diffuse mesangial sclerosis and features otherwise similar to those seen on the prior biopsy. The infant was managed with peritoneal dialysis but experienced excessive weight gain secondary to dialysis fluid and generalized edema. He developed feeding dysfunction requiring Nissen fundoplication and gastrostomy tube and underwent right lensectomy and pupilloplasty as well as bilateral inguinal hernia repair during this time. His respiratory function improved, but he continued to require supplemental oxygen. The infant was eventually deemed stable enough for discharge; however, before he could be discharged, he developed severe gastroenteritis. His clinical status worsened over the next few days, and he ultimately died.

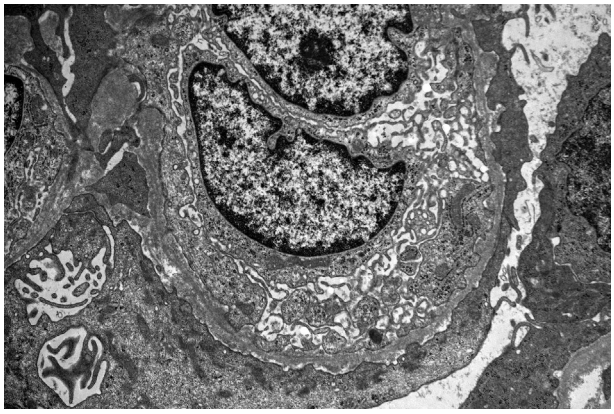

Figure 2. Ultrastructural examination of glomerular basement membranes shows irregular remodeling with areas of scalloping and lamellation, in addition to complete foot process effacement.

An autopsy performed approximately 8 hours after death of the patient showed increased subcutaneous adipose tissue and anasarca. Microcephaly, microencephaly, microcerebellum, bilateral microphthalmia, and lung hypoplasia were also documented. Microscopically, there was evidence of global hypoxia and areas of hypercellular, disorganized cortex (Figure 3) and neuronal depletion and disorganization of the CA3 region of the hippocampus and dentate nucleus of the cerebellum. The lungs demonstrated alveolar simplification, consistent with pulmonary hypoplasia, and there were increased alveolar macrophages with aggregates of foamy and pigmented macrophages.

DISCUSSION

CNS is defined as nephrotic syndrome in an infant less than 3 months of age. Although CNS may be secondary to perinatal infections such as syphilis, toxoplasma, HIV, rubella, and cytomegalovirus,[3] most cases are the result of mutations affecting the glomerular filtration barrier. This barrier is composed of 3 layers, the fenestrated endothelium, GBM, and the podocyte slit diaphragm. The most common mutations in CNS affect genes related to the slit diaphragm or podocyte function, including *NPHS1*, *NPHS2*, and *WT1*.[4] Mutations in *NPHS1*, which codes for nephrin, a cell-adhesion molecule present at the slit diaphragm in the kidney and within the brain and pancreas, lead to CNS of the Finnish type. Defects in podocin, an anchoring protein of the slit diaphragm encoded by *NPHS2*, are seen in 25% of cases of CNS that lack *NPHS1* mutations and may cause focal segmental glomerulosclerosis in older children as well.[3] Mutations in *WT1*, which encodes for a transcription factor related to gonadal and renal development and which is present in the podocytes of mature kidneys, lead to a spectrum of

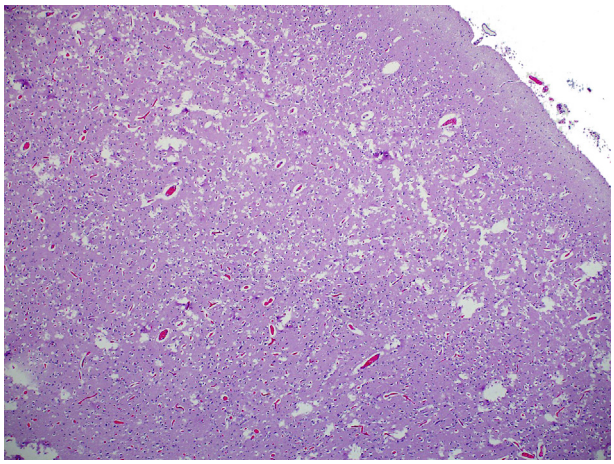

Figure 3. A representative section from the right parietal lobe shows focal mildly hypercellular, disorganized cortex without evidence of normal lamellation and a haphazard arrangement of neurons (hematoxylin and eosin, original magnification ×40).

disorders resulting in nephrotic syndrome, including Denys-Drash and Frasier syndromes.

CNS additionally occurs from mutations affecting structures and functions other than the slit diaphragm, such as those seen in Pierson syndrome, nail-patella syndrome, Galloway Mowat syndrome, carbohydrate-deficient glycoprotein syndrome, and respiratory chain disorders.[3] Pierson syndrome is an autosomal recessive condition caused by mutations in *LAMB2,* which leads to a loss of laminin β2, a major component of GBMs. Lamininis are heterotrimeric glycoproteins found in basement membranes throughout the body and consist of several types of α, β, and γ chains, with α5β2γ1 predominating in the GBM.[5] Additionally, the β2 chain is found in the synaptic basement membrane of neuromuscular junctions, perineurial and arterial basement membranes, and several ocular structures including retinal basement membranes, the capsule of the lens, Bowman's layer, and basement membranes surrounding ciliary and iris muscles.[6,7] The distribution of laminin β2 matches the pattern of involvement seen in Pierson syndrome, which usually presents with characteristic ocular abnormalities in addition to CNS, although the GBM is more severely and uniformly affected than other sites. This is supported by reports of patients with less severe *LAMB2* mutations and partial expression of laminin β2 showing a spectrum of phenotypic manifestations but invariably presenting with renal dysfunction.[4,8,9,S1] Morphologically, infants with *LAMB2* mutations tend to show diffuse mesangial sclerosis with extensive foot process effacement and alterations of the GBM by ultrastructural examination; however, other morphologic changes such as minimal change disease and focal segmental glomerulosclerosis have also been reported, most often in patients with overall milder phenotypes.[S2]

Unlike renal involvement, the ocular changes associated with *LAMB2* mutations are variable and in some cases may be noted before the onset of renal dysfunction. Microcoria, which is defined as a pupillary diameter < 2 mm, is the most well-described ocular manifestation of Pierson syndrome, whereas other findings such as iris abnormalities, glaucoma, cataracts, and retinal changes have also been noted.[6] Other extrarenal manifestations of *LAMB2* mutations have additionally been reported, predominantly in patients with less severe mutations who survive infancy, and include neurodevelopmental deficits with delayed motor and cognitive development, hypotonia,[8] hearing deficits,[9] and bone and skeletal changes.[S3]

Our patient showed numerous gross and microscopic central nervous system abnormalities at autopsy, including cortical hypercellularity and disorganization as well as depletion and disorganization of neurons involving the hippocampus and dentate nucleus of the cerebellum. Few studies have reported on central nervous system changes seen with *LAMB2* mutations, which appear to be related to the severity of the mutation.[S4,S5] In one study, mutations affecting laminin β2 in mice led to disruption of the pial basement membrane with ectopic distribution of cortical plate cells and abnormal development of radial glial cells. These mice showed decreased brain size compared with wild-type mice with numerous defects in cortical organization and altered distribution of Cajal-Retzius cells. Importantly, many of these morphologic changes were focal, with large areas of the cortex exhibiting normal cellular morphology and organization.[S5] The localized nature of these changes may explain the unremarkable neuropathologic findings at autopsy in some reported cases of patients with *LAMB2* mutations,[S4] and our case provides strong evidence that laminin β2 plays an important role in human brain development.

The prognosis for patients with Pierson syndrome is poor, with most patients progressing to end-stage renal disease in infancy and most dying before age 2.[S2] Treatment for Pierson syndrome is supportive and directed at controlling the effects of renal failure and nephrotic syndrome. Bilateral nephrectomy may be performed in cases with severe CNS, and most cases require renal replacement therapy and transplant. One study demonstrated a response to injected laminin α5β2γ1 in mice, but the response was limited and did not prevent progression of nephrotic syndrome.[S6]

In summary, we present a case of Pierson syndrome with associated renal, ocular, and unique neurologic abnormalities. The spectrum of phenotypic changes associated with *LAMB2* mutations is still expanding, and further investigation into the various clinical and morphologic presentations associated with these

Table 1. Key teaching points

1. Pierson syndrome is an autosomal recessive condition associated with *LAMB2* mutations and loss of laminin β2 expression.
2. Patients classically present with congenital nephrotic syndrome and characteristic ocular abnormalities including microcoria.
3. Renal biopsy most commonly demonstrates diffuse mesangial sclerosis with Alport-like alterations of glomerular basement membranes by electron microscopy.
4. Additional extrarenal manifestations involving the central nervous and skeletal systems may also be found in patients with *LAMB2* mutations.
5. The role of laminin β2 in the central nervous system is not completely understood, and the full spectrum of changes seen with *LAMB2* mutations remains to be completely explored.
6. The prognosis for Pierson syndrome is poor; however, patients with partial expression of laminin β2 may have a less severe clinical course.

mutations is important to better identify and manage affected individuals (Table 1).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Pierson M, Cordier J, Hervouuet F, et al. [An unusual congenital and familial congenital malformative combination involving the eye and kidney]. *J Genet Hum*. 1963;12:184–213.
2. Zenker M, Tralau T, Lennert T, et al. Congenital nephrosis, mesangial sclerosis, and distinct eye abnormalities with microcoria: an autosomal recessive syndrome. *Am J Med Genet A*. 2004;130A:138–145.
3. VanDeVoorde R, Witte D, Kogan J, et al. Pierson syndrome: a novel cause of congenital nephrotic syndrome. *Pediatrics*. 2006;118:e501–e505.
4. Kagan M, Cohen AH, Matejas V, et al. A milder variant of Pierson syndrome. *Pediatr Nephrol*. 2007;23:323–327.
5. Chen YM, Kikkawa Y, Miner JH. A missense *LAMB2* mutation causes congenital nephrotic syndrome by impairing laminin secretion. *J Am Soc Nephrol*. 2011;22:849–858.
6. Bredrup C, Matejas V, Barrow M, et al. Ophthalmological aspects of Pierson syndrome. *Am J Ophthalmol*. 2008;146:602–611.
7. Zenker M, Aigner T, Wendler O, et al. Human laminin β2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. *Hum Mol Genet*. 2004;13:2625–2632.
8. Choi HJ, Lee BH, Kang JH, et al. Variable phenotype of Pierson syndrome. *Pediatr Nephrol*. 2008;23:995–1000.
9. Kino J, Tsukaguchi H, Kimata T, et al. Nephron development and extrarenal features in a child with congenital nephrotic syndrome caused by null *LAMB2* mutations. *BMC Nephrol*. 2017;8:220.