Case Report

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NPHP Gene Related Nephronophthisis in Bahrain: Case Series and Literature Review

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ABSTRACT

Nephronophthisis (NPHP) is a rare, autosomal recessive disorder that often progresses to end-stage renal disease (ESRD) in early adulthood. It is caused by mutations in genes encoding proteins involved in primary cilia function. In addition to renal involvement, NPHP can present with various extrarenal manifestations, including ocular, skeletal, hepatic, neurological, and cardiac abnormalities. Recent studies have also highlighted the potential association of NPHP with male infertility. This article presents three case studies of adult onset NPHP patients from a tertiary hospital in Bahrain, highlighting the clinical presentation and emphasizing the importance of genetic testing in establishing a definitive diagnosis. The cases highlight the diverse clinical spectrum of NPHP, ranging from isolated renal involvement to more complex syndromes. Early diagnosis and genetic counseling are crucial for providing appropriate care and support to patients and their families.

Keywords: Nephronophthisis (NPHP); End-Stage Renal Disease (ESRD); Primary Cilia; Genetic Testing; Whole Exome Sequencing; Extrarenal Manifestations

Abbreviations: ESRD: End-Stage Renal Disease; NPHP: Nephronophthisis; NGS: Next-Generation sequencing; CNV: Copy Number Variation; ACMG: American College of Medical Genetics and Genomics

Introduction

Nephronophthisis (NPHP) is a leading genetic cause of early-onset end-stage renal disease (ESRD), that is inherited in an autosomal recessive pattern. This condition typically progresses to ESRD within the first three decades of life. Its incidence varies geographically, ranging from 1 in 62,000 live births in Finland to 1 in 1 million in the United States [1,2]. NPHP is caused by mutations in genes encoding nephrocystin proteins, which play crucial roles in the function of primary cilia, basal bodies, and centrosomes. These genetic defects lead to renal dysfunction and a variety of extrarenal manifestations [2]. NPHP was initially described in 1945 by Smith and Graham as "medullary cystic kidney disease [3]." Six years later, Fanconi et al. introduced the term "familial juvenile nephronophthisis" to characterize this condition [4]. The term "nephronophthisis" is derived from Greek and translates to "disintegration of nephrons," reflecting a key histopathological characteristic of the disease [5]. This article presents our clinical experience with adult onset NPHP in Bahrain focusing on renal manifestations. Additionally, we explore extrarenal manifestations and the underlying genetic basis of this disorder, incorporating recent literature updates.

Case Presentation

Case 1

A 26-year-old Bahraini male underwent a living non-related kidney transplant in 2019 after being diagnosed with end-stage renal disease (ESRD) at age 19. A previous renal biopsy revealed chronic interstitial inflammation, but the underlying cause of his ESRD remained unclear. To further investigate the underlying cause of the

patient's kidney disease, whole- exome sequencing was performed using next-generation sequencing (NGS), including mitochondrial genome and copy number variation (CNV) analysis. The genetic analysis revealed a pathogenic two-copy loss (homozygous deletion) of approximately 121 kb within the chromosomal region 2q13. This deletion encompasses three genes, including NPHP1, which is implicated in nephronophthisis. This result confirmed the genetic diagnosis of autosomal recessive nephronophthisis type 1.

The patient's family history revealed that he was born after 11 years of infertility treatment. There were no antenatal or postnatal complications with normal developmental milestones. He had three siblings born naturally. His parents are blood related, and a paternal cousin experienced a kidney abnormality and developed kidney failure in childhood. Genetic testing was performed on two of his asymptomatic siblings. The results showed that his brother was a carrier of the gene mutation, while his sister inherited two copies of the mutated gene (homozygous mutation). This condition is associated with an increased risk of developing ESRD. Consequently, his sister was referred to the nephrology department for further assessment. Currently, the patient is in good health post-transplant with normal renal function and regular follow-up visits to the nephrology clinic. Additionally, he is receiving care from endocrinology and urology specialists to address infertility-related concerns.

Case 2

A 34-year-old man, previously healthy, presented with renal failure of unknown etiology. Comprehensive biochemical and imaging investigations failed to identify a specific cause. Due to the small size of his kidneys, a renal biopsy was not feasible. The patient subsequently required hemodialysis for 18 months until a successful kidney transplant from his brother in May 2024. The patient did not have any antenatal or postnatal complications and had normal developmental milestones. His parents are not blood related. Family history revealed that his paternal uncle developed diabetic nephropathy in old age, and his paternal grandmother had renal problems later in life. To further investigate the underlying genetic cause of the patient's kidney disease, whole exome sequencing was performed. The results identified the same gene mutation as in Case 1, confirming a diagnosis of autosomal recessive NPHP1-related disease. It's important to note that these two cases are from unrelated families. Genetic testing of the kidney donor sibling revealed normal results. Post-transplant, the patient has remained stable with no acute rejection or urinary complications. A DJ stent was removed in July 2024. The patient's current clinical status is excellent, with normal renal function and ongoing regular follow-up at the nephrology clinic.

Case 3

A 55-year-old Bahraini male with a history of retinitis pigmentosa and unexplained renal failure since the age of 20 underwent his third renal transplant in September 2017. The patient did not have any antenatal or postnatal complications and had normal developmental milestones. His parents are blood related. Family history revealed that the patient's mother had renal failure in old age. To further investigate the underlying cause of the patient's kidney disease, whole exome sequencing was performed, and a homozygous variant of uncertain significance was identified in the NPHP4 gene, associated with Senior-Loken syndrome 4. This genetic finding is potentially linked to the patient's clinical presentation of retinitis pigmentosa and unexplained renal failure. The patient has remained stable post-transplant, with no acute rejection or urinary complications. Regular follow-up at the nephrology clinic is ongoing. (Figures 1-3) depict the family pedigrees for the patients in cases 1,2,3.

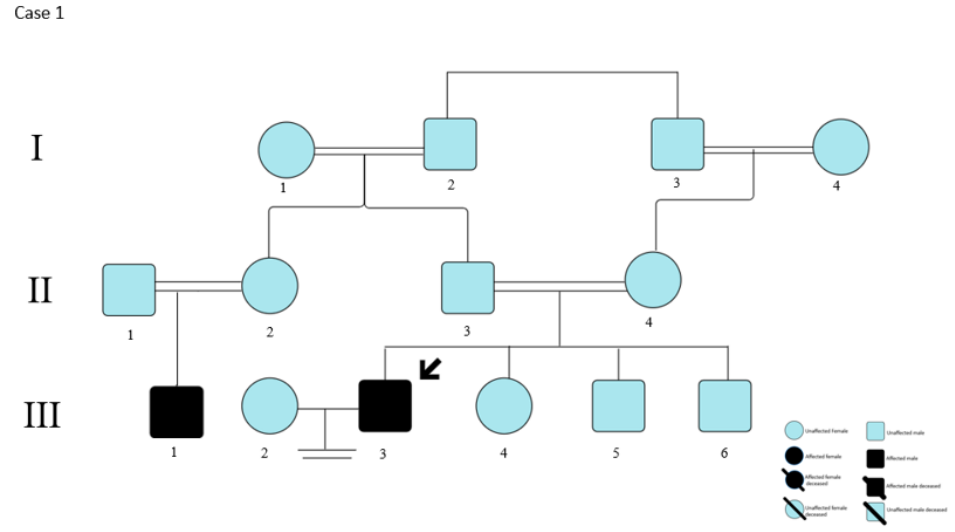

Figure 1: Illustrates the family pedigree for the patient in Case 1.

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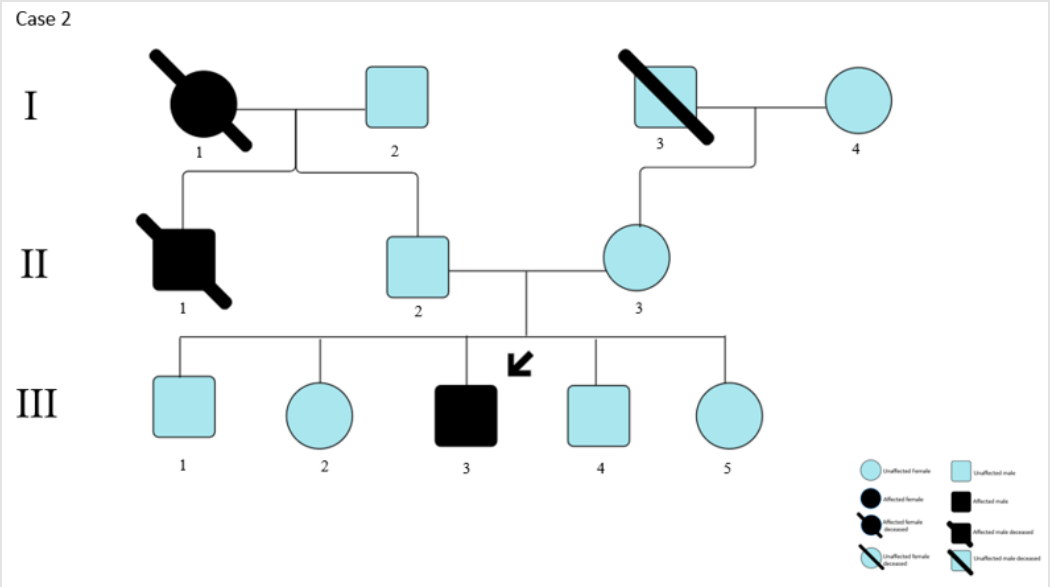

Figure 2: Illustrates the family pedigree for the patient in Case 2.

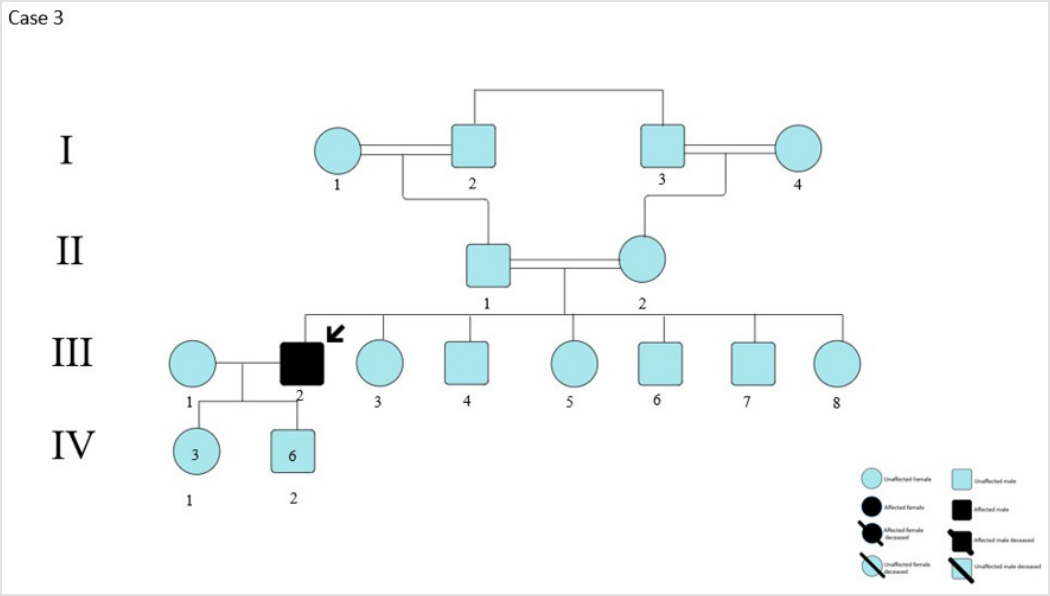

Figure 3: Illustrates the family pedigree for the patient in Case 3.

Discussion

Nephronophthisis (NPHP) is an autosomal recessive tubulointerstitial kidney disease primarily caused by homozygous variants in NPHP genes [6]. These genes encode proteins predominantly expressed in centrosomes and primary cilia, classifying NPHP as a ciliopathy [7]. To date, over 20 genes have been identified as potential contributing factors for NPHP when mutated [8]. The specific gene and type of mutation play a critical role in determining the severity of the disease, including the age of onset and the extent of organ involvement [5]. Of note, mutations in a single NPHP gene can result in a diverse spectrum of clinical phenotypes, ranging from isolated NPHP to more complex conditions such as Senior–Loken syndrome, Joubert

syndrome, and severe neonatal lethal forms like Meckel–Gruber syndrome [8]. At our tertiary care center, we encountered three cases of adult-onset NPHP from Bahrain. To determine the underlying genetic cause of their kidney disease, these individuals were referred to the genetics department for further evaluation. To diagnose these cases of early- onset renal failure of unknown etiology, whole exome sequencing with copy number variant analysis, including mitochondrial genome sequencing, was performed by an international laboratory. The process involved fragmenting genomic DNA enzymatically, enriching target regions using DNA capture probes covering approximately 41 Mb of the human coding exome and the mitochondrial genome and sequencing the generated library on an Illumina platform to ensure sufficient coverage. All relevant variants related to the phenotype of the patient were reported. Clinical reevaluation for all identified variants was performed to enhance phenotype-genotype correlation.

In the first case, and by utilizing the NGS-based CNV analysis, a pathogenic homozygous deletion (two copy loss) of 121kb involving the 2q13 chromosomal region encompassing the NPHP1 gene was detected. This deletion was classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Cascade screening was performed for two of his asymptomatic siblings over 21 years of age, consistent with our carrier testing policy. The sister was found to harbor the same homozygous deletion, while the brother was identified as a heterozygous carrier of the variant. In the second case, NGS-based CNV analysis was also employed. A 121 kb two-copy loss (homozygous deletion) encompassing 3 genes (MALL, MTLN, NPHP1), including the NPHP1 gene, was detected. The exact deletion breakpoints could not be determined based on the sequence data. However, large deletions involving this gene have been frequently reported in nephronophthisis patients. Therefore, this variant is classified as pathogenic (class 1) according to ACMG guidelines. Carrier screening was performed for one of his asymptomatic siblings, who was found to be negative for the targeted mutation and was therefore selected as a kidney donor for his brother. In the third case, no pathogenic or likely pathogenic variants were identified. However, a novel homozygous NPHP4 gene mutation (c.4179T>A; p. Phe1393Leu) was discovered. To the best of our knowledge, this variant has not been previously reported in the literature and is therefore classified as a variant of uncertain significance. Unfortunately, genetic testing of the parents and other unaffected siblings was not feasible. Given the association of pathogenic NPHP4 gene variants with Nephronophthisis-4, and the patient's early-onset renal failure and evidence of retinopathy, the identified novel mutation was considered a potential causative factor, particularly considering the great genetic heterogeneity of the condition. NPHP1 mutations, primarily large homozygous deletions, are the most frequent cause of Nephronophthisis, accounting for approximately 20% of cases [9]. NPHP1 encodes nephrocystin-1, a protein known to interact with various molecules involved in cell adhesion and signaling pathways [10]. Additionally, NPHP4, identified through homozygosity mapping and linkage analysis in patients lacking mutations in NPHP1, NPHP2, or NPHP3, localizes to primary cilia and centrosomes, interacting with key cellular proteins [11].

Clinical Manifestations

Nephronophthisis (NPHP) is a progressive kidney disease characterized by impaired renal concentrating ability, chronic tubulointerstitial nephritis, and cystic kidney disease. Patients typically present with polyuria, polydipsia, nocturnal enuresis, anemia, and growth retardation. Urinalysis is usually bland in the early stages, without evidence of proteinuria, hematuria, or cellular element. However, as the disease progresses, proteinuria may develop into secondary glomerulosclerosis [2]. Clinically, three clinical subtypes of NPHP have been recognized based on the median age of onset of ESRD: infantile, juvenile, and adolescent/adult [7,12]. While these are the traditional clinical subtypes, recent case reports have expanded the spectrum of NPHP, highlighting cases of later-onset disease, with ESRD occurring in patients between the ages of 27 and 56 years [13-16].

Extrarenal Manifestations

NPHP can be associated with a range of extrarenal manifestations, affecting approximately 10-20% of patients. These can include ocular abnormalities such as retinitis pigmentosa, skeletal defects, hepatic fibrosis, neurological abnormalities, and cardiac defects [12,17-21]. Furthermore, NPHP is a core clinical feature of several genetic syndromes, such as Senior-Loken, Joubert, Meckel-Gruber, Cogan, Sensenbrenner, and Jeune (asphyxiating thoracic dystrophy) syndromes. [2,6]. Ocular manifestations are the most prevalent extrarenal manifestation of NPHP, with retinitis pigmentosa being the most frequent [7]. Early-onset retinitis pigmentosa can mimic Leber's congenital amaurosis, while late-onset disease presents with progressive vision loss and night blindness [22,23]. A less common ocular manifestation is oculomotor apraxia type Cogan, characterized by impaired horizontal gaze and nystagmus [24]. Retinal degeneration occurs in approximately 10-15% of individuals with NPHP. NPHP associated with retinitis pigmentosa is called Senior-Løken syndrome [6].

Infertility

NPHP1 has been identified as a potential contributor to male fertility. A study by Devi et al. revealed that NPHP1 is expressed in the spermatozoa of fertile men, while aberrant expression patterns are observed in many infertile men. NPHP1's role in spermatogenesis involves maintaining cell-cell adhesion between Sertoli and germ cells, regulating cell cycle progression, contributing to the formation and function of cilia and flagella, and participating in signaling pathways essential for spermatogenesis. These findings suggest that NPHP1 could serve as a valuable biomarker for assessing male fertility and may offer potential therapeutic targets for male infertility [25].

Clinical Diagnosis

Diagnosing NPHP involves a combination of clinical features and genetic testing. While clinical signs like polyuria and polydipsia starting in childhood suggest NPHP, they are not definitive. Genetic testing is the most reliable method, with whole-exome sequencing being the preferred approach. Using this method, a causative single-gene mutation can be detected in up to 60% of cases depending on the composition of the cohort. Renal biopsy, once a common diagnostic tool, is now limited to specific cases where it can help distinguish NPHP from other conditions. Family history and extrarenal symptoms like retinal degeneration are also important factors considered during diagnosis [2,5,8].

Treatment

Nephronophthisis (NPHP) is currently lacking a definitive cure. Treatment primarily focuses on managing symptoms, slowing disease progression, and preparing for renal replacement therapy, preferably kidney transplantation as the disease does not recur after transplantation [2]. Recent insights into the underlying molecular mechanisms of NPHP have opened new opportunities for potential therapeutic interventions including the use of V2 receptor antagonists like tolvaptan and mTOR inhibitors such as rapamycin. While these approaches show promise in preclinical models, clinical trials in NPHP patients are essential to validate their efficacy. The complexity of NPHP, including diverse genetic mutations and variable clinical presentations, poses significant challenges in developing targeted therapies. However, ongoing research offers hope for more effective treatments and, potentially, a cure for this debilitating disease [2,8].

Conclusion

Nephronophthisis (NPHP) is a complex genetic disorder primarily affecting the kidneys, but it can also manifest with various extrarenal features. The underlying genetic basis involves mutations in genes encoding proteins essential for primary cilia function. Genetic advancements, particularly whole exome sequencing, have significantly improved the diagnosis and understanding of NPHP. While NPHP predominantly leads to renal failure, it's important to recognize its potential association with extrarenal manifestations, including ocular, skeletal, hepatic, neurological, and cardiac abnormalities. In recent years, the link between NPHP and male infertility has gained attention, highlighting the diverse impact of this disorder. Early diagnosis and genetic counseling are essential for patients with NPHP to provide appropriate care and support to individuals and families affected by this condition. Continued research is needed to further elucidate the complex genetic mechanisms underlying NPHP and to develop targeted therapies for this debilitating disease.

Declaration of Conflicting Interests

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Ethical Approval

Ethical approval was obtained from the research and research ethics committee of the Government Hospitals. Verbal informed consent was obtained from all patients.

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