A new mutation associated with Pierson syndrome

Ferit Kulali[a], M.D.; Sebnem Calkavur[a], M.D.; Cemaliye Basaran[b], M.D.; Erkin Serdaroglu[b], M.D.; Melis Kose[c], M.D. and Merve Saka Guvenc[d] M.D.

ABSTRACT

Pierson syndrome is characterized by congenital nephrotic syndrome and bilateral microcoria. Genetically, mutations in the *LAMB2* gene, which encodes the laminin β2 chain, lead to this disorder. To date, 98 cases and 50 different mutations have been reported in literature. There are no specific therapies for Pierson syndrome and treatment is supportive. The prognosis is poor because of progressive impairment of renal function and complications of renal failure.

We report a novel homozygous mutation (c.1890G>T, p.Q630H) in the *LAMB2* gene in a patient with Pierson syndrome who had atypical phenotypic feature such as epidermolysis bullosa.

Key words: *Pierson syndrome, nephrotic syndrome, epidermolysis bullosa, whole exome sequencing, infant.*

http://dx.doi.org/10.5546/aap.2020.eng.e288

To cite: Kulali F, Calkavur S, Basaran C, Serdaroglu E, et al. A new mutation associated with Pierson syndrome. *Arch Argent Pediatr* 2020;118(3):e288-e291.

INTRODUCTION

Congenital nephrotic syndrome (CNS) consists of clinically and genetically heterogeneous disorders.[1] Etiologically, it is divided into two parts, primary and secondary CNS. Whereas genetic disorders in the glomerular microstructure cause primary CNS, perinatal infections lead to secondary CNS.[2] Some of the genes involved in the etiology of primary CNS are *NPHS1, NPHS2, WT1, LAMB2* and *PLCE1*.[3] Laminins are the main component of the basal membrane and play an important role in cell adhesion, proliferation, differentiation, and migration. The β2 isoform (laminin β2) is found especially in the glomerular basement membrane, ocular structures, and neuromuscular synapses.[4] Mutations in the *LAMB2* gene encoding laminin β2 cause Pierson's syndrome. This syndrome was first described by Pierson et al.,[4] in 1963 and it is characterized by CNS and microcoria that is the most prominent clinical finding of a complex ocular developmental disorder. To date, 98 cases and 50 different mutations have been reported.[5] Many of the previously described cases have reported early-onset chronic renal failure, severe neurodevelopmental disorders, microcephaly and blindness.[4] There are no specific therapies for Pierson syndrome and treatment is supportive.[6] The prognosis is usually poor because of progressive impairment of renal function and complications of renal failure.[7]

We report a novel homozygous mutation in the *LAMB2* gene in a patient having Pierson's syndrome with atypical phenotypic features such as epidermolysis bullosa.

Case:

A 51-day-old girl was brought with a ten-day history of swollen eyes and legs. She was the first child of healthy consanguineous parents with no known family history of genetic disorders. She had been delivered by cesarean section at 34 weeks of gestation and her birth weight was 1835 g (10-25th percentiles). Her placental weight was not recorded. During pregnancy, however, the mother had been closely monitored for intrauterine growth retardation and oligohydramnios.

On admission, the patient's body weight was 2980 g (10th percentile) and body length was 45 cm (< 3th percentile). She had edema of various parts of the body such as the face, hands, legs, back, and genitals. The arterial blood

a. Division of Neonatology, Dr. Behcet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey.
b. Division of Pediatric Nephrology, Dr. Behcet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey.
c. Division of Pediatric Metabolism, Dr. Behcet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey.
d. Department of Medical Genetics, Tepecik Training and Research Hospital, Izmir, Turkey.

E-mail address:
Ferit Kulali, M.D.: fkulali@hotmail.com

Funding: None.

Conflict of interest: None.

Received: 3-25-2019
Accepted: 10-28-2019

pressure was 113/53 (67) mmHg. The evidence of hypoproteinemia (2.2 g/dL), hypoalbuminemia (0.9 g/dL), and proteinuria (3+ urine protein on dipstick) confirmed the diagnosis of CNS. Spot urine albumin and spot urine protein/creatinine ratio were high (>500 μg/mL and 186.4, respectively). Serum creatinine level was 2.4 mg/dL and serum sodium level was 117 mmol/L. As well as metabolic screening tests, serological tests for toxoplasmosis, syphilis, rubella, cytomegalovirus, herpes virus types 1 and 2, hepatitis B and C viruses, and HIV were also negative. Renal ultrasonography revealed normal kidney size with increased parenchymal echogenicity and loss of corticomedullary differentiation. Due to incomplete mydriasis following the atropine application, a detailed eye examination could not be performed. Microcoria and anterior segment dysgenesis were detected.

On the 60th day, the bullous lesions starting from the eyelids spread rapidly to the trunk and extremities (*Figure 1*). Biopsy taken from bullous lesions were compatible with junctional epidermolysis bullosa (*Figure 2*). The parents

FIGURE 1. *Late stage vesiculobullous skin lesions*

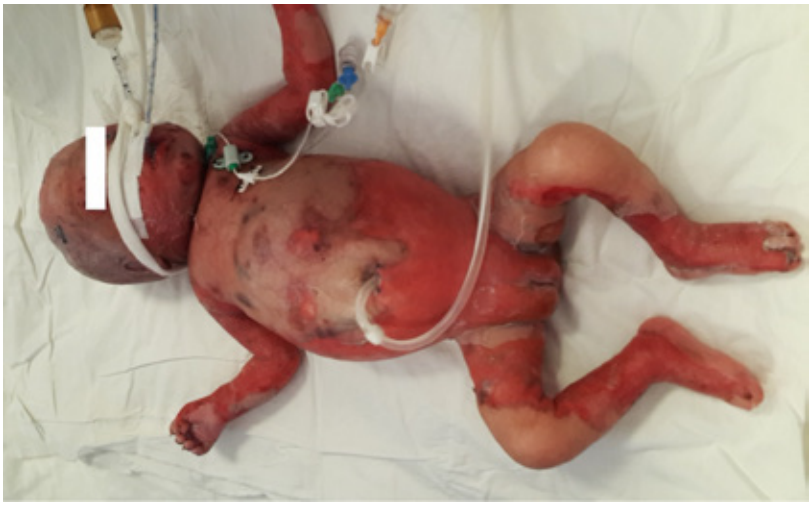
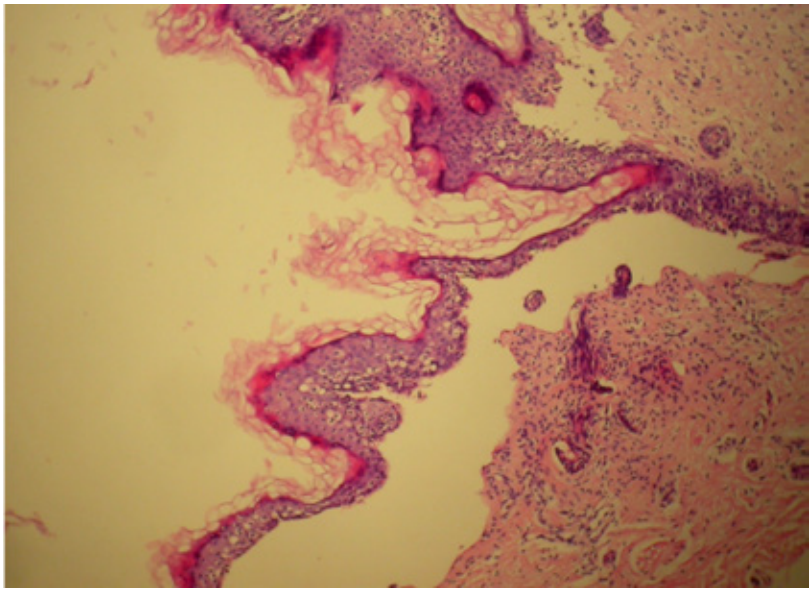


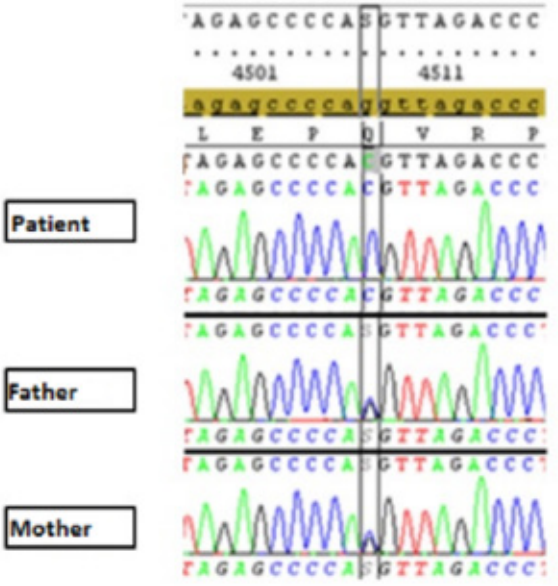
FIGURE 2. *Vesicles at dermo-epidermal junction (H&E, x100)*



refused a kidney biopsy of the baby. The patient was initially treated with furosemide and albumin infusion. However, despite appropriate medical treatment, she had no urine output and had ongoing renal dysfunction and bicarbonate-resistant metabolic acidosis. On the 90th day, she underwent peritoneal dialysis. Following the dialysis treatment, edema disappeared, blood sodium and creatinine levels and blood pressure returned to the normal levels. In the treatment of the skin lesions, a lipidocolloid wound dressing (Urgotul®) and topical furacin application were used. The need for albumin infusion gradually decreased within six weeks. The patient died on the 129th day of the treatment due to an infectious condition.

Genetic studies: At postnatal day 54, karyotype analysis was performed previously and it did not reveal any numerical or structural chromosomal aberrations. Because of congenital nephrotic syndrome, sequence analysis of *NPHS1*, *NPHS2*, and *WT1* genes was studied and found normal. At postnatal day 74, whole exome sequencing was carried out due to the unusual association of congenital nephrotic syndrome and epidermolysis bullosa and a homozygous c.1890G>T, p.Q630H change in the 14th exon of the *LAMB2* gene was detected. This condition was further confirmed using the Sanger sequence analysis at postnatal day 77. Both parents were heterozygous for the same alteration (*Figure 3*). The family was informed that the risk of having a sick child for each pregnancy was 25 %. Prenatal diagnosis and preimplantation genetic diagnosis options for future pregnancies were discussed.

FIGURE 3. *Results of the LAMB2 gene analysis of the patient and her parents*



DISCUSSION

Pierson syndrome is a very rare reason of CNS[8] and is caused by mutations in the *LAMB2* gene, which encodes laminins that are key constituents of the basement membrane. The *LAMB2* gene is located on chromosome 3p21.31 and has autosomal recessive inheritance.[9] This syndrome was first described in 1963 in two sisters having CNS and microcoria.[10] They had a severe nephrotic syndrome that began in the newborn period, rapidly progressed to end-stage renal failure and caused death in the first two weeks of life. In the current case, consanguinity supported the autosomal recessive heredity. Based on the presence of proteinuria, hypoalbuminemia, and edema, the patient was initially diagnosed with CNS; but additional findings such as high blood pressure and microcoria were not consistent with the typical CNS. Renal USG demonstrated findings consistent with CNS such as loss of corticomedullary differentiation and increased renal size and parenchymal echogenicity. Renal biopsy is used to confirm the diagnosis, but it is not helpful to identify the underlying etiology and does not always provide reliable results.[2] Since laminin is one of the major components of the glomerular basal membrane (GBM), some structural changes are expected to occur in GBM in patients with Pierson syndrome.[11] The major renal biopsy findings are diffuse mesangial matrix increase or focal segmental glomerulosclerosis lesions, absent or markedly decreased GBM displaying for laminin β2 chain, and irregular thick and thin zones on both sides of the lamina densa of the GBM with lamellation.[12] Differential diagnosis includes other causes of congenital/early nephrotic syndrome having abnormal GBM, such as Galloway-Mowat syndrome.[4,12] Because the parents refused, we did not perform a kidney biopsy. Whole exome sequencing revealed that she was homozygous for a novel *LAMB2* mutation c.1890G>T, p.Q630H. When they were, all assessed together, a diagnosis of Pierson syndrome was made.

Several organs, particularly the kidney and the eyes, are affected in Pierson's syndrome. Renal involvement consists of a wide spectrum of manifestations ranging from mild podocyte

destruction to diffuse mesangial sclerosis.[11] The onset is either prior to or shortly after the delivery. In the current case, intrauterine growth retardation, oligohydramnios, and high creatinine levels suggest a prenatal onset.

Ocular involvement is the most important symptom of the disease and microcoria is the most common ocular finding. Several other ocular abnormalities such as iris anomalies, cataracts, abnormal lens shape, retinal anomalies, and high-grade myopia have also been previously described.[13] Consistent with the literature, our patient had microcoria and anterior segment dysgenesis.

While many patients with Pierson's syndrome have severe neurodevelopmental disorders and muscle weakness,[9] we did not find any such evidence in our patient. Of note, skin biopsy revealed junctional epidermolysis bullosa. Epidermolysis bullosa is a genetic disorder caused by mutations in genes encoding structural proteins of the skin.[14] There are four major subgroups of this disorder: simplex, junctional, dystrophic and Kindler syndrome.[14] The coexistence of nephrotic syndrome, microcoria and junctional epidermolysis bullosa in our patient suggests a mutation in the laminin protein, which is an important component of the renal, ocular and skin basement membranes.

There are no specific therapies for Pierson syndrome and treatment is supportive.[6] The supportive treatment includes management of water and electrolytic balance as well as albumin transfusion and dialysis therapy when necessary. Kidney transplantation is the only treatment option for patient with Pierson syndrome who had end-stage renal disease.[7] The prognosis is poor because of progressive impairment of renal function and complications of renal failure.[7]

In conclusion, patients with CNS should also be assessed for other organ involvement and diagnostic studies should include genetic testing. ■

REFERENCES

1. Wang J, Mao JH. The etiology of congenital nephrotic syndrome: current status and challenges. *World J Pediatr*. 2016; 12(2):149-58.
2. Pleasant LD, Kiessling SG. Congenital nephrotic syndrome. In: Chishti AS, Alam S, Kiessling SG, eds. *Kidney and Urinary Tract Diseases in the Newborn*. Heidelberg: Springer; 2014. Págs.275-86.
3. Downie ML, Gallibois C, Parekh RS, Noone DG. Nephrotic syndrome in infants and children: pathophysiology and management. *Paediatr Int Child Health*. 2017; 37(4):248-58.
4. Kagan M, Cohen AH, Matejas V, Vlangos C, Zenker M. A milder variant of Pierson syndrome. *Pediatr Nephrol*. 2008; 23(2):323-7.
5. Beaufils C, Farlay D, Machuca-Gayet I, Fassier A, et al. Skeletal impairment in Pierson syndrome: Is there a role for laminin β2 in bone physiology? *Bone*. 2018; 106:187-93.
6. Chew C, Lennon R. Basement Membrane Defects in Genetic Kidney Diseases. Front Pediatr. 2018;6:11.
7. Guler S, Cimen S, Acott P, Whelan K, Molinari M. Kidney transplantation in a child with Pierson syndrome. *Pediatr Transplant.* 2017; 21(8):e13076.
8. Lionel AP, Joseph LK, Simon A. Pierson syndrome - a rare cause of congenital nephrotic syndrome. *Indian J Pediatr*. 2014; 81(12):1416-7.
9. Matejas V, Hinkes B, Alkandari F, Al-Gazali L, et al. Mutations in the human laminin β2 (LAMB2) gene and the associated phenotypic spectrum. *Hum Mutat.* 2010; 31(9):992-1002.
10. Pierson M, Cordier J, Hervouuet F, Rauber G. An unusual congenital and familial congenital malformative combination involving the eye and kidney. *J Genet Hum*. 1963; 12:184-213.
11. Choi HJ, Lee BH, Kang JH, Jeong HJ, et al. Variable phenotype of Pierson syndrome. *Pediatr Nephrol*. 2008; 23(6):995-1000.
12. Lusco MA, Najafian B, Alpers CE, Fogo AB. AJKD Atlas of Renal Pathology: Pierson Syndrome. *Am J Kidney Dis*. 2018; 71(4):e3-4.
13. Zemrani B, Cachat F, Bonny O, Giannoni E, et al. A novel LAMB2 gene mutation associated with a severe phenotype in a neonate with Pierson syndrome. *Eur J Med Res*. 2016; 21:19.
14. Fine JD, Bruckner-Tuderman L, Eady RAJ, Bauer EA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol.* 2014; 70(6):1103-26.