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A NOVEL MUTATION OF LAMININ β-2 GENE IN PIERSON SYNDROME MANIFESTED WITH NEPHROTIC SYNDROME IN THE EARLY NEONATAL PERIOD

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Summary: *A novel mutation of laminin β-2 gene in Pierson syndrome manifested with nephrotic syndrome in the early neonatal period:* Pierson syndrome is a rare autosomal recessive disorder which is mainly characterized by congenital nephrotic syndrome (CNS), diffuse mesangial sclerosis (DMS) and distinct ocular abnormalities, including microcoria. Most affected children exhibit early onset of chronic renal failure, neurodevelopmental deficits, and blindness. It is caused by a homozygous or compound heterozygous mutation in the gene encoding laminin beta-2 (LAMB2) on chromosome 3p21. In this article, we report on a patient with CNS, bilateral megalocornea and microcoria. The patient had developed renal failure at very early postnatal period and died of septic shock. A novel homozygous donor splice mutation (IVS4 + 2T > C) in LAMB2 gene was identified in the patient.

Key-words: Syndrome – Microcoria – Chromosome – Mutation.

INTRODUCTION

The term Congenital Nephrotic Syndrome (CNS) refers to a disease, which is present at birth or within the three first months of life. Defined molecular causes of CNS are, mutations of the genes encoding nephrin in Finnish type CNS (NPHS1) and podocin in autosomal recessive steroid-resistant nephrotic syndrome (NPHS2). Autosomal dominant WT1 mutations can also cause CNS and DMS in patients with Denys–Drash syndrome (4).

Pierson syndrome, an autosomal recessive disorder described by Pierson *et al.* is among the rare causes of CNS (10). It typically comprises CNS and peculiar ocular maldevelopment. LAMB2 gene mutations were found to be responsible for Pierson syndrome (12). Here, we report a novel homozygous donor splice mutation (IVS4 + 2T > C) in the LAMB2 gene in a patient diagnosed with Pierson syndrome presenting with CNS, bilateral megalocornea and microcoria.

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CASE REPORT

A 1860 g female infant was delivered vaginally at 37 weeks of gestation to a 31-year-old gravida 4 para 2 mother. The pregnancy was uneventful. There was no family history of consanguinity, any inheritable disorders, and renal or ophthalmologic problems. She was immediately transferred to a neonatal intensive care unit on her third day of life due to respiratory distress. Despite, sufficient oxygen, fluid and electrolyte support, baby developed oliguria, disseminated edema, and respiratory failure. Physical examination revealed subfebrile fever 37.1°C, a heart rate of 170/min, respiratory rate of 78/min, blood pressure 62/28 mmHg, and weight 2000 g (<5th percentile), head circumference was 29 cm (<5th percentile). She had slightly decreased muscle tone but demonstrated adequate reflexes. She also had periorbital and pretibial edema with suspicious bilateral microcoria and megalocornea (Fig. 1). Laboratory examination revealed hemoglobin: 8.7 g/dL, hematocrit: 25.9%, blood urea nitrogen: 23 mg/dL, creatinine: 2.91 mg/dL, sodium: 126 mEq/L, potassium: 3.4 mEq/L, chloride: 103 mEq/L, calcium: 8.9 mg/dL, phosphor: 7 mg/dL, total protein: 3 g/dL, albumine: 1.4 g/dL, total cholesterol: 161 mg/dL, tryglyceride: 557 mg/dL. Urinalysis revealed pH: 6.5, density: 1015, protein: ++++, with a protein/creatinin ratio of 20. Thus, significant proteinuria, hypoalbuminemia, and persistent renal dysfunction led to the diagnosis of CNS with renal failure. Viral studies including TORCH and hepatitis B were all negative. Connective tissue disorders were excluded by negative antinuclear antibody (ANA), and anti-double stranded DNA (anti-dsDNA), and normal levels of complement proteins C3 and C4.

Renal ultrasonography (US) showed normal-sized kidneys, bilaterally dilated renal pelves and communicating calices, increased paranchymal echogenicity, and marked dilation of the collecting system. Renal Doppler US was normal. Bilateral megalocornea and microcoria was confirmed on ophthalmological examination.

The patient was diagnosed with Pierson syndrome with clinical findings of early-onset renal impairment, CNS, and microcoria. Chromosomal analysis showed normal karyotype, 46 XX. No mutation was found in the podocin and nephrin genes. A novel homozygous donor splice mutation (IVS4 + 2T > C) in LAMB2 gene was identified in the patient (Fig. 2). The mother was heterozygous for the LAMB2 gene mutation. Mutation analysis could not be performed on the father due to social reasons.

During the hospitalization period, BUN and creatinine levels were increased and electrolyte imbalance developed. Multiple antihypertensive medications were used to control blood pressure. Peritoneal dialy-

sis was required on 9th day of life. Despite of appropriate management of renal failure, the patient's general health status deteriorated and died due to renal failure and septic shock on postnatal 101th day.

Figure 1: Bilateral megalocornea and microcoria of the patient.

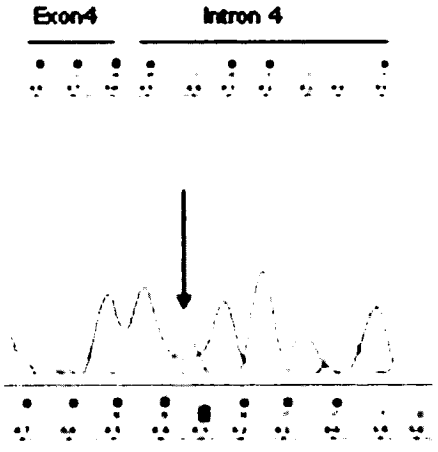

Figure 2: A novel homozygous donor splice mutation (IVS4 + 2T > C) in LAMB2.

DISCUSSION

Pierson syndrome is a rare autosomal recessive disorder which is characterized by CNS, DMS, and distinct ocular abnormalities, including microcoria and hypoplasia of the ciliary and pupillary muscles, as well as other anomalies. This condition was first described by Pierson *et al.* in two sisters with CNS and peculiar eye abnormalities (2). Renal manifestations of Pierson syndrome include prenatal or neonatal onset of nephrosis and renal failure associated with DMS. The onset ages of nephrotic syndrome in patients with Pierson syndrome can be divided into four groups: within 1 month, 1-3 months, 3 months to 1 year and after 1 year. The predominant onset age is reported as being 3 months (5, 12, 13). The renal function is deteriorated within one year after onset in the majority of patients. In our patient the manifestations of CNS and renal failure was appeared on 3rd day of life. To our knowledge there are only seven reports on Pierson syndrome with early onset (< 1st week of life) CNS (6).

The ocular manifestations in Pierson syndrome comprise abnormalities of cornea, iris, lens and retina. The typical ocular finding is nonreactive microcorium which is seen in most of the cases. In addition, other abnormalities including microphthalmia, myopia, nystagmus, lenticonus, cataract, retinal detachment, abnormal vision, glaucoma, and remains of the primary vitreous body have also been reported (1). The cause of profound vision impairment, which is apparently present at birth and non-progressive, has not been clarified. It has been proposed that LAMB2 containing laminins might be required for the proper attachment of the retina, similar to the role of laminin-5 at the dermoepidermal junction (8). The girl we reported herein presented with the classical ocular abnormality and bilateral microcoria. In Pierson syndrome, other symptoms have also been previously reported, such as nervous symptoms, dyspnea, muscular hypotonia, growth and development retardation, psychomotor delay and atrial septal defect (11).

In 2004, Zenker *et al.* reported 2 unrelated families, 1 Turkish and 1 Arabic, with CNS and distinct ocular anomalies (13). Eleven children from the 2 families presented with a similar course of renal disease and died before the age of 2 months. The histopathological result of the kidney confirmed DMS. Ocular anomalies included enlarged or large-appearing corneas, suggesting buphthalmos in some cases, and extremely narrow, nonreactive pupils. The authors identified homozygous or compound heterozygous mutations of LAMB2 on chromosome 3p14–p22 in these patients with Pierson syndrome. Recently, Mohney *et al.* performed a retrospective chart review and prospective family examination of an extended consanguineous family of 52 mem-

bers. Their study described a novel mutation of LAMB2 (c.440A → G; His147R) and further expanded the spectrum of eye and renal manifestations associated with defects in the LAMB2 chain (9).

It has been confirmed that Pierson syndrome is caused by mutations of LAMB2 gene, which is located on chromosome 3. Laminins, a family of extracellular matrix glycoproteins, are the major noncollagenous constituent of basement membranes. LAMB2 is rich in the basement membrane of muscles at the neuromuscular junctions, kidney glomerulus and vascular smooth muscle. It is known to be abundantly expressed in the GBM where it is thought to play a key role in anchoring as well as differentiation of podocyte foot processes (2). Miner *et al.* have reported transgenic mice in which the LAMB2 chain gene was inactivated by homologous recombination, showing defects in the maturation of neuromuscular junctions and impairment of glomerular filtration (7).

LAMB2 gene mutations comprise missense, nonsense, and splice site mutations, as well as small deletions and insertions, found either as homozygous or compound heterozygous sequence changes in patients affected by typical Pierson syndrome or its milder variants. The majority of mutations are predicted to lead to a premature translational stop codon. Mutations creating premature stop codons are almost evenly distributed along the LAMB2 gene (6).

In our patient, all exons and exon-intron boundaries of LAMB2 gene were analyzed by direct sequencing for any mutations. A novel homozygous donor splice mutation (IVS4 + 2T > C) was identified. The mother was heterozygous for the same mutation. Although we were not able to show its effect on RNA splicing due to unavailability of RNA, we thought that this mutation was responsible for the phenotype of the patient due to the following reasons: 1) mutation was found at the consensus site, 2) one of the parents was carrier for the same mutation thereby confirming autosomal recessive inheritance, 3) the consequences of the mutation via in slico analysis by using automated splice-site analysis software predicted an abolished site.

There were some undefined relations between phenotype and genotype. All individuals carrying homozygous or compound heterozygous LAMB2 mutations were affected by NS in the first decade, the vast majority in the first year of life. Although an ascertainment bias cannot be excluded, the current data suggest that kidney involvement is an invariant manifestation of genetic defects of the LAMB2 gene. However, some patients may be recognized because of their ocular findings, and the renal symptoms only arrive thereafter. Hasselbacher *et al.* stated that homozygosity or compound heterozygosity for LAMB2 mutations conferring complete loss of function appear to be associated

consistently with the typical features of Pierson syndrome, including neonatal renal failure, severe ocular abnormalities, and neurologic impairment in long-term survivors, whereas patients with nontruncating (missense) LAMB2 mutations may display variable phenotypes ranging from a milder variant of Pierson syndrome to isolated CNS (3). According to available data, there is only one report of Pierson syndrome with early onset renal failure (< 1st week of life) and a homozygous LAMB2 gene mutation at exon 7 (DNAc.825T>A) (6). Renal failure developed on the 3rd day of life in our patient and we defined a novel donor splice mutation (IVS4 + 2T > C) in the LAMB2 gene. Whether this mutation alone is solely responsible for early onset renal failure in our patient or if modifying factors are yet to be elucidated, meticulous eye examination seems also important in patients with congenital nephrotic syndrome in terms of Pierson syndrome

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