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CASE REPORT

Pierson Syndrome Associated with Hypothyroidism and Septic Shock

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متلازمة بيرسون المرتبطة بقصور الغدة الدرقية والصدمة الإنتانية

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ABSTRACT: Pierson syndrome is caused by mutations in the *laminin β2* gene causing absent β2 laminin, which is a normal component of the basement membranes of the mature glomerulus, structures in the anterior eye and neuromuscular junctions. The mutations manifest as congenital nephrotic syndrome and microcoria which are characteristic ocular features of this disease. These mutations may also result in neurological abnormalities such as hypotonia and psychomotor retardation. We report a two-month old boy who presented to the Pediatrics Department of Dr. Ruth K. M. Pfau Civil Hospital, Karachi, Pakistan, in 2015, with the typical features of microcoria and congenital nephrotic syndrome. The hypocalcaemia, hypoproteinaemia and probable immunocompromised state consequent to nephrotic syndrome resulted in seizures, hypothyroidism and urosepsis. Despite being treated aggressively with high dose antibiotics, ionotropic support, angiotensin-converting enzyme inhibitors, thyroxine replacement and nutritional support, the infant died due to significant multiorgan disease including renal failure and septic shock.

Keywords: Pierson Syndrome; Microcoria and Congenital Nephrotic Syndrome; Congenital Microcoria; Hypothyroidism; Septic Shock; Case Report; Pakistan.

الملخص: تحدث متلازمة بيرسون بسبب طفرات في جين لامينين بيتا 2 المؤدية الى فقدان لامينين بيتا 2 وهو مكون طبيعي للأغشية القاعدية للكُبيبة الناضجة والمكونات في الجزء الأمامي للعين والوصلات العصبية العضلية. تظهر هذه الطفرات كمتلازمة كلوية خلقية وصِغَر الحَدَقَة والتي تعتبر من السمات البصرية المميزة لهذا المرض. قد تؤدي هذه الطفرات أيضًا إلى اختلالات عصبية مثل نقص التوتر العضلي والتخلف النفسي الحركي. نبلغ هنا عن طفل يبلغ من العمر شهرين قدم إلى قسم طب الأطفال في مستشفى الدكتورة روث فاو المدني، كراتشي، باكستان في عام 2015، ولديه الصفات المميزة لصِغَر الحَدَقَة والمتلازمة الكلوية الخلقية. أدى نقص كالسيوم وبروتينات الدم وحالة الضعف المحتمل للمناعة والناتجة عن المتلازمة الكلوية إلى حدوث نوبات صرع وقصور في الغدة الدرقية ونَتَن في البول. على الرغم من علاج المريض بقوة عن طريق جرعات عالية من المضادات الحيوية والدعم المؤثر في التقلص العضلي ومثبطات الإنزيم المحَوِّل للأنجيوتنسين وتعويض هرمون الغدة الدرقية والدعم الغذائي فقد توفي الرضيع بسبب اعتلال جسيم في أعضاء متعددة بما في ذلك الفشل الكلوي والصدمة الإنتانية.

الكلمات المفتاحية: متلازمة بيرسون؛ صِغَر الحَدَقَة ومتلازمة كلوية خلقية؛ صِغَر الحَدَقَة الخلقي؛ قصور الغدة الدرقية؛ صدمة إنتانية؛ تقرير حالة؛ باكستان.

Pierson syndrome is a rare disease inherited in an autosomal recessive pattern, often fatal within a few months of life; it is known to mainly affect the eyes and kidneys at infancy.[1] Those infants that survive are affected by developmental and neurological abnormalities.[2,3] This syndrome is caused by homozygous or compound heterozygous mutations on chromosome 3p21 in the *laminin β2* (*LAMB2*) gene.[4] This causes absent *β2* laminin, which is a normal component of the basement membranes of the mature glomerulus, structures in the anterior eye and neuromuscular junctions. Kidney involvement presents within three months of life in the form of congenital nephrotic syndrome (NS) which can cause complications such as hypercoagulability, hypothyroidism, growth delay and immunosuppression. The disease generally has a poor prognosis due to renal failure and hence most infants do not survive.[5] There have been less than 100 cases of Pierson syndrome described in literature so far and the exact prevalence of this syndrome is not yet known.[5,6] Previously, a case of Pierson Syndrome in a child born to a Pakistani couple living in Spain has been reported. However, to the best of the authors' knowledge, no cases in Pakistan have been reported in the literature.[7] This report presents the case of an infant with Pierson syndrome and hypothyroidism complicated by sepsis.

Case Report

A two-month old boy, weighing 3.4 kg, presented to the Pediatrics Department of Dr. Ruth K. M. Pfau

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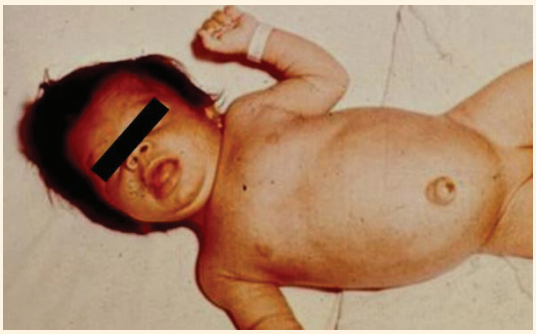

Figure 1: Photograph of a two-month old boy with Pierson syndrome and hypothyroidism showing macroglossia, umbilical hernia and generaliaed oedema.

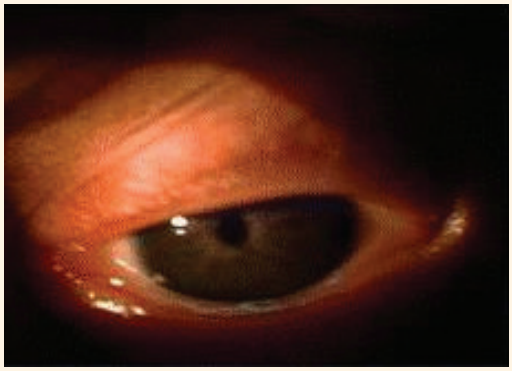

Figure 2: Photograph of the eye of a two-month old boy with Pierson syndrome showing a fixed pupil and non-reactiveness to light (i.e. microcoria).

Civil Hospital, Karachi, Pakistan, in 2015, with a history of fever, seizures and generalised oedema for one month and decreased urine output for one week. The infant would have one to two episodes of generalised tonic-clonic seizures per day without loss of consciousness in between the episodes. Later, oedema developed starting from the legs and periorbital area and progressed to the entire body. History of undocumented, low-grade fever was present which occurred on-and-off for one month. No history of haematuria or dysuria was reported. The infant had not achieved any developmental milestones at presentation; social smile was not present and he did not respond to loud voices or to the voice of the mother.

The patient was born at home by normal vaginal delivery to a consanguineous couple after an uneventful pregnancy, during which the mother did not receive any antenatal care. He had three other siblings, of whom one brother died at the age of one month, due to seizures. The brother's seizures were generalised tonic-clonic with loss of consciousness but without fever. The brother was taken to a nearby hospital where he was given an injection to control the seizures; however, the seizures did not stop and he soon died. The parents noticed a similar generalised oedema in the brother but did not seek medical care. Further information could not be obtained as medical records of the sibling were not available and thus the underlying cause of the seizures could not be confirmed.

Table 1: Biochemical investigation findings of a two-month-old boy with Pierson syndrome at admission

Biochemical investigation	Finding	Normal value
Haemoglobin level in g/dL	9.0	9.5–13.5
Haematocrit level in %	25.9	29–41
Mean corpuscle volume in femtolitres	82.2	72.0–82.0
Total leucocyte count in $\times 10^9$/L	24	4.5–11.0
Platelet count in $\times 10^9$/L	319	150–400
C-reactive protein level in mg/dL	108	<0.3
Serum calcium level in mg/dL	4.5	8.0–10.7
Total liver protein level in g/dL	2.5	5.1–7.3
Albumin level in g/dL	0.7	2.8–5.0
Globulin level in g/dL	1.8	2.0–3.5
Prothrombin time in seconds	22.4	12.2–15.5
Activated partial thromboplastin time in seconds	35.6	26.5–35.5
International normalised ratio	1.62	0.8–1.2
Spot urinary protein to creatinine ratio	80.3	<0.2
Serum cholesterol level in mg/dL	409	50–120
Serum triglyceride level in mg/dL	380	20–150
Thyroid stimulating hormone level in mIU/mL	20.2	0.6–10.1
Free T4 level in ng/dL	0.26	0.8–2
Free T3 level in ng/dL	0.20	0.24–0.65

IU = international units.

Upon examination at the time of admission, the patient was afebrile, obtunded with shortness of breath and generalised pitting oedema. Length and weight were found to be less than the 3rd centile. Occipitofrontal circumference was 35 cm. Heart rate and respiratory rate were increased and blood pressure was 99/75 mmHg (>90th centile). Peripheries were cold and capillary refill time was delayed. There was mild anaemia. Both anterior and posterior fontanelles were wide open. The infant had macroglossia, umbilical hernia and generalised oedema. These findings were suggestive of congenital nephrotic syndrome and hypothyroidism [Figure 1]. Abdomen was grossly distended and non-tender, with evidence of free fluid.

The patient's liver span was 6 cm and gut sounds were audible. On neurological examination, Glasgow Coma Scale (GCS) was 10/15 (eye = 3, verbal = 2 and motor = 5). Pupils were fixed, equal in size and non-reactive to light (microcoria) [Figure 2]. Moro, rooting, sucking and grasping reflexes were weak. On motor examination, power was found to be 3/5 with increased tone and diminished reflexes in all four limbs.

On laboratory investigation, complete blood panel showed mild anaemia. Total leucocyte count (TLC) was elevated with 44% neutrophils and 53% lymphocytes. Platelet count was normal but C-reactive protein was raised. Blood urea nitrogen, creatinine, random blood sugar and electrolytes were within normal ranges. Serum calcium levels were below normal. Arterial blood gasses were suggestive of metabolic acidosis. Liver function tests showed decreased levels of total protein, albumin and globulin. Prothrombin time, activated partial thromboplastin time and international normalised ratio were all raised. Detailed urine report revealed 3+ proteinuria, 3+ granular casts, 2+ leukocytes, 2+ blood and 45 to 50 red blood cells/high power field. Spot urinary protein to creatinine ratio was raised. Blood cultures were negative but urine culture showed growth of E. coli of more than 100,000 colony-forming unit/mL. Serum cholesterol and triglyceride levels were also raised. These findings indicated a diagnosis of congenital NS. Thyroid profile showed raised thyroid stimulating hormone and low levels of free T4 and free T3 [Table 1]. Ultrasound abdomen confirmed gross ascites. Both kidneys were of normal size with grade 3 parenchymal changes. Chest X-ray was normal.

The characteristic features of microcoria and congenital NS helped establish a diagnosis of Pierson Syndrome. Tachycardia, tachypnoea, increased TLC, metabolic acidosis, altered GCS and positive urine culture lead to the diagnosis of urosepsis, for which broad-spectrum antibiotics (amikacin, vancomycin, cefotaxime and cefepime), intravenous (IV) fluids and IV dopamine were started with strict input and output charting. A progressive decrease in renal output was noted and urea and creatinine continued to rise. Maintenance fluid was restricted to essential fluid and urinary losses. The infant was diuresed with furosemide and enalapril (angiotensin-converting enzyme [ACE] inhibitor) was started for proteinuria along with albumin infusion. Calcium was replaced intravenously in the form of calcium gluconate and oral thyroxine was started for hypothyroidism. Blood products were then also transfused in the form of packed red cells and fresh frozen plasma. Despite being treated aggressively with high dose antibiotics, ionotropic support, ACE inhibitors, thyroxine replacement and nutritional support, the infant died due to significant multiorgan disease including renal failure and septic shock.

Informed consent from the patient's guardian was obtained for publication purposes.

Discussion

Pierson syndrome is named after the scientist who described the first case of congenital nephrotic syndrome associated with microcoria while Zenker et al. later confirmed it as a separate disorder involving both kidneys and eyes due to a mutation in *LAMB2* gene.[1,8] The *LAMB2* gene is needed for the production of *β2* laminin and some cases might have a severely reduced production of *β2* laminin instead of complete absence, accounting for milder versions of the disease.[9]

Microcoria is the most characteristic ocular feature of Pierson syndrome with the pupil being unresponsive to light or mydriatics.[1] Other features such as flat iris, cataract, retinal degeneration, high myopia, megacornea, retinal detachment and persistent fetal vasculature have also been reported.[10] However. these abnormalities may always not be obvious or even present, thus it is imperative to examine the eyes of newborns with kidney problems.[1] In the current case, the patient did present with microcoria.

Other syndromes may involve the kidney, but Pierson syndrome specifically causes congenital NS, characterised by proteinuria, hypercholesterolemia and triglyceridaemia. Loss of protein causes hypoalbuminemia and fluid retention manifesting as oedema. Histologically there is diffuse mesangial sclerosis and crescent formation.[2] Congenital NS is associated with enlargement of placenta and increased alpha-fetoprotein antenatally.[2] In the current case, since the mother delivered the baby at home and did not have any tests done during pregnancy, these factors could not be examined.

Due to the history of seizures and death, possibly due to a similar case of sepsis in one sibling, two healthy remaining siblings and the parent's consanguineous marriage, it was assumed that the disease affecting the family was an autosomal recessive disorder. Thus, autosomal dominant isolated congenital microcoria was excluded. Multiorgan disease, as was present in the current patient, is also not a feature of this disorder.[1] Autosomal recessive polycystic kidney disease with sepsis, seemed unlikely due to the presence of Pierson syndrome's most characteristic feature of microcoria. Galloway-Mowat syndrome is another autosomal recessive ocular-renal disorder, in which infants have

low birth weight, hypotonia and hiatus hernia; 80% of these infants have microcephaly and micrognathia may be severe.[1,11] The current patient did not have these features, therefore, Galloway-Mowat syndrome was excluded.

Proteinuria can sometimes cause loss of other proteins in the urine leading to further complications. Loss of thyroid proteins, causing hypothyroidism can manifest as a low T3, T4 and increased TSH as seen in the current patient.[12] Thyroxine supplementation should be started in these patients to prevent adverse effects such as lack of brain development.[12] Eventual kidney failure leads to the early fatality of congenital nephrotic syndrome and only renal transplant has been shown to be effective while corticosteroids are of no value.[12] Nephrectomy has also been shown to reverse the hypothyroid state thus proving the kidney-related cause.[13] In Pakistan, nephrectomy in children less than 10 kg is not possible due to lack of advanced techniques. In addition, in the current patient renal transplantation, with the necessary prior administration of immunosuppressants, was impossible due to the ongoing sepsis.

Loss of immunoglobulins causes an immuno-compromised state leading to infections; sepsis is a leading cause of death in children with nephrotic syndrome.[13] A prior case of Pierson syndrome being complicated by sepsis has been reported in the literature.[4] The current patient presented with urosepsis as shown by the urine culture and high white blood cell count, for which he was aggressively managed with antibiotics and ionotropic support. Mild anaemia was present, which can be explained by the reduced erythropoietin production and loss of erythropoietin and transferrin in the urine.[3,14] Similarly, loss of vitamin D-binding protein and albumin (which decreases bound calcium) can cause hypocalcaemia which may contribute to seizures.[15] For this, the patient was given IV calcium gluconate. In general, these complications can be reversed by managing the proteinuria.

Lack of *β2* laminin at the neuromuscular junctions affects the development of the infant.[15] Hypotonia, psychomotor retardation and blindness are the most consistent findings.[15] Thus, patients who survive infancy may still suffer from these neurological abnormalities. As in the current case, there may be delayed developmental milestones.

Finally, the current patient had all the features of congenital nephrotic syndrome, which along with microcoria helped to establish the diagnosis of Pierson syndrome. Biopsy for histopathological analysis was not possible due to the unstable condition of the patient. As Pierson syndrome is inherited in an autosomal recessive pattern, it is more likely to be found in consanguineous marriages with multiple children being affected, as was found in the current case. Confirmatory testing should be done by genetic analysis; however, due to a lack of adequate resources for mutation analysis at the authors' institution and limited analysis being done at certain institutes which are too expensive, it was not possible to obtain this significant information.

In terms of the outcome of congenital NS, it is fatal within a few years due to renal failure and nephrectomy and renal transplant are the only modalities to save the infant's life. It is necessary to counsel parents of such patients regarding the limited treatment options for this disease and the importance of lifelong monitoring. Ophthalmic and neurological screening for patients of congenital NS should be done, along with regular monitoring of thyroid function tests. Consanguineous parents must be warned about the possibility of their offspring being affected by congenital NS and antenatal check-ups for any indication to congenital NS in the foetus must be suggested. The option of genetic diagnosis by analysing the *LAMB2* gene must also be explained to the parents.

Conclusion

Pierson syndrome consisting of microcoria and congenital NS has a poor prognosis due to renal failure. The current patient had the additional complications of hypothyroidism and septic shock, which along with renal failure proved fatal for the infant.

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