# Pierson Syndrome: A Case Report with a Neonatal Cardiac Association Based on a Novel Mutation in the LAMB2 Gene

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## ABSTRACT

Congenital nephrotic syndrome (CNS) combined with eye abnormalities including microcoria (small pupils that don't respond to light) and abnormal lens shape can suggest a clinical diagnosis of Pierson syndrome (which mainly affects the kidneys and eyes). Mutations in the genes NPHS1, NPHS2, and WT1 are known to account for the majority of CNS cases, whereas a definitive diagnosis of Pierson syndrome can be established by the detection of a causative mutation in both copies of a patient's LAMB2 gene (encoding laminin β2). CNS can manifest in utero (ultrasound may reveal hyperechogenic kidneys and oligohydramnios), or during the first 3 months of life. Pierson syndrome is an autosomal recessive disorder comprised of CNS and distinct ocular abnormalities. The prognosis of this extremely rare disorder is very poor, with the most babies developing end-stage renal disease. Those who do survive tend to show the neurodevelopmental delay and visual loss. We report a case of neonatal Pierson syndrome in conjunction with complex cyanotic cardiac disease in which a novel homozygous mutation in the LAMB2 gene was detected. The clinical association of Pierson syndrome with heart manifestation is a novel finding, reported here for the 1st time.

**Key words:**
Autosomal recessive, congenital heart disease, congenital nephrotic syndrome, microcoria, Pierson syndrome

## INTRODUCTION

Nephrotic syndrome (NS), the association of gross proteinuria, hypoalbuminemia, edema, and hyperlipidemia, is often a life-threatening condition when manifest NS in the 1st year of life (NSFL). NSFL has been classified as congenital NS (CNS), manifesting in utero or during the first 3 months of life,[1] or infantile NS, with onset between 4 months and 1-year of age.[2] CNS comprises a heterogeneous group of mostly genetic conditions and carries a poor prognosis, with the majority of patients progressing to end-stage renal disease.[3]

Primary CNS is caused by genetic alterations of the glomerular microstructure that cause massive proteinuria unresponsive to immunosuppressive therapies, whereas secondary CNS is often caused by an immune-mediated injury to the glomerular basement membrane. Mutations in the NPHS1, NPHS2, and WT1 genes are known to account for the majority of CNS cases.[2] However, in some individuals with CNS, particularly in patients with syndromic forms, the genetic basis remains unclear.

Pierson syndrome is an autosomal recessive disorder comprising CNS with diffuse mesangial sclerosis and distinct ocular abnormalities which include microcoria, hypoplasia of the ciliary and pupillary muscles, as well as other anomalies.[2,4,5] Many patients die early, and those who survive tend to show the neurodevelopmental delay and visual loss.[6] Pierson syndrome was first described by Pierson *et al.* in 1963.[4] Among the recent advances in our understanding of genetic causes of CNS, is the discovery of

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mutations in the LAMB2 gene, encoding laminin β2, as the underlying cause of Pierson syndrome.[7]

We report a case of neonatal Pierson syndrome with complex cyanotic cardiac disease due to a novel homozygous mutation in the LAMB2 gene. The cardiac manifestation is a new association in a neonate, which has not previously been reported in the literature.

## CASE REPORT

The baby girl was born to a 22-year-old gravida 2 para 1-mother with a birth weight of 2600 g at 36 weeks gestation with Apgar scores of 9 and 10, at 1 and 5 min, respectively. Her antenatal ultrasound was normal. Parents are first cousins. At 36 h of age the baby was admitted to the neonatal intensive care unit due to cyanosis; an emergency echocardiography showed complex congenital heart disease (CHD) featuring mitral atresia, hypoplastic left ventricle, D-transposed great arteries, double outlet right ventricle, subaortic stenosis with hypoplastic descending aorta, unrestricted interatrial communication with large patent ductus arteriosus. All these features signify single ventricle physiology with hypoplastic left heart [Figures 1 and 2] and she was started on prostaglandin E1. The baby had obvious dysmorphism with small facial features, low set ears, mild micrognathia and over-riding of the little fingers. Karyotyping and microarray were both normal. At 5 days of age she developed severe edema, severe proteinuria (>300 mg/dl [4+ (more than 2 g/day)], hypoalbuminemia [12 g/dl (normal range 26–41 g/L)] and protein/creatinine ratio was 12,777 [normal range 0–45 mg/mmol]). The baby was then suspected to have CNS. Complete blood count, serum electrolytes, thyroid function test, immunoglobulin levels, head, and abdominal ultrasound were all normal. TORCH screening and blood culture were negative. Eye examination showed microcoria (pupil size right 1 mm and left 2 mm) and left-sided total retinal detachment [Figure 3]. Fundus examination of the right eye was unremarkable (fundus pictures with RetCam are not available as the baby died).

Pierson syndrome was suspected, so full gene sequencing of LAMB2 (including exon-intron boundaries) was carried out using Sanger sequencing. A previously unreported homozygous variant in exon 28 of the LAMB2 gene (c.4616G>A, p.Arg1539Gln) was detected. This variant is located in a highly conserved amino acid position. In silico prediction programs (SIFT and Mutation Taster) indicate it's probably damaging, whereas Align-GVGD predicts toleration. This is the 1st time it's been detected in a very large mutation database containing c.250,000 variants (CentoMDTM). Both parents are heterozygous carriers of this LAMB2 variant, located in exon 28 of the

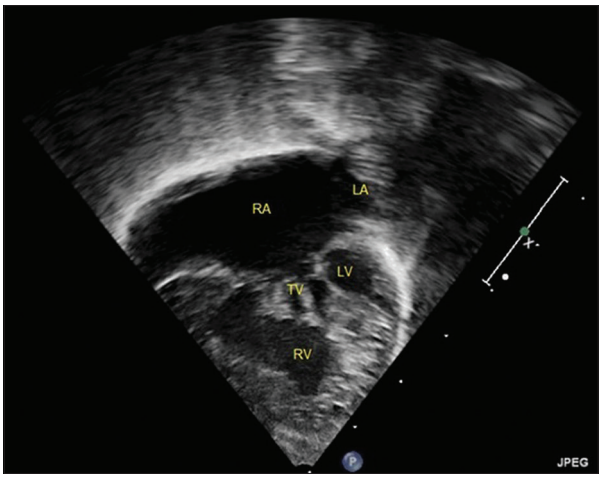


**Figure 1:** Transthoracic echocardiography (four chamber view) is showing mitral atresia, hypoplastic left ventricle, well developed right ventricle, intact interventricular septum and unrestricted interatrial communication (secundum atrial septal defect), signifying single ventricle physiology with hypoplastic left heart

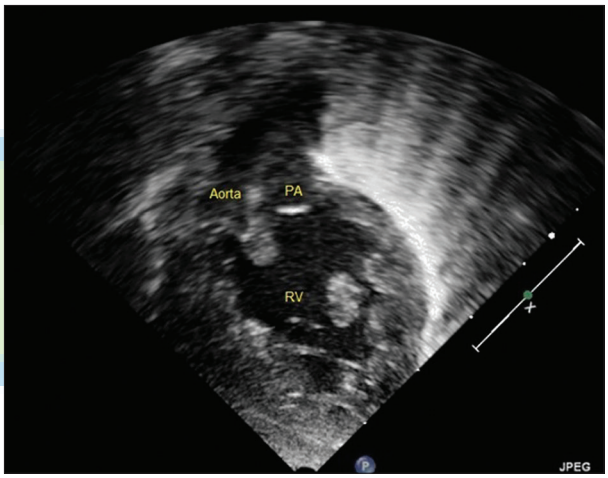


**Figure 2:** Two-dimensional subcostal transthoracic echocardiographic view is showing parallel D-transposed great vessels (aorta right anterior and pulmonary artery left posterior) originating from the well-developed right ventricle (double outlet right ventricle)

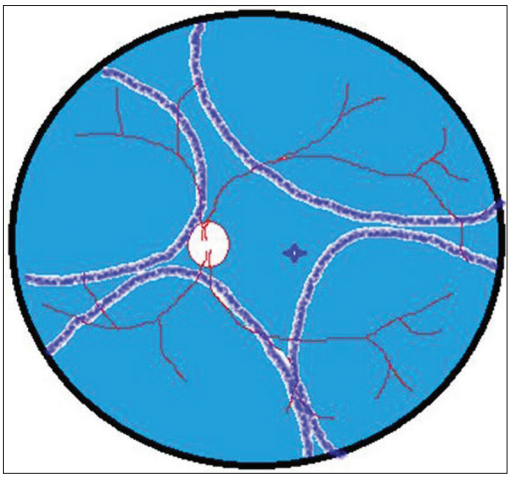

**Figure 3:** Schematic diagram of left eye fundus depicting total exudative retinal detachment

gene. In light of the clinical and genetic testing information, we conclude that this variant is likely to be a disease-causing mutation.

The baby was on ventilation support and received multiple doses of albumin transfusion however she deteriorated clinically and died at the age of 21 days.

## DISCUSSION

CNS is subdivided into primary and secondary types. Primary CNS has been attributed to a variety of syndromes with autosomal recessive inheritance. For purposes of clarification, these syndromes may be divided into those with gene products that affect the glomerular slit diaphragm, those that affect genitourinary development and those with unknown or unique effects.[6] Secondary CNS is usually caused by perinatal infections such as congenital syphilis, toxoplasmosis, rubella, cytomegalovirus, HIV, and hepatitis B.[8] Finally, CNS has been reported in infantile systemic lupus erythematosus.[9]

Diagnosing the cause and the mechanisms of CNS in an individual patient is a difficult task and this requires careful analysis of clinical and laboratory data, the morphological picture on biopsy and genetic testing. In our patient, the diagnosis of Pierson syndrome was suspected because of the CNS and ocular anomalies and was confirmed by genetic testing. Pierson syndrome was initially described as a lethal condition, due to early onset renal failure with microcoria as a pathognomonic sign; the term "microcoria–congenital nephrosis syndrome" was therefore suggested.[5] However, it was pointed out that ocular abnormalities may be more variable or even lacking.[10,11] In our case, the baby had bilateral microcoria and right sided total retinal detachment.

CHD has rarely been reported in conjunction with CNS, pulmonary stenosis, subaortic stenosis, and patent ductus arteriosus.[8,12] In our case, the baby presented with complex cyanotic heart disease, which is noteworthy because the cardiac association has not previously been reported in Pierson syndrome.

Pierson syndrome is inherited in an autosomal recessive fashion and in our case this was coupled with consanguinity (parents were first cousins). The underlying genetic cause of Pierson syndrome is a pathogenic mutation in both copies of the LAMB2 gene which encodes laminin β2 (OMIM No. 609049).[13] Mutation analysis of LAMB2 in our baby revealed a previously unreported homozygous variant in exon 28 of the LAMB2 gene (c.4616G>A p.Arg1539Gln) which we conclude is likely to be disease-causing.

Pierson syndrome is an important differential diagnosis in children with CNS. First, two-thirds of nephrotic syndrome manifesting in the 1st year of life can be explained by mutations in only four genes (NPHS1, NPHS2, WT1 or LAMB2).[13] The precise incidence is not known to date, but it seems that Pierson syndrome is the fourth most common cause for CNS after Finnish type nephrosis, autosomal recessive steroid-resistant nephrotic syndrome, and Denys–Drash syndrome.[2]

## CONCLUSION

LAMB2 testing should be considered in any patient with CNS or infantile nephrosis and should be performed initially when an ocular abnormality is present. Currently, CHD must be considered as an association of Pierson syndrome. Consanguinity could in theory have had a compounding genetic effect leading to this novel presentation of Pierson syndrome, however, further genetic studies would be required to investigate this suggestion.

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### Conflicts of interest

There are no conflicts of interest.

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