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Case Report

Senior-Loken Syndrome: A Rare Case Report of A Novel *NPHP4* Gene Mutation in A Child From Bangladesh

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ABSTRACT

Background and Aim: Senior Loken syndrome describes patients with nephronophthisis along with retinal dystrophy. The first signs of renal involvement include polyuria and polydipsia, which occur due to impaired urinary concentration capabilities. Nephronophthisis progresses to end-stage renal disease by the age of 20. Retinal abnormalities can range from severe infantile retinal dystrophy to the more typical form of retinitis pigmentosa. Other associated features of this syndrome include skeletal and dermatological abnormalities, as well as cerebellar issues.

Case Presentation: Here, we reported a case of Senior–Loken syndrome with polyuria, polydipsia, and nocturnal enuresis followed by the features of advanced renal disease, such as growth retardation and moderate anemia. He was also myopic and demonstrated tessellated fundus during the fundoscopic examination.

Conclusion: To date, there are no case reports published in the Bangladeshi medical literature regarding this rare autosomal recessive disorder among pediatric patients. Therefore, this case report aims to increase awareness among clinicians to detect these patients early, as the management implemented may prevent or delay the need for renal replacement therapy and preserve eyesight.

Keywords: Senior-Loken syndrome, Nephronophthisis, Chronic kidney disease, Retinitis pigmentosa

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Introduction

Senior-Loken syndrome (S-L) is an autosomal recessive disorder and a variant of nephronophthisis (NPHP)-related conditions, characterized by cystic kidney disease along with retinal dystrophy, which can manifest as either retinitis pigmentosa or Leber congenital amaurosis [1]. It was first described by Senior et al. in 1961, who reported a family in which six of 13 children had suffered from nephronophthisis and tapetoretinal degeneration [2]. Loken et al. also discovered the same condition in two siblings in the same year, where both siblings experienced blindness and renal failure; both had undergone kidney biopsies that revealed renal tubular atrophy and dilatation [3]. This is a devastating disorder that leads to blindness and renal failure. The visual outcome is usually poor, and there has been no definitive treatment available to date [1]. Pigmentary retinal changes are observed during the ophthalmoscopic examination, which can be proven by performing an electroretinogram (ERG) [4]. This syndrome accounts for 10-15% of childhood genetic kidney disease cases classified as NPHP, which affects about 1 in 50,000 births [5]. NPHP is the most prevalent genetic cause of end-stage kidney disease (ESKD) in the first three decades of life [6]. It is an autosomal recessive kidney disorder characterized by chronic tubulointerstitial nephritis, ultimately resulting in ESKD [7-11]. The initial clinical features of renal involvement are polyuria and polydipsia resulting from defective urinary concentrating ability. Most cases present late after renal failure is already advanced [5]. Invariably, affected individuals develop ESKD by the age of 20 years [8]. Renal transplantation seems to be the best course of action for the patients with ESKD [1].

Case Presentation

A nine-year-old immunized boy (Figure 1), the first child of his consanguineous parents, was admitted to the Department of Pediatric Nephrology at BSMMU with complaints of not growing well compared to his peers for the past two years, as well as generalized weakness and pallor for the past six months. He had a history of polyuria, polydipsia, nocturnal enuresis, and myopia. He had no history of fever, passage of red-colored urine, dribbling of urine, or straining during micturition, nor did he report any rashes, joint pain, bony changes, breathing difficulties, altered consciousness, family history of similar issues, or use of any offending drugs.

On examination, he is vitally stable, moderately pale, and stunted, with myopia present. Systemic examination revealed normal findings. Investigations showed hemoglobin at 7.6 gm/dL, serum creatinine at 3.2 mg/dL, eGFR at 15.3 mL/min/1.73 m² (stage 4 chronic kidney disease [CKD]), serum urea at 134.6 mg/dL, and serum electrolytes as follows: Na^+: 136 mmol/L, K^+: 3.9 mmol/L, Cl^-: 110 mmol/L, TCO_2: 13.4 mmol/L, PO_4^{3-}: 7.7 mg/dL, and parathyroid hormone (PTH): 131 pg/mL. Urine routine examination revealed pus cells: 0-4/HPF, RBC: 0-3/HPF, and protein: Trace. Ultrasound (USG) revealed bilateral mild renomegaly with renal parenchymal changes and bilateral renal cysts. Echocardiogram findings were normal. Fundoscopic examination showed a tessellated fundus, with a cup-to-disc (CD) ratio of 0.5 in the right eye and 0.3 in the left eye, with no presence of sector retinitis pigmentosa, Leber congenital amaurosis, or tapeto-retinal degeneration (Figure 2).

Genetic studies revealed the following: Gene (Transcript): NPHP4(-), location: Intron 21, variant: c.3044+1G>C (5′ splice site), zygosity: Homozygous, disease (OMIM): NPHP -4 (OMIM#606966) or Senior-Loken syndrome-4 (OMIM#606996), inheritance: Autosomal recessive, classification: Pathogenic. He is currently receiving all the supportive treatments for CKD and is being prepared for future renal replacement therapy.

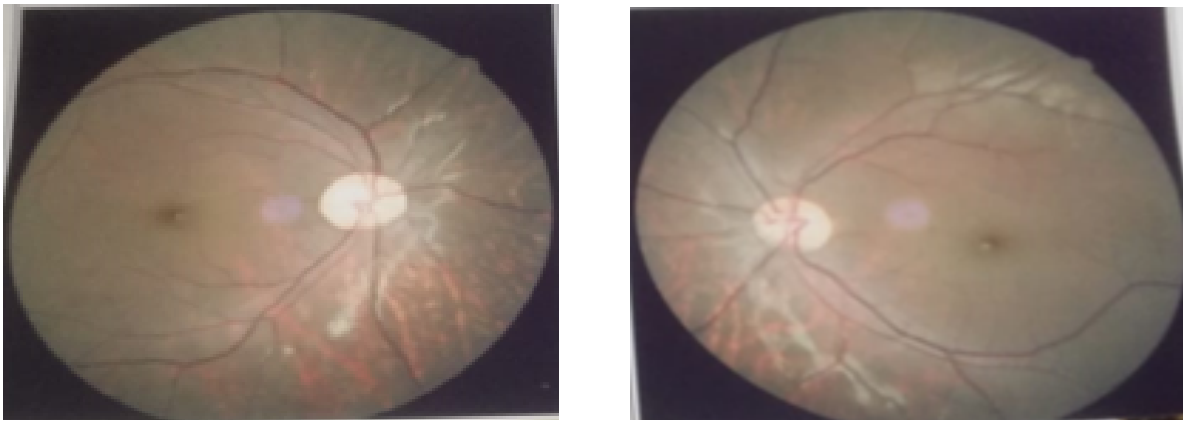
Discussion

NPHP is a collection of cystic kidney diseases that are inherited in an autosomal recessive manner. It is the most prevalent genetic cause of ESKD in children and young adults, particularly during the first two decades of life [4]. Renal medullary cystic disorders were first described by Smith and Graham in 1941 and then by Fanconi in 1951, which led to the nomenclature of juvenile familial NPHP. Senior and Loken for the first time in 1961 described the association of nephronopthisis and tapetoretinal degeneration [5]. This condition occurs in about 10-15% of all cases of NPHP. Other names for this syndrome are renal retinal dysplasia, hereditary renal retinal syndrome, and renal dysplasia-blindness. Renal involvement manifests as NPHP with chronic tubulointerstitial nephritis, which evolves into end-stage renal disease by approximately the second decade of life. NPHP is primarily caused by mutations in nine genes (NPHP 1-9). There are three clinical variants of nephronophthisis categorized by the age at which end-stage renal disease occurs: Severe infantile, juvenile, and adolescent nephronophthisis. Genetic analysis of our patient identified a pathogenic homozygous NPHP4(-) mutation.

Figure 1. Photo of our patient

Polyuria is the first symptom that develops around six years of age and is associated with nocturnal enuresis and polydipsia, followed by signs and symptoms of advanced renal disease, such as growth retardation. Similar findings were also present in our patient. Anemia occurs early in the disease course and becomes severe in comparison to other children with renal diseases. This anemia results from a defect in the function and regulation of erythropoietin-producing cells. We also found our patient to be moderately anemic. Patients with urinary abnormalities typically exhibit an inability to concentrate urine and salt wasting [4]. Approximately 70% of patients have cysts measuring 1-15 mm in diameter, primarily located at the cortico-medullary junction and medulla. While the disease is reported to have cysts occurring late in the course, recent investigations can detect them early. A CT scan of the kidneys is the preferred imaging modality, but renal ultrasound can also be a useful test for detecting renal cysts [12, 13]. However, these tests are not always diagnostic for NPHP, as cysts may be absent even in the late stages of the disease [11]. Sonographic findings of hyperechogenic kidneys that are slightly or normally sized are consistent with a diagnosis of NPHP [14]. Ultrasound in our patient showed bilateral renal cysts, and both kidneys were mildly enlarged with increased cortical echogenicity and decreased corticomedullary differentiation. The triad of renal tubular cell atrophy with cyst development, interstitial infiltration, and interstitial fibrosis are characteristic features found in renal histopathological examinations [15]. However, all patients eventually progress to ESKD and require renal replacement therapy, such as peritoneal dialysis, hemodialysis, or preemptive kidney transplantation [4].

Ocular involvement can range from severe, early-onset Leber congenital amaurosis to late-onset pigmentary retinal degeneration. Tapeto-retinal degeneration is the most prevalent type of retinal degeneration, and its characteristics and severity can differ among individual patients. Progressive degeneration of the choroid and retina is a characteristic of this condition. In contrast, retinitis pigmentosa involves bone spicule degeneration, which starts from the periphery of the retina and extends further to encompass the entire retina and choroid [16]. The color fundoscopic examination of our patient showed a tessellated fundus, with a CD ratio of 0.5 in the right eye and 0.3 in the left eye, and the absence of sector retinitis pigmentosa, Leber congenital amaurosis, and tapeto-retinal degeneration. Additional ocular abnormalities may include cataracts, Coats' disease, and keratoconus. These



a) b)

Figure 2. a,b) Color fundus photographs of both eyes of our patient, showing findings suggestive of a tessellated fundus

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ocular changes typically begin in childhood or early adolescence, leading patients to experience a range of symptoms from night blindness to total blindness. The ERG response may show a decrease or be absent, indicating reduced function of the retinal rod cells. Therefore, the ERG can assist in the early diagnosis of the condition prior to the onset of symptoms or fundoscopic examination. As the retinal disease generally progresses over time, regular annual ophthalmological evaluations are recommended starting from the time of diagnosis [5].

Some less common features of this disease include: A) Hypoplasia or aplasia of the cerebellar vermis, which is usually recognized by the "molar tooth" sign found on an axial view of an MRI of the brain; B) Developmental delays of variable severity; C) Ataxia; D) Reduced visual acuity along with nystagmus, sluggish pupillary reactions, photophobia, and hyperopia; and E) Systemic hypertension resulting from renal damage [5]. Our patient did not exhibit any of these features.

Currently, there is no cure for NPHP. Management focuses on slowing the progression toward renal failure, which will eventually necessitate renal replacement therapy, either through dialysis or kidney transplantation. Research is underway on the potential use of newer agents, such as vasopressin V2 receptor antagonists, which may alter cyst formation and help slow the disease's progression [17].

There are no reported cases of this rare autosomal recessive disorder in the medical literature of Bangladesh among the pediatric population. Our case report aims to increase clinicians' awareness of these patients early on and to provide management that might delay the need for renal replacement therapy and preserve eyesight.

Conclusion

Senior-Loken syndrome has a devastating effect on the lives of the affected individuals. These patients usually need dialysis or renal transplantation by the time they reach adolescence. Meanwhile, their retinas also deteriorate simultaneously, leading to blindness as well. It has become protocol now for patients with nephronophthisis to have comprehensive ophthalmological evaluations annually, including an ERG, to detect ocular abnormalities at an early stage and preserve eyesight for a longer period. Children diagnosed with primary tapeto-retinal degeneration should have regular blood pressure monitoring, assessment of their urinary concentrating ability, and renal ultrasounds. If these patients are diagnosed early through consistent follow-up and screening tests, careful management of hypertension and dietary protein restrictions could potentially postpone the need for renal replacement therapy. We observed a novel pathogenic gene mutation in our patient that confirms our diagnosis. This is a devastating autosomal recessive disorder that typically occurs in consanguineous marriages. Therefore, appropriate premarital genetic counseling is essential.

Ethical Considerations

Compliance with ethical guidelines

Informed consent was obtained from the patient and his parents.

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Authors' contributions

All authors had equal contributions to writing every section of this case report.

Conflict of interest

The authors declared no conflict of interest.

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