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Pierson Syndrome: Case Report

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Abstract

***Background*:** Pierson syndrome comprises of congenital nephrotic syndrome (CNS) and peculiar ocular changes. LAMB2 gene mutation has been reported to be causative reason for this rare autosomal recessive disorder. ***Methods*:** An observational case series reports comprising of two children presenting with symptoms like heavy proteinuria, haematuria are being discussed. Physical examination along with ophthalmological assessment, hearing assessment, varied blood investigations, urinalysis, renal biopsy and gene testing were carried out to diagnose the condition. ***Results*:** Pearson syndrome was detected with mutations of LAMB2 gene detected by Whole Exom Sequencing test in one of the case study. The Ocular abnormality in both patients comprised of squint hypertropia, a new variant ocular finding related to Pearson syndrome. ***Conclusions*:** The clinical finding of squint hypertropia is a novel finding associated with Pearson syndrome, reported here for the first time.

Keywords: Autosomal recessive; Pearson syndrome; Congenital Nephrotic Syndrome, Children.

INTRODUCTION

Pierson syndrome, a rare congenital disorder, manifests in early childhood or even earlier in utero with a recent estimated incidence of 1/1000,000 live births [1, 2]. This autosomal recessive disorder, discovered by Pearson *et al*., in 1963 [3], has been reported in approximately 40 families globally till date [4, 5]. It manifests majorly with features of congenital nephrotic syndrome (CNS) along with extra-renal abnormalities [1]. Congenital nephrotic syndrome exhibits heterogeneity with features like proteinuria, hyperlipidaemia, oedema and hypoalbuminemia [6]. Extra-renal characteristics in this uncommon disease involves mainly ocular disorders along with bone marrow disorders, liver disorders and developmental delays [7]. Heart manifestation in this syndrome is the latest finding reported in Germany [8]. The peculiar findings associated with this disorder involves renal abnormalities along with microcoria (ocular abnormality in which pupil is less than 5 mm). Other ocular manifestations reported in past literature includes abnormal cornea, abnormal lens, abnormal retina, cataract, strabismus etc [9-12].

The renal abnormal manifestations are seen across three age groups (a. less than three months, b. 3 months upto 1 year, c.> 1-year-old) with majority of cases reported in the former group i.e. less than three months [13, 14]. This uncommon disorder is the result of rare mutation in gene LAMβ2 (Laminin; Beta 2) [14], located at chromosome 3 with Gene Map Locus 3p21.31. The (OMIM) Online Mendelian Inheritance in Man number of this disease is reported to be 609049 [11]. Around 50 mutations of this gene has been reported in the past literature [4, 5]. The mutations vary from missense, nonsense, splice-site mutations to deletions and insertions [5, 15, 16]. The disease severity varies according to gene mutation with severe mutations form i.e. end renal failure with ocular abnormalities and developmental delays to less severe phenotype

Pierson syndrome patients usually have a poor prognosis along with health deterioration owing to

impaired renal failure or it's impending complications [17]. The alarming high mortality amongst children is attributed to this disease highlights the repercussion of being fatal in spite of its rare occurrence. Early reporting and diagnosis is vital in effective management for curbing mortality or increasing the longevity of the patient.

Further, it is essential to point out less severe phenotype mutation cases in the clinical settings to avoid their deterioration. With this background, we herein discuss case series highlighting two cases with similar symptoms as reported in Pierson syndrome. Additionally, Pierson Syndrome cases have been reported across the world in Korea, China, India, Germany etc [2, 4, 8, 16, 18]. However, in the Arab world, only UAE (United Arab Emirates) had reported the characteristics of this disorder in the past. This study is, thereby, first of its kind with the rare cases being reported first time from Saudi Arabia, country of Arab world.

MATERIAL AND METHODS

We hereby report an observational case series of two children with similar manifestations like Pierson syndrome. Early referral to nephrology unit was done at security forces Hospital . Nephrology department providing all needful services across varying age groups. The patients referred to the Nephrology department were in the third category of age group as seen in Pierson syndrome i.e. >1-year-old. One patient was referred with a chief complaint of recurrent proteinuria along with haematuria whereas the other patient reported frequent urination since past one year. The second patient had already undergone urine analysis before being referred to Nephrology department.

The past medical history along with vaccination details and checkout for developmental delays were done for patients referred to Nephrology department. Their vital signs like breathing rate, heart rate, body temperature and blood pressure were recorded. Ophthalmology examinations were done to rule out any ocular abnormalities along with hearing assessment. Blood investigations comprising of Complete Blood Count, Anti-Nuclear Antibody test, Hepatitis test, Liver Function test, Bone profile, lipid profile, C3, C4, Immunoglobulin level, Micro-albumin urine, anti DNA etc. were carried out. Additionally, urinalysis along with urine-protein-creatinine ratio estimates were conducted. Patients also underwent renal biopsy and gene testing (Whole Exome Sequencing tests) for confirming gene mutation if any.

We used Patient information sheet to collect information regarding patient age, gender, chief complaint, familial history, past medical history, symptoms, vital statistics recording, date of reporting in the hospital, Investigations done, date of referral to Nephrology department, hearing and ophthalmic assessments, results of blood sample and other investigations like urine analysis, gene testing and renal biopsies and probable/differential diagnosis. The study protocol was approved by the Ethics Committee of the institute and informed consent was sought in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of the children.

CASE PRESENTATIONS

This case series comprises two cases in the age group > 1-year-old children (median age – 6 years) depicting symptoms like proteinuria, and haematuria with ocular abnormalities as seen in Pierson syndrome. Familial history was explored to observe similar findings in related persons. The following cases describes detailed description of the symptoms seen, investigations done and the findings of the cases. The table below (Table 1: case representation) also highlights the key aspects of the case reports.

Case 1

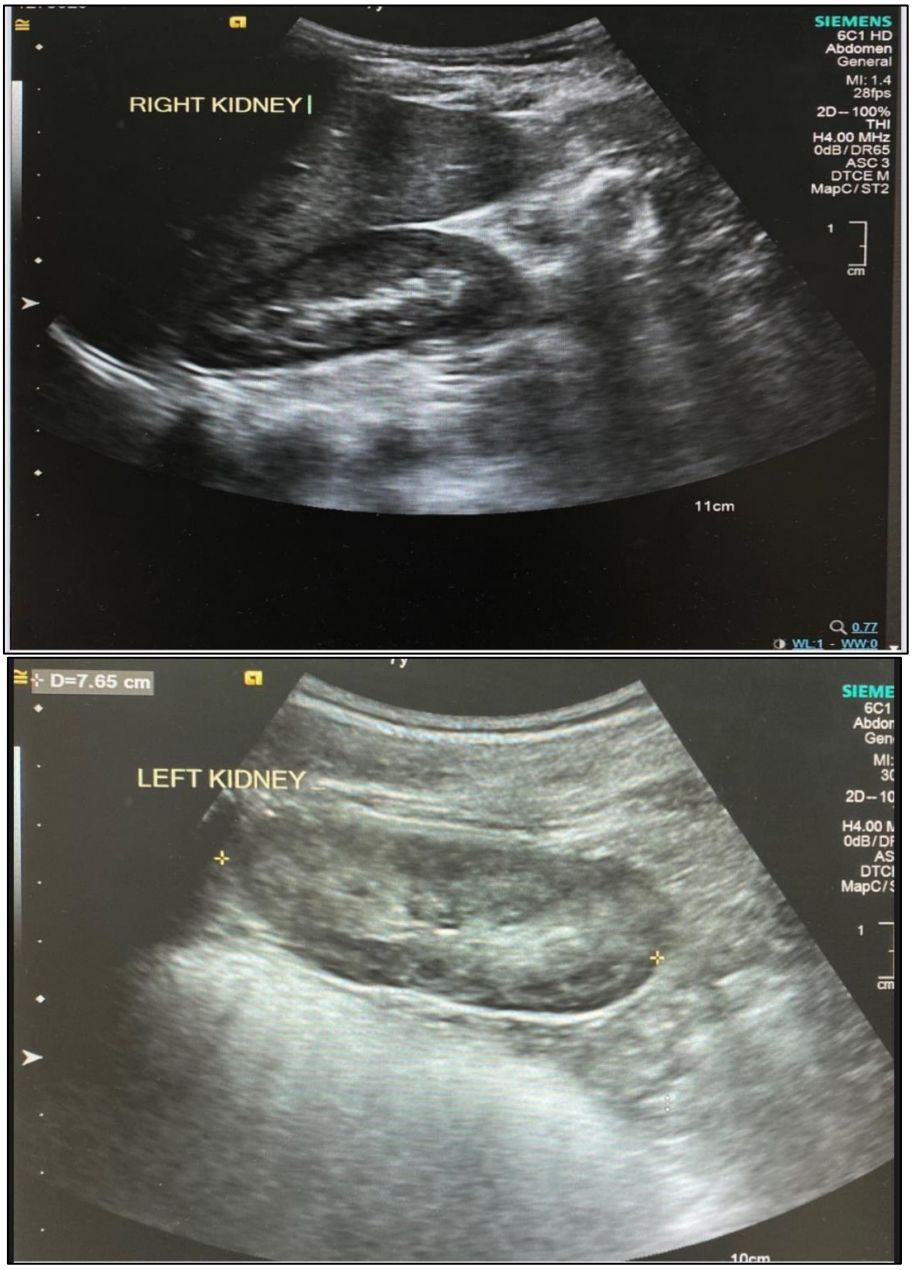
A seven-year-old girl born with normal spontaneous vaginal delivery to consanguineous healthy parents (cousins or related to each other) reported to Comprehensive specialist clinics for security forces hospital with chief complaint of recurrent proteinuria, haematuria which was accidentally discovered one year ago by her mother. The other four siblings of the patient were healthy but one brother had reportedly had recurrent episodes of recurrent hematuria and pyuria.The early referral of the patient was done for nephrology assessment.

The systemic review revealed no abnormalities. Patient's past medical history was recorded. The patient had been wearing thick glasses along with regular follow ups visits to the ophthalmologist. The patient's history revealed that vaccination was updated and she had no developmental delays. The patient on medical examination was active and well hydrated with vital signs reported as the following: body temperature- 36.8 degrees Celsius, Respiratory rate 22 breaths per minute, 100 beats per minute and Blood pressure reported to be 105/70 mm Hg. The Hearing assessment revealed no abnormalities. Ophthalmological examination revealed Retinal detachment

The blood investigations revealed normal levels of Liver Function test, Bone profile, lipid profile, C3, C4, Immunoglobulin level. Patient tested negative for hepatitis and absence of Anti-Nuclear Antibody was revealed. The laboratory tests like urinalysis revealed 2+ protein and 2+ blood in urine. The anti-streptolysin titres value was very high, estimated to be 254 (Normal range < 150); indicating glomerulonephritis. The patient's protein-urine/creatinine-urine ratio was significantly high and reported to be 362 mg/mmol

(normal value less than 50, 50-300 – proteinuria, > 300 nephrotic) indicating renal damage.

The renal biopsy conducted at King Faisal Specialist Hospital & Research Centre by the consultant pathologist revealed 1 of 30 glomeruli globally sclerosed. The pathological findings were consistent with IgM Nephropathy (an autoimmune disease that affects the filters (glomeruli) of the kidneys). There were no other significant findings in the renal biopsy and the ultrastructural examination was inconclusive with differential diagnosis of hereditary nephritis or Alport syndrome (a hereditary disorder affecting kidneys). However, the gene testing done through Whole Exome Sequencing tests confirmed the gene mutation of Laminin Beta 2 (LAMB2) in the patient as per American College of Medical Genetics and Genomics (ACMG) guidelines; confirming Pierson syndrome and ruling out other kidney disease variants.



Case 1: The both kidneys demonstrate normal echogenicity and corticcomedullary differentiation. No renal mass, calculi or hydronephrosis, Unremarkable examination

Case 2

A five-year-old boy born with normal spontaneous vaginal delivery to consanguineous healthy parents (cousins or related to each other) reported to Comprehensive specialist clinics for security forces with chief complaint of frequent urination since one year. The urinalysis revealed presence of blood and pus cells in urine. The parents of the child repeated the test several times to rule out any misdiagnosis but tests revealed same results. The four siblings of the patient

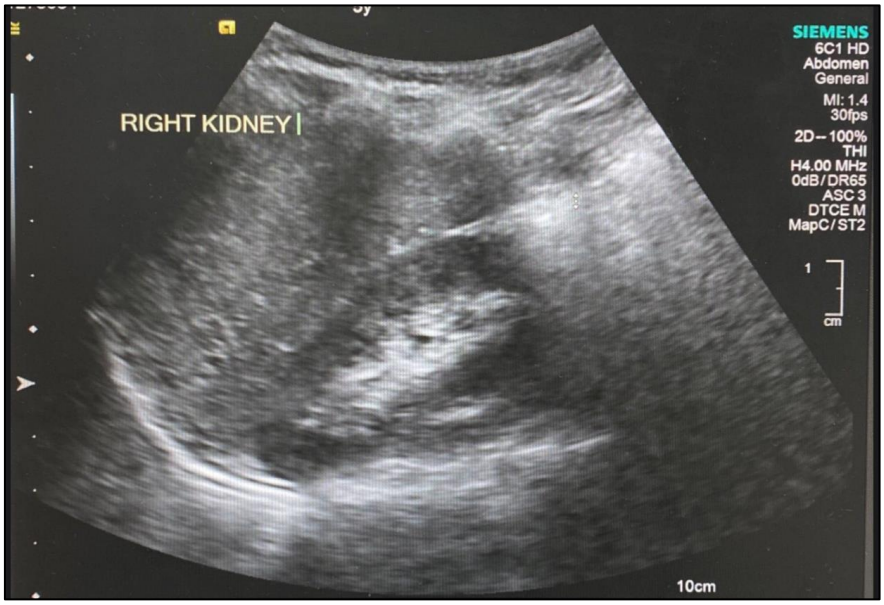
were healthy but one sister had recurrent episodes of haematuria and pyuria. The early referral of the patient was done for nephrology assessment.

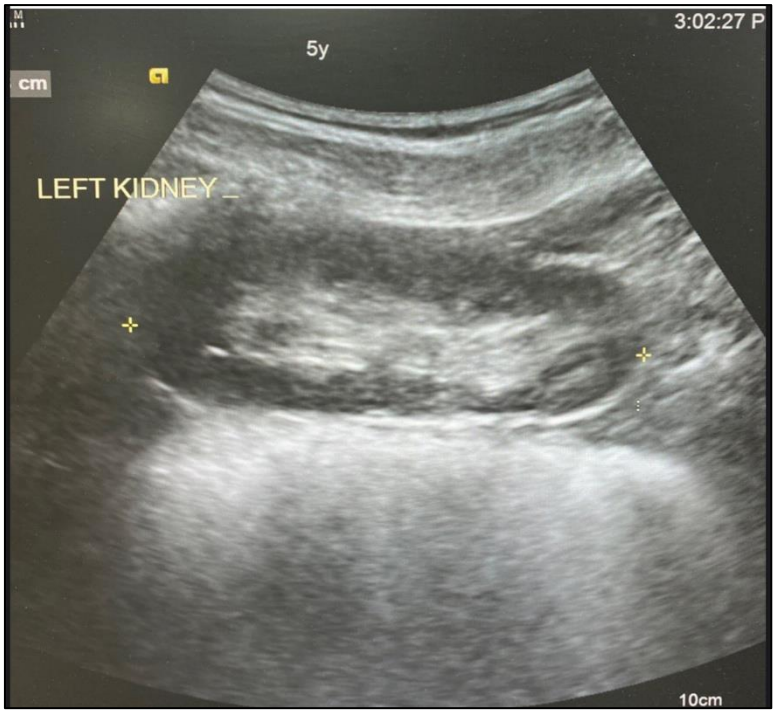
The systemic review revealed no abnormalities. Patient's past medical history was recorded in which patient reported urodynamic study revealing proteinuria post urinary tract infection. The patient has been wearing thick glasses and patient had regular follow ups with ophthalmologist. The patient's vaccination was updated and had no developmental delays. The patient on medical examination was active and well hydrated with vital signs reported as the following: body temperature- 36.5 degrees Celsius, Respiratory rate 30 breaths per minute, 111 beats per minute and Blood pressure reported to be 100/55 mmHg. His growth parameters were normal. The Hearing assessment revealed no abnormalities. Ophthalmological examination revealed Squint hypertropia. The blood investigations revealed normal levels of Liver Function test, Bone profile, lipid profile, C3, C4, Immunoglobulin level. Patient tested negative for hepatitis and absence of Anti-Nuclear Antibody was revealed. The laboratory tests like urinalysis revealed 2+ protein and 2+ blood in urine. The patient's protein-urine/creatinine-urine ratio was high indicating proteinuria at 103.8 mg/mmol (normal value less than 50, 50-300 – proteinuria, > 300 nephrotic).

The renal biopsy conducted at King Faisal Specialist Hospital & Research Centre by the consultant pathologist revealed 1 of 56 glomeruli globally sclerosed. There were no other significant findings in the renal biopsy and the ultrastructural examination was inconclusive with differential diagnosis of hereditary nephritis or Alport syndrome (a hereditary disorder affecting kidneys). The Whole Exome Sequencing tests confirmed the gene mutation of Laminin Beta 2 (LAMB2).

Table 1: General Case Representations

General Case Presentation		
Details	**Case 1**	**Case 2**
Age	5	7
Sex	Male	Female
Parental consanguinity	Present	Present
Ocular abnormalities	Retinal detachment	Squint hypertropia
Blood tests (CBC, ANA, hepatitis, LFT, Bone profile, lipid profile etc.)	Normal findings	Normal findings
Protein in urine	2 +	2+
Blood in urine	2+	2+
Pro-U/Crea-U Ratio (mg/mmol)	103.8	362
Renal biopsy findings	1 of 56 glomeruli sclerosed globally	1 of 30 glomeruli sclerosed globally
Gene testing	Confirmed LAMB2 gene	Confirmed LAMB2 gene





Case 2: The both kidneys demonstrate normal echogenicity and corticcomedullary differentiation. No renal mass, calculi or hydronephrosis, Unremarkable examination

DISCUSSION

Pierson syndrome, a rare congenital disorder discovered in 1963 by Pearson [3], is mainly pathognomonic of Congenital nephrotic syndrome and ocular disorder 1]. The other manifestations may be present in the form of liver disorders, deafness, bone disorders, developmental delays etc. A recent study in Germany has reported association of heart anomaly with this disease for the first time globally [8]. The seven-year-old girl's case study presented in the current study consisted of proteinuria, haematuria (2+ protein and 2+ blood in urine) and extremely high protein-urine/creatinine-urine ratio (362 mg/mmol)indicating congenital nephrotic syndrome. High anti-streptolysin titres value (254) too was indicative of glomerulonephritis. Further, her parents were cousins or related and reported history of frequent proteinuria and haematuria in their another child indicated familial pattern of the disease being autosomal recessive.

Past literature reiterates the fact that consanguineous couples are at greater risk of congenital disorders in their offspring [19, 20]. The current study also reported 1 of 56 glomeruli globally sclerosed in 5-year-old boy in one case and 1 0f 30 globally sclerosed in 7-year-old girl in other case. Similar findings were reported in a study of China origin reporting the syndrome for the first time in a 3-year-old age with 4 of her 14 glomeruli globally sclerosed [4].

The peculiar sign of Microcoria was absent in the patient, making it difficult to diagnose the disease until final confirmation with genetic determination of mutant LAMB2 gene in one patient; indicative of Pearson syndrome. The genetic alterations responsible for this disease was reported years later [11], even though the syndrome was described first in 1963 [3]. The recent advances in genomic sequencing have revealed mutations in Laminin beta 2 gene expanding the clinical continuum of the disorders associated with this gene [21]. The gene mutations are varied exhibiting a spectrum of mutations ranging from missense, nonsense, splice-site mutations, deletions, insertions and truncating mutations [5, 15, 16].

Earlier, truncated mutations were held responsible for severity of the disease. However, this has been questioned with less severe cases of Pierson syndrome reported owing to truncated mutations. The lately reasoning of the concept of less severe form of disease due to truncated mutations remains unknown. Though one reasoning cited in this regard has been expression of mutant gene with different phenotypes. Past evidence example reported same mutation in members of the same family but with different phenotypes. However, the factors associated with the different phenotypes are unknown [4, 16].

Additionally, it has also been stated in the past with regard to mutations that non truncated mutant Laminin Beta 2 result in its partial expression thereby causing less severe phenotype with mild symptoms of the same disorder. However, gene testing does not reveal the type of mutation in LAMB2 gene responsible for the disorder in the current study in one case report and the other case report gene confirmation results are still awaited. Nevertheless, it can be assumed that truncated mutation with mild phenotype or the non-

truncated mutation with mild phenotype can be responsible for the disorder in the current study keeping in mind the odds of rare age group along with mild symptoms [4, 22].

The ocular abnormalities reported in the past varied from iris anomalies, abnormal lens shape with cataracts, retinal abnormalities or high-grade myopia. The ocular irregularities are not universal in nature in this syndrome [9-12]. The current study is congruent with such findings with the presence of ocular abnormality of squint hypertropia in both patients; a sign reported for first time in association with Pearson syndrome. Further, our patients were devoid of any developmental delays or other co-morbidities like liver and bone disorders; nervous system anomalies, deafness as reported in past literature.

The rare syndrome has been reported in less than 100 patients with mutant gene in less than 50 families in the medical literature worldwide [4, 5]. The patients with varied symptoms have been reported globally from Korea, Germany, China, Italy, Arab countries, India etc [2, 4, 8, 16, 18]. The onset ages of renal manifestations vary across three age groups as aforementioned with majority of cases reported in the age group of less than three months. An earlier study cited the reporting of this syndrome in the age group in age group > 1 year to be around 6.7% [12] (1 in 15 families) and majority being in the predominant age group of three months. However, the current case report on the contrary reports symptoms of Pearson syndrome in children aged 5 years and 7 years old. Additionally, the past cases have reported high fatality owing to renal failure and even in patients switched to peritoneal dialysis, that too surprisingly at a very early age which is again contrasting to the current study.

The early diagnosis of the disease is crucial for its effective management. Another point to kept in mind is the differential diagnosis of Pierson syndrome in children varying from CNS (Congenital Nephrotic syndrome) to Alport syndrome, Finnish type nephrosis, autosomal recessive steroid-resistant nephrotic syndrome, and Denys–Drash syndrome [23]. All these also are indicative of nephrotic abnormalities. Further, the varied range of symptoms with discovery of new symptoms in recent times makes the diagnosis of the disease more complex. Therefore, the confirmation of mutation of gene LAMB2 is crucial. However, the current study has the limitation of pending gene testing results in one case study. The same case study had a differential diagnosis of Alport syndrome/interstitial nephritis; citing the importance of above discussed point.

The patients with severe renal disorders in this syndrome ultimately end in renal failure with extremely poor prognosis, as reported in past, adding to the global mortality burden despite being such a rare disease. Peritoneal dialysis has been suggested at the earliest for increasing the age longevity and higher survival rate. However, the outcomes of the same are not very promising. The renal transplantation is suggested to be crucial step in aiding the increased survival rate. Further, some studies suggest nutritional interventions in the form of vitamins supplements, ketogenic diets for this disorder [2, 24-26]. The current study is limited in this area as management of the cases has not been reported yet. Nonetheless, the correct and early diagnosis aids in early interventions and management of the Pierson syndrome. Though the individual may have compromised life style, effective early interventions can contribute in increasing life span.

CONCLUSION

Gene testing to rule out any mutation of LAMB2 should be carried out without fail in children with symptoms of CNS or ocular abnormalities for early diagnosis. Consanguinity theoretically reinstates the same with more occurrence of genetic disorders in offspring of such parents. Currently, hypertropia squint must be considered as an associative symptom of Pierson syndrome. However, further genetic studies would be required to investigate this suggestion.

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