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CASE REPORT

Nephronophthisis 13 caused by *WDR19* variants with pancytopenia: case report

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Abstract

We present a case of nephronophthisis 13 that resulted from *WDR19* variants. The patient, a nine-year-old Japanese boy, had detection of mild proteinuria during a school urine screening. Urinalysis revealed mild proteinuria without hematuria. Blood tests indicated pancytopenia, mild elevation of liver enzymes, and kidney dysfunction. Ultrasound examination disclosed hepatosplenomegaly. Abdominal computed tomography and bone marrow assessments ruled out malignant tumors. Subsequent kidney and liver biopsies suggested nephronophthisis and congenital hepatic fibrosis. Furthermore, comprehensive genetic analysis through next-generation sequencing revealed compound heterozygous variants in *WDR19* (NM_025132.4), including the previously reported c.3533G > A, p.(Arg1178Gln), and c.3703G > A, p.(Glu1235Lys) variants, confirming the diagnosis of nephronophthisis 13. There is potential need for liver and kidney transplantation in patients with nephronophthisis and hepatic fibrosis. Early diagnosis is therefore crucial to mitigate delays in treating complications associated with kidney and hepatic insufficiency and to facilitate preparation of transplantation. To achieve early diagnosis of nephronophthisis, it is imperative to consider it as a differential diagnosis when extrarenal symptoms and kidney dysfunction coexist, particularly when mild proteinuria is observed through opportunistic urinalysis. Genetic testing is important because nephronophthisis manifests as diverse symptoms, necessitating an accurate diagnosis. Next-generation sequencing was shown to be invaluable for the genetic diagnosis of nephronophthisis, given the numerous identified causative genes.

Keywords Nephronophthisis 13 · *WDR19* · Congenital hepatic fibrosis · Kidney and liver transplantation

Introduction

Ciliopathies constitute a group of disorders linked to the dysfunction of primary cilia, encompassing conditions such as polycystic kidney disease and nephronophthisis. Nephronophthisis, an autosomal recessive genetic disorder, is the predominant cause of inherited diseases in individuals with end stage kidney disease (ESKD) up to the age of 30 years [1]. Disruption of the primary cilia results in the degradation of the tubular basement membrane and lymphocytic infiltration of tubules, leading to tubular atrophy and cyst formation, primarily at the corticomedullary junction [2]. *WDR19* is located at 4p14 and encodes intraflagellar transport (IFT) A, a crucial component of IFT complex. Transport to the cilia tip is facilitated by kinesin motors and IFT B, while retrograde transport back to the base involves dynein motors and IFT A [2]. Ciliary dysfunction induced by *WDR19* variants triggers the onset of nephronophthisis.

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WDR19 accounts for 0.5% of nephronophthisis-related genes, representing a rare causative gene [3]. Abnormalities in IFT A are also associated with nephronophthisis accompanied by skeletal anomalies, with *WDR19* variants reported as causative genes for Jeune syndrome and Sensenbrenner syndrome [4]. In a previous report, *WDR19* variants resulted in isolated renal manifestations, establishing its recognition as a causative gene for nephronophthisis 13 (NPHP13) (MIM#614377) [5]. Furthermore, NPHP13 may induce liver complications such as congenital hepatic fibrosis (CHF) or Caroli disease, which stem from ductal plate malformation [4]. CHF often remains asymptomatic, more likely manifesting as portal hypertension and hepatomegaly in children than as liver impairment [6, 7]. Nephronophthisis can reportedly result in various hepatic complications, but there have been no reports of its diagnosis resulting from pancytopenia due to CHF [6]. In this report, we describe a patient with nephronophthisis and renal dysfunction accompanied by pancytopenia diagnosed after an abnormal urine screening.

Case report

Proteinuria was detected in a nine-year-old Japanese boy by routine school screening, so he was referred to our hospital. He was born to non-consanguineous, healthy parents, had no significant medical history, no intellectual disabilities and no ophthalmological abnormalities. Upon physical examination, his height was 132.5 cm (−0.2 SD), weight was 28.4 kg (−0.4 SD), and blood pressure was 110/58 mmHg. There were no distinctive facial features, conjunctival pallor, abnormal eye movements, polydactyly, skeletal abnormalities or other notable findings. Blood tests revealed pancytopenia (white blood cell count 2900/μL, hemoglobin 10.6 g/dL, platelet count 108,000/μL), decreased kidney function [serum creatinine (Cr) 1.07 mg/dL, estimated glomerular filtration rate 45 ml/min/1.73 m^2], and mild elevation of liver enzymes (aspartate aminotransferase 58 IU/L, alanine aminotransferase 46 IU/L). Other data related to the hepatobiliary system [albumin (Alb) 4.4 g/dL, γ-glutamyl transpeptidase (γ-GTP) 106 IU/L, total bilirubin 0.4 mg/dL, amylase 212 IU/L] and markers of hepatic fibrosis [hyaluronic acid 27.2 ng/mL, type IV collagen 4.4 ng/mL, M2BPGi (−)] were within normal ranges. Urinalysis revealed a specific gravity of 1.012, a Cr level of 46.5 mg/dL, no hematuria, a urinary protein/creatinine ratio of 0.38 g/gCr, and a β2-microglobulin (β2MG) concentration of 1260 μg/dL. Abdominal ultrasound revealed a renal length of 9.6 cm (+1.8 SD), increased renal parenchymal echogenicity, abnormal hepatic echogenicity, irregular liver margins, and hepatosplenomegaly. The patient underwent abdominal contrast-enhanced computed tomography (CE-CT) and bone marrow examination to rule out malignancy due to the pancytopenia, mild renal enlargement, and hepatosplenomegaly (Fig. 1). CE-CT showed no tumorous lesions, and bone marrow examination revealed no abnormal cells. Concurrent liver and kidney biopsy results arose suspicion of nephronophthisis-related diseases. Renal histopathology revealed tubular dilatation in the renal medulla and irregular changes in the tubular basement membrane, suggesting nephronophthisis (Fig. 2a). Hepatic histopathology revealed significant fibrosis and abnormal bile ducts in the portal areas, indicating CHF (Fig. 2b). Furthermore, comprehensive genetic analysis using next-generation sequencing (NGS) identified a compound heterozygous variant in *WDR19* [NM_025132.4: c.3533G > A, p.(Arg1178Gln), and c.3703G > A, p.(Glu1235Lys)] (Supplemental Fig. 1). The variants were identified as pathogenic variants in The Human Gene Mutation Database (HGMD) (https://www.hgmd.cf.ac.uk/ac/, CM139117 and CM139116). Based on these findings, we diagnosed the patient with nephronophthisis associated with *WDR19* variants. After diagnosis, there were no abnormalities in assessments for esophageal varices associated with portal hypertension and ocular findings related to nephronophthisis. Despite no progression of liver impairment or symptoms of portal hypertension, there was rapid decline in kidney function within a year after diagnosis. At the time of writing, we are therefore preparing to perform kidney transplantation before liver transplantation.

Discussion

Nephronophthisis associated with *WDR19* variants may occasionally manifest as concomitant pancytopenia. Due to primary ciliary abnormalities, nephronophthisis manifests

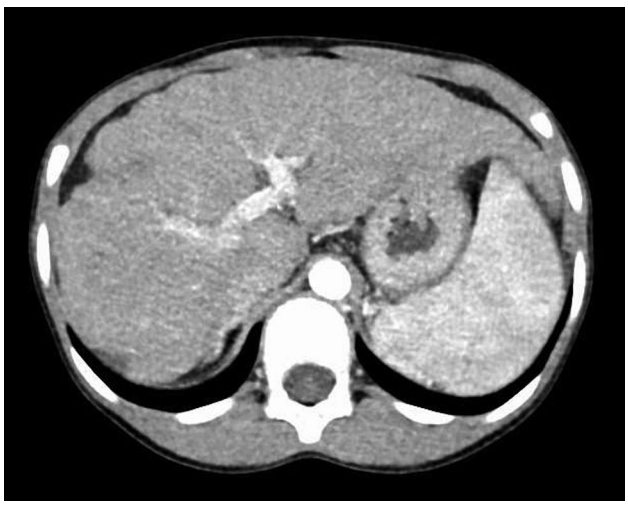

Fig. 1 Contrast-enhanced computed tomography shows hepatosplenomegaly

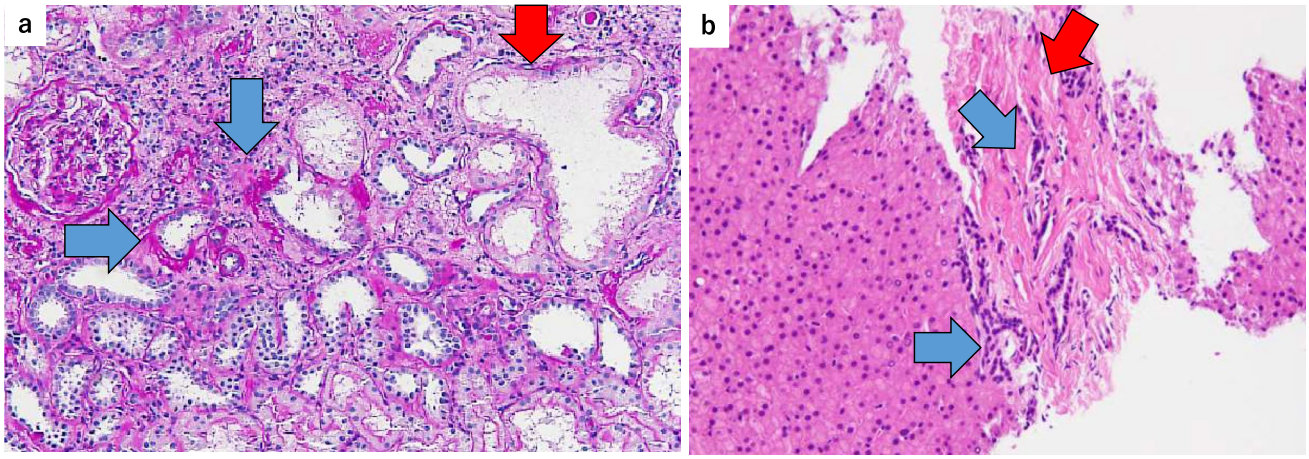

Fig. 2 Pathological findings of kidney biopsy (**a**) and liver biopsy (**b**). **a** Periodic acid-Schiff (PAS) staining of formalin-fixed paraffin-embedded (FFPE) tissue sections. There is inflammatory cell infiltration and fibrosis (blue arrow) in the tubulointerstitial lesion. The renal tubules are cystic and dilated (red arrow) with some atrophy. **b** Bile duct hyperplasia with abnormal morphology (blue arrow) and surrounding significant fibrosis (red arrow) are observed in the portal vein area

as various extrarenal symptoms. Nephronophthisis associated with the *WDR19* variant is linked to symptoms in the kidneys, liver, retina, bones, and the skin. Clinically, it is classified as nephronophthisis 13 (NPHP13), Senior-Loken syndrome, Jeune syndrome, or Sensenbrenner syndrome, depending on the combination of affected organs [4]. Our patient with *WDR19* variants (c.3533G > A and c.3703G > A) was diagnosed with NPHP13 because symptoms were observed only in the kidneys and liver. However, among previously reported cases with the *WDR19* c.3533G > A variants, only two out of 14 cases presented with hepatic and renal symptoms [8–13]. Other cases had a wide range of manifestations, including ophthalmologic abnormalities in nine cases, bone formation anomalies in five cases, and ectodermal system abnormalities in two cases [8–13]. There are currently no reports on the relationship between phenotype and genotype, it is unknown what determines the phenotype in *WDR19* variants. Regarding the liver phenotype associated with NPHP13, there have been reports of CHF, Caroli disease (CD), and Caroli syndrome [17]. CHF is characterized by malformation of bile duct structures with abnormal branching and progressive fibrosis of intrahepatic portal tracts [17]. Meanwhile, CD is characterized by dilated remnants of the ductal plate representing large interlobar bile ducts, while Caroli syndrome is a combination of CD and liver fibrosis. Histologically, chronic inflammation in the portal area is usually seen with dilated bile ducts in CD, whereas fibrotic enlargement of the portal area without inflammation is observed in CHF. In this case, the degeneration of bile ducts and strong fibrosis, as well as the absence of chronic inflammation and bile duct dilatation in the portal area led to diagnosis as CHF [17]. Nephronophthisis often presents with hepatic complications, but its association with CHF is more common in patients with NPHP13 [18]. In addition to CHF, pancytopenia was also observed in our patient. Pancytopenia can arise from various causes, including but not limited to malignant tumors, infections, autoimmune disorders and medications. However, in the current case, the patient had no infection, no abnormalities were detected in autoantibody screening, and he had not taken medications. Additionally, bone marrow examination and CE-CT scans ruled out malignant tumors. Ectopic varices were not observed, but CT scans revealed splenomegaly and nodularity on the surface of the liver, as well as collateral circulation in the portal vein system. Based on these findings, we concluded that pancytopenia was caused by portal hypertension due to CHF. CHF has been reported to be associated with NPHP3, NPHP4 [18], Joubert syndrome and related disorders [19], COACH syndrome [20], Bardet-Biedl syndrome [21], and oral-facial-digital syndrome [22]. Nephronophthisis and nephronophthisis-related diseases may have clinical presentations similar to our case. In cases in which there is a combination of kidney dysfunction and symptoms related to portal hypertension, such as pancytopenia, it is important to consider nephronophthisis as differential diagnosis.

Furthermore, comprehensive genetic analysis is useful for confirming diagnosis of suspected nephronophthisis. Nephronophthisis has more than 35 diverse clinical manifestations, with more than 187 associated genes reported [23]. Identifying the causative gene from clinical symptoms alone is challenging. Reports on NPHP13 are limited, but in one study, the average age of onset of end-stage kidney disease (ESKD) was 5.2 ± 4.6 years [18], while in others, the median age of ESKD onset was 6.0 years (range: 1.5–10.5 years) [4, 8]. NPHP13 may be a form of

nephronophthisis that leads to ESKD relatively early in life. However, nephronophthisis often lacks overt symptoms, and due to the scarcity of investigative opportunities, diagnosis is frequently delayed. Our patient presented with concurrent renal dysfunction and CHF at time of referral, but there were no subjective symptoms. A thorough investigation for minor abnormalities detected by a school urine screening ultimately led to the diagnosis. Urine screening of three-year-old children and school urine screening can be important in diagnosis of nephronophthisis. Furthermore, most patients with nephronophthisis develop ESKD, and half of those with CHF develop liver failure and require liver transplantation [3, 24]. In this case, the diagnosis was made before the patient reached ESKD, so serious complications from organ failure could be avoided and we could offer the option of undergoing kidney transplantation without the need to introduce dialysis. Diagnosing nephronophthisis in the early stages may be challenging, but it is crucial to make a diagnosis before the patient becomes susceptible to potentially fatal complications associated with organ failure.

In summary, our patient with pancytopenia and mild urine protein was diagnosed with NPHP13 harboring the *WDR19* variant. To achieve early diagnosis of nephronophthisis, it is crucial to consider nephronophthisis as a differential diagnosis when extrarenal symptoms and kidney dysfunction coexist. Additionally, it is essential to promptly conduct comprehensive genetic analysis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13730-024-00871-5.

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Declarations

Conflicts of interest All the authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number #108) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient's parents.

References

1. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med. 2011;364(16):1533–43.
2. Emma F, et al. Pediatric nephrology. 8th ed. Springer Nature Reference. Springer Nature Switzerland. xxviii, 2022, p. 1047–2134.
3. Bredrup C, Saunier S, Oud MM, Fiskerstrand T, Hoischen A, Brackman D, Leh SM, Midtbø M, Filhol E, Bole-Feysot C, Nitschké P, Gilissen C, Haugen OH, Sanders JS, Stolte-Dijkstra I, Mans DA, Steenbergen EJ, Hamel BC, Matignon M, Pfundt R, Jeanpierre C, Boman H, Rødahl E, Veltman JA, Knappskog PM, Knoers NV, Roepman R, Arts HH. Ciliopathies with skeletal anomalies and renal insufficiency due to mutations in the IFT-A gene WDR19. Am J Hum Genet. 2011;89(5):634–43.
4. Halbritter J, Porath JD, Diaz KA, Braun DA, Kohl S, Chaki M, Allen SJ, Soliman NA, Hildebrandt F, Otto EA, GPN Study Group. Identification of 99 novel mutations in a worldwide cohort of 1,056 patients with a nephronophthisis-related ciliopathy. Hum Genet. 2013;132(8):865–84.
5. Keyser MN, Huang M, Newton K, Benador N, Beauchamp-Walters J, Bird LM. A unique pancreatic phenotype in a child with a WDR19-related ciliopathy: a case report and literature review of pancreatic involvement in ciliopathies. Am J Med Genet A. 2022;188(7):2242–5.
6. Zhu B, Du Z, Wang Z, Li Y, Zhang J, Zhu H. Congenital hepatic fibrosis in children and adults: clinical manifestations, management, and outcome-case series and literature review. Gastroenterol Res Pract. 2020;2020:8284274.
7. Mirza H, Besse W, Somlo S, Weinreb J, Kenney B, Jain D. An update on ductal plate malformations and fibropolycystic diseases of the liver. Hum Pathol. 2023;132:102–13.
8. Lee JM, Ahn YH, Kang HG, Ha II, Lee K, Moon KC, Lee JH, Park YS, Cho YM, Bae JS, Kim NK, Park WY, Cheong HI. Nephronophthisis 13: implications of its association with Caroli disease and altered intracellular localization of WDR19 in the kidney. Pediatr Nephrol. 2015;30(9):1451–8.
9. Zhang Q, Xu M, Verriotto JD, Li Y, Wang H, Gan L, Lam BL, Chen R. Next-generation sequencing-based molecular diagnosis of 35 Hispanic retinitis pigmentosa probands. Sci Rep. 2016;6:32792.
10. Rim JH, Lee ST, Gee HY, Lee BJ, Choi JR, Park HW, Han SH, Han J. Accuracy of next-generation sequencing for molecular diagnosis in patients with infantile nystagmus syndrome. JAMA Ophthalmol. 2017;135(12):1376–85.
11. Yoshikawa T, Kamei K, Nagata H, Saida K, Sato M, Ogura M, Ito S, Miyazaki O, Urushihara M, Kondo S, Sugawara N, Ishizuka K, Hamasaki Y, Shishido S, Morisada N, Iijima K, Nagata M, Yoshikawa T, Ogata K, Ishikura K. Diversity of renal phenotypes in patients with WDR19 mutations: two case reports. Nephrology (Carlton). 2017;22(7):566–71.
12. Ryan R, Failler M, Reilly ML, Garfa-Traore M, Delous M, Fihol E, Reboul T, Bole-Feysot C, Nitschke P, Baudouin V, Ameselem S, Escudier E, Legendre M, Benmerah A, Saunier S. Functional characterization of tektin-1 in motile cilia and evidence for TEKT1 as a new candidate gene for motile ciliopathies. Hum Mol Genet. 2018;27(2):266–82.
13. Al Alawi I, Al Salmi I, Al Rahbi F, Al Riyami M, Al Kalbani N, Al Ghaithi B, Al Mawali A, Sayer JA. Molecular genetic diagnosis of Omani patients with inherited cystic kidney disease. Kidney Int Rep. 2019;4(12):1751–9.
14. Hanany M, Rivolta C, Sharon D. Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. Proc Natl Acad Sci U S A. 2020;117(5):2710–6.
15. Surl D, Shin S, Lee ST, Choi JR, Lee J, Byeon S, Han SH, Lim HT, Han J. Copy number variations and multiallelic variants in Korean patients with Leber congenital amaurosis. Mol Vis. 2020;26:26–35.
16. Hammarsjö A, Pettersson M, Chitayat D, Handa A, Anderlid BM, Bartocci M, Basel D, Batkovskyte D, Delza-Meireles A, Conner P, Eisfeldt J, Girisha KM, Chung BH, Horemuzova E, Hyodo H, Kornejeva L, Lagerstedt-Robinson K, Lin AE, Magnusson M, Moosa S, Nayak SS, Nilsson D, Ohashi-Fukuda N, Stranneheim H, Taylan F, Traberg R, Voss U, Wirta V, Nordgren A, Nishimura G, Lindstrand A, Grigelioniene G. High diagnostic yield in

skeletal ciliopathies using massively parallel genome sequencing, structural variant screening and RNA analyses. J Hum Genet. 2021;66(10):995–1008.
17. Rawat D, Kelly DA, Milford DV, Sharif K, Lloyd C, McKiernan PJ. Phenotypic variation and long-term outcome in children with congenital hepatic fibrosis. J Pediatr Gastroenterol Nutr. 2013;57(2):161–6.
18. Park E, Lee JM, Ahn YH, Kang HG, Ha II, Lee JH, Park YS, Kim NK, Park WY, Cheong HI. Hepatorenal fibrocystic diseases in children. Pediatr Nephrol. 2016;31(1):113–9.
19. Miyazawa K, Hara Y, Shimizu K, Nakanishi W, Tokodai K, Nakanishi C, Miyagi S, Kawagishi N, Ohuchi N. Hassab's operation for Joubert syndrome with congenital hepatic fibrosis: a case report. Int J Surg Case Rep. 2017;34:134–8.
20. Sambharia M, Freese ME, Donato F, Bathla G, Abukhiran IMM, Dantuma MI, Mansilla MA, Thomas CP. Suspected autosomal recessive polycystic kidney disease but cerebellar vermis hypoplasia, oligophrenia ataxia, coloboma, and hepatic fibrosis (COACH) Syndrome in retrospect, a delayed diagnosis aided by genotyping and reverse phenotyping: a case report and a review of the literature. Nephron. 2023;148:1–9.
21. Horiuchi K, Kogiso T, Sagawa T, Ito T, Taniai M, Miura K, Hattori M, Morisada N, Hashimoto E, Tokushige K. Bardet-Biedl syndrome caused by skipping of SCLT1 complicated by microvesicular steatohepatitis. Intern Med. 2020;59(21):2719–24.
22. Adès LC, Clapton WK, Morphett A, Morris LL, Haan EA. Polydactyly, campomelia, ambiguous genitalia, cystic dysplastic kidneys, and cerebral malformation in a fetus of consanguineous parents: a new multiple malformation syndrome, or a severe form of oral-facial-digital syndrome type IV? Am J Med Genet. 1994;49(2):211–7.
23. Reiter JF, Leroux MR. Genes and molecular pathways underpinning ciliopathies. Nat Rev Mol Cell Biol. 2017;18(9):533–47.
24. Wu WK, Ziogas IA, Izzy M, Pai AK, Hafberg ET, Matsuoka LK, Alexopoulos SP. Liver transplantation for congenital hepatic fibrosis. Transpl Int. 2021;34(7):1281–92.