American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e941413
DOI: 10.12659/AJCR.941413

Received: 2023.06.09
Accepted: 2023.09.26
Available online: 2023.10.17
Published: 2023.11.22

Autosomal Recessive Adolescent Syndromic Nephronophthisis Caused by a Novel Compound Heterozygous Pathogenic Variant

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1 Oyintayo Ajiboye
E 2 Jaime E. Vengoechea
BE 3 Ritu Gupta
E 1 Koba Lomashvili

1 Department of Medicine, Renal Division, Emory University School of Medicine, Atlanta, GA, USA
2 Department of Human Genetics, Emory University, Atlanta, GA, USA
3 Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

Corresponding Author: Oyintayo Ajiboye, e-mail: Oyintayoajiboye3@gmail.com
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 19-year-old
Final Diagnosis: Nephronophthisis
Symptoms: Fatigue • poor appetite
Clinical Procedure: —
Specialty: Genetics • Nephrology

Objective: Rare disease

Background: Nephronophthisis, an autosomal recessive ciliopathy involving mutations in primary cilium genes, is characterized by chronic tubulointerstitial nephritis and a defective urine concentrating capacity. It accounts for about 5% of renal failure in children and adolescents and usually progresses to end-stage renal disease before the age of 30 years. Nephronophthisis is associated with extrarenal manifestations, including retinitis pigmentosa in Senior-Loken syndrome (SLS), and liver fibrosis in 10-20% of cases. While some presenting patterns could be characteristic, patients may have atypical presentation, making diagnosis difficult. Tubulointerstitial fibrosis is the predominant feature on histology and as such, diagnosis depends mostly on genetic testing. Despite advances in renal genomics over the years with a better understanding of primary cilia and ciliary theory, about 40% of nephronophthisis cases go undiagnosed. As the underlying genetic etiologies are not fully understood, morphologic pathologic findings are non-specific, and treatment options are limited to dialysis and transplantation.

Case Report: We describe a unique case of a patient with adolescent nephronophthisis who presented with advanced chronic kidney disease and severe pancytopenia, who progressed to end-stage renal disease at the age of 19, and was found to have syndromic nephronophthisis with compound heterozygous inheritance.

Conclusions: This report highlights the atypical presentation patterns that can be seen in syndromic nephronophthisis, the importance of genetic diagnosis when there is a high index of suspicion, and the need to further study genetic variants to better understand and diagnose the disease and to develop targeted therapy.

Keywords: Genetic Diseases, Inborn • Genetics • Nephronophthisis 3 • Pancytopenia • Renal Dialysis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/941413

1961 — 2 16

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Ciliopathies are a group of disorders defined by defects in the formation or function of primary cilia, which are specialized hair-like organelles that protrude from the surface of nearly all cells and have been found to have diverse physiologic roles in the human body [1,2]. There are presently over 950 known cilia-related genes and pathogenic variants resulting in abnormal or reduced abundance of cilia proteins [2]. Nephronophthisis (NPHP), a ciliopathy inherited in an autosomal recessive pattern, is characterized by chronic tubulointerstitial nephritis and a defective urine concentrating capacity, which leads to end-stage renal disease before the age of 30 years [1-3]. The *NPHP3* gene, linked with some variants of NPHP, encodes for nephrocystin 3, a ciliary protein that is part of the WNT-1 canonical signaling pathway during embryogenesis [4]. NPHP is associated with extrarenal associations in 10-20% of cases, the genetic basis of which is not fully understood, and they are usually not seen at initial presentation [1,3]. We describe a unique case of a patient with adolescent nephronophthisis who presented with advanced chronic kidney disease and severe pancytopenia, a presenting feature not commonly seen in nephronophthisis.

Case Report

A 19-year-old woman presented as a transfer patient for further evaluation of pancytopenia and renal failure. She was first noted to have elevated creatinine and anemia 1 year prior to presentation during admission for COVID-19 at an outside hospital. She received blood transfusions, with symptomatic improvement, but did not follow up with her primary care provider (PCP) after discharge. She later developed unintentional weight loss of about 8 kg over 6 months, poor appetite, fatigue, abdominal pain, and intermittent nausea with vomiting, which led to her seek care from her primary care provider (PCP). Routine blood work revealed severe pancytopenia and elevated creatinine and she was advised to go to the emergency room. Records obtained from the transferring hospital were notable for abdominal imaging showing features of chronic liver disease, bilateral normal-sized echogenic kidneys, and splenomegaly. She received multiple blood transfusions, was started on hemodialysis, and was transferred to our center for further evaluation.

At presentation, she had no obvious anomalies, height of 160 cm, was afebrile, vital signs were normal, she was not hypertensive, and had no history of hypertension. Physical examination was significant for palpable splenomegaly. A laboratory panel was significant for mild hypokalemia, blood urea nitrogen of 39 mg/dl, serum creatinine of 7.27 mg/dl, pancytopenia (total leukocytes of 700/mcl, hemoglobin of 7.5 gm/dl, platelet count of 28 000/mcl), normal AST/ALT, alkaline phosphatase elevated to 162 unit/L, INR-1.5, urine protein creatinine ratio of 2.3 gm/gm, UPEP with immunofixation showing polyclonal IgG, and bland urine microscopy. Of note, she had no known family history of hematological malignancy or kidney disease.

Due to persistent pancytopenia despite packed red blood cell and platelet transfusions suggestive of a primary hematological disorder, we performed a bone marrow biopsy, which showed hypocellular marrow with trilineage hematopoiesis, no evidence of dysplasia, and normal karyotype. MRI of the abdomen revealed a normal-appearing pancreas and kidneys, morphologic features of chronic liver disease, fissural widening and lobar redistribution, and marked splenomegaly with massive para esophageal varices consistent with portal hypertension. Given the MRI findings, we also performed a liver biopsy, which revealed patchy irregular portal fibrous bands with focal bridging septa, and abnormal portal vasculature with an increased number of bile ducts, consistent with congenital hepatic fibrosis. Kidney biopsy, initially deferred due to severe thrombocytopenia despite transfusion, showed mild focal global and segmental glomerulosclerosis with areas of glomerular hypoperfusion, mild-to-moderate chronic interstitial inflammation (lymphocyte predominant) with advanced interstitial fibrosis and tubular atrophy (IFTA) (**Figure 1**), and duplication of tubular basement membranes (**Figure 2**). Of note, average urine output during her hospital was 1.9 L/day.

Due to the constellation of clinical findings, a consult was placed with medical genetics, who ordered a trio of whole-exome sequencing via a CLIA-certified lab (GeneDx). The test revealed a frameshift pathogenic variant of the *NPHP3* gene (c.434_437del p.E145Vfs*3) inherited from her father and a missense likely pathogenic variant also in *NPHP3* (c.430 *A>G p.(K144E)* inherited from her mother (see ClinVar entry: RCV002266984). The results were reported in accordance with the 2015 American College of Medical Genetics guidelines. Combining the molecular information with her histopathology and clinical presentation, we established a clinical-pathologic-molecular diagnosis of syndromic nephronophthisis. To evaluate for other associations, we performed a brain MRI, which showed normal brain morphology and signal intensity.

The patient is now on home hemodialysis 4 times per week via a radio-cephalic fistula and is currently listed for simultaneous liver kidney transplant. She follows up with a hematologist as an outpatient for management of her pancytopenia, receives packed red blood cell 1-2 times per month via an outpatient infusion clinic and platelet transfusion on an as-needed basis. A complete blood count done in our center 17 months after diagnosis showed, total leukocytes 500/mcl, hemoglobin 6.3 gm/dl, and platelet count 22 000/mcl.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

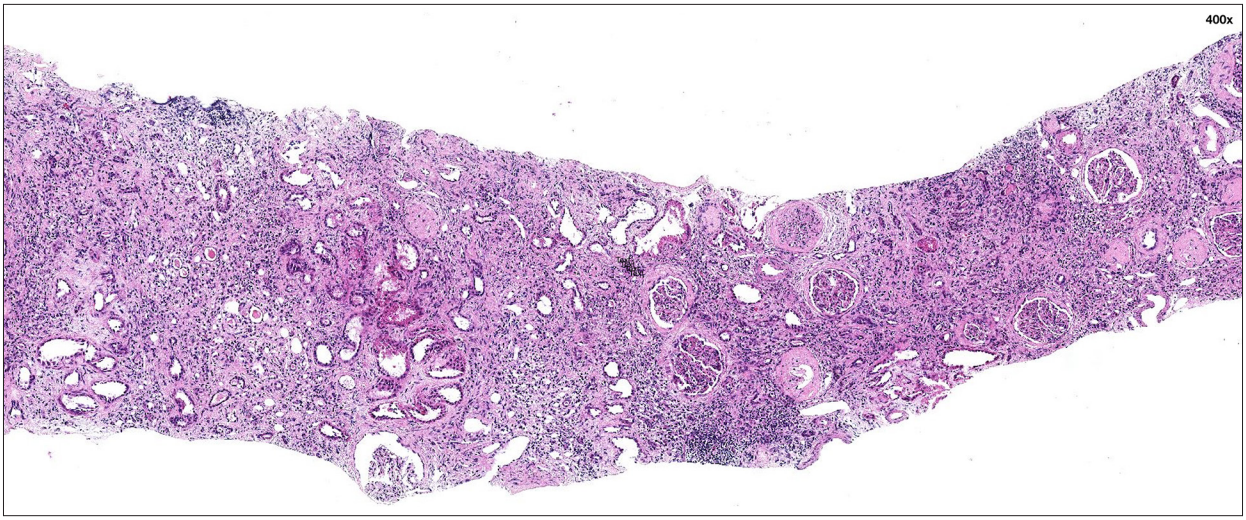

Figure 1. Kidney biopsy with marked interstitial fibrosis and tubular atrophy (IFTA) with areas of chronic interstitial inflammation (hematoxylin-eosin stain).

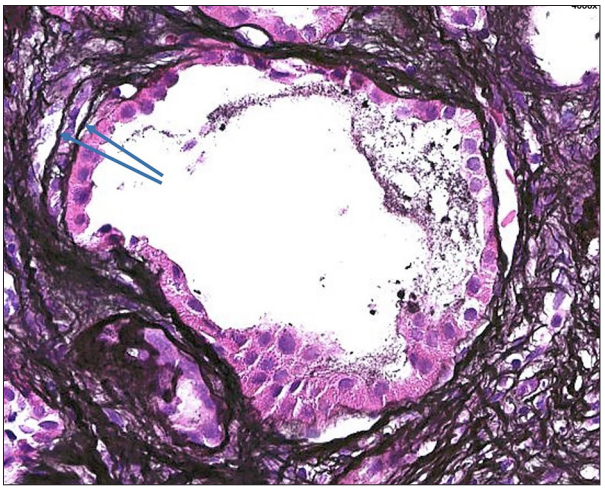

Figure 2. Tubular basement membrane duplication (blue arrows) (Jones-Methenamine silver stain).

Discussion

Nephronophthisis (NPHP) accounts for about 5% of renal failure in children and adolescents and usually progresses to end-stage renal disease (ESRD) by the third decade of life [1,5]. There are 3 clinical subtypes of NPHP depending on the age when kidney replacement is required: infantile, juvenile, and adolescent or adult NPHP, with a median age of 1, 13, and 19 years for ESRD onset, respectively [1,2,4]. Initial symptoms are usually polyuria and polydipsia, which may go unnoticed, and cases of oligohydramnios have been reported in infantile NPHP. Juvenile NPHP is the most prevalent subtype and presents with growth retardation, functional iron deficiency, and other features typically seen in chronic kidney disease. Adolescent NPHP has a similar presentation to juvenile NPHP, but the patients progress to ESRD at a later age, as seen in this case [1,3,6].

Extrarenal manifestations occur in 10% to 20% of nephronophthisis cases. Infantile NPHP has been associated with situs inversus, cardiac ventricular septal defect, and Meckel-Grube syndrome (MGS) [5,7]. Other extrarenal involvements include tapeto-retinal degeneration, retinitis pigmentosa in Senior-Loken syndrome (SLS), central nervous system malformations in Joubert syndrome, Juene syndrome and other related skeletal disorders, and liver involvement [1,5,8]. The major pathogenic basis for extrarenal manifestation is thought to be related to the multiorgan presence of primary cilia throughout the body, commonly referred to as the ciliary theory [5,6]. Liver involvement, commonly referred to as hepatorenal fibrocystic disease, is mostly associated with autosomal recessive polycystic kidney disease (ARPKD), and to a lesser extent with NPHP [9]. Microscopic features of congenital hepatic fibrosis (CHF) may be present at birth, but abnormal liver echogenicity, splenomegaly, and features of portal hypertension are only seen at later ages, as in our patient, and more in individuals with ARPKD [10]. The hepatocellular function is usually well preserved, with only normal to mildly elevated liver enzymes [10]. Presentation in late childhood with features of pancytopenia and splenomegaly usually warrants a detailed evaluation, which may include a liver biopsy due to the possibility of several etiologies, especially when the pathogenesis of the renal involvement is not fully understood [10]. In our patient, the pancytopenia was presumed to be a peripheral type, due to splenic sequestration.

Establishing a diagnosis of nephronophthisis depends on characteristic clinical findings, including imaging, renal histopathology, and, ultimately, genetic testing. Renal ultrasound in juvenile and adolescent NPHP shows normal-to-slightly reduced-sized kidneys with increased echogenicity and, as the disease progresses, cysts are seen at the corticomedullary junction in

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

about 50% of affected patients [1,11]. In contrast to the other forms of NPHP, enlarged echogenic kidneys with a lack of corticomedullary differentiation are usually seen on renal ultrasound in infantile NPHP [12]. Renal histology classically reveals tubulointerstitial fibrosis with diffuse chronic interstitial inflammation, tubular basement membrane thickening and duplication, and cortical or corticomedullary microcysts [1,6]. On liver histology, individuals with associated congenital hepatic fibrosis usually have portal fibrosis and bile duct proliferation. In advanced cases, porto-portal bridging may be present, as in our patient [6,9]. Genetic testing may be performed with a multi-gene ciliopathy panel in cases where the diagnosis is highly suspicious. In cases with a puzzling presentation, such as in this case report, whole-exome sequencing is an option, preferably including samples of both parents. Any genetic testing should be done with appropriate pre-test counselling. Molecular confirmation of NPHP is possible in about 60% of affected individuals by identifying the pathogenic variants in the NPHP-associated genes [1,13,14]. Our patient was found to have an autosomal recessive inheritance of the *NPHP3* gene with compound heterozygous variants: a pathogenic variant (p.E145Vfs*3) inherited from her father and a likely pathogenic variant (p.K144E) inherited from her mother. The frameshift variant was first described by Halbritter et al in 2012, where it was identified in the heterozygous state in infantile NPHP, but a variant on the other allele was not identified [15]. The missense likely pathogenic variant, found on the opposite NPHP3 allele, has not been previously published as pathogenic or benign to the best of our knowledge, but has been observed with a pathogenic variant on the opposite allele in another individual with nephronophthisis at GeneDx.

There are about 25 known gene-disease associations with NPHP and most of these variants result in loss of function of the proteins [5,14]. Proteomic studies have revealed these proteins form macromolecular complexes known as nephrocystin modules, which work simultaneously to support ciliogenesis and ciliary function [5,14]. Nephrocystin 1 encoded by *NPHP1*, is an adaptor protein found on primary cilia and renal epithelial cells. It interacts with molecules involved in cell adhesion and signaling and with other NPHP gene products, including *NPHP2, 3, 4, and 8* and altogether are part of a common pathway in the primary cilium of kidney cells [5,6,13]. *NPHP1* pathogenic variants are the most common cause of NPHP in 20-40% of cases and are mostly associated with the juvenile form [5,10]. *NPHP2* is mostly associated with infantile NPHP, while *NPHP3* is usually associated with adolescent NPHP and some cases of infantile NPHP [5,13]. Congenital hepatic fibrosis is mostly associated with pathogenic variants in *NPHP2* and *NPHP3* [10]. The latter is expressed in neural tissue, kidney tubules, retina, biliary tract, and the liver, which may explain the wide phenotypic nature, as observed in our patient [13].

Despite the advances in kidney genomics, there is no targeted therapy for NPHP. Management is mostly supportive when chronic kidney disease develops, and as patients progress to ESRD, transplantation and dialysis are the available treatment options [1,5]. A study by Wen et al, evaluating the outcomes of transplantation in children with hepatorenal fibrocystic disease who received kidney, liver, or simultaneous liver kidney (SLK) transplantation over a 20-year period (1990-2010) using the United States Scientific Registry of Transplant Recipients, showed approximately 80% of the patients received kidney transplantation and 5% required SLK. Of note, only 20 out of the 716 patients with hepato-renal fibrocystic disease (HRFCD) in this registry had a diagnosis of NPHP and all received kidney transplant only [16]. This is quite different from our patient, who presented with advanced liver disease and will require a simultaneous liver kidney transplant.

Conclusions

NPHP is a known genetic disease in children and adolescents with chronic kidney disease and ESRD. Patients with HRFCD associated with NPHP are a smaller subset with non-specific, clinical features and with a significant percentage of affected individuals not fully diagnosed with our current understanding of the genomics of these patients. This report highlights the atypical presentation patterns that can be seen in syndromic nephronophthisis with HRFCD, the importance of genetic diagnosis when there is a high index of suspicion, and the need to further study genetic mutations to better understand and diagnose the disease with the hope of offering targeted therapy.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Stokman M, Lilien M, Knoers N. Nephronophthisis-related ciliopathies. 2016 Jun 23 [Updated 2023 Mar 2]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK368475/
2. Stokman MF, Saunier S, Benmerah A. Renal ciliopathies: Sorting out therapeutic approaches for nephronophthisis. Front Cell Dev Biol. 2021;9:653138
3. Omran H, Fernandez C, Jung M, et al. Identification of a new gene locus for adolescent nephronophthisis, on chromosome 3q22 in a large Venezuelan pedigree. Am J Hum Genet. 2000;66(1):118-27

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

4. Bergmann C, Fliegauf M, Brüchle NO, et al. Loss of nephrocystin-3 function can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia. Am J Hum Genet. 2008;82(4):959-70
5. McConnachie DJ, Stow JL, Mallett AJ. Ciliopathies and the kidney: A review. Am J Kidney Dis. 2021;77(3):410-19
6. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. J Am Soc Nephrol. 2007;18(6):1855-71
7. Otto EA, Schermer B, Obara T, et al. Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. Nat Genet. 2003;34(4):413-20
8. Olbrich H, Fliegauf M, Hoefele J, et al. Mutations in a novel gene, NPHP3, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis. Nat Genet. 2003;34(4):455-59
9. Park E, Lee JM, Ahn YH, et al. Hepatorenal fibrocystic diseases in children. Pediatr Nephrol. 2015;31(1):113-19
10. Gunay-Aygun M. Liver and kidney disease in ciliopathies. Am J Med Genet C Semin Med Genet. 2009;151C(4):296-306
11. Blowey DL, Querfeld U, Geary D, et al. Ultrasound findings in juvenile nephronophthisis. Pediatr Nephrol 1996;10(1):22-24
12. Haider NB, Carmi R, Shalev H, et al. A Bedouin kindred with infantile nephronophthisis demonstrates linkage to chromosome 9 by homozygosity mapping. Am J Hum Genet. 1998;63(5):1404-10
13. Olinger E, Alawi IA, Al Riyami MS, et al. A discarded synonymous variant in NPHP3 explains nephronophthisis and congenital hepatic fibrosis in several families. Hum Mutat. 2021;42(10):1221-28
14. Renkema KY, Giles RH, Lilien MR, et al. The KOUNCIL Consortium: From genetic defects to therapeutic development for nephronophthisis. Front Pediatr. 2018;6:131
15. Halbritter J, Diaz K, Chaki M, et al. High-throughput mutation analysis in patients with a nephronophthisis-associated ciliopathy applying multiplexed barcoded array-based PCR amplification and next-generation sequencing. J Med Genet. 2012;49(12):756-67
16. Wen JW, Furth SL, Ruebner RL. Kidney and liver transplantation in children with fibrocystic liver-kidney disease: Data from the US Scientific Registry of Transplant Recipients: 1990-2010. Pediatr Transplant. 2014;18(7):726-32

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]