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【 CASE REPORT 】

Different Clinical Courses of Nephronophthisis in Dizygotic Twins

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Abstract:

Siblings with nephronophthisis occasionally show different clinical courses; however, the reasons for this remain unclear. We herein report cases of nephronophthisis in a pair of dizygotic twins with different clinical courses. The brother developed end-stage kidney disease at 17 years old; however, his sister did not show kidney insufficiency. Kidney biopsies revealed severe tubulointerstitial damage at 14 and 22 years old in the brother and sister, respectively. Both had a homozygous *NPHP1* deletion with different heterozygous mutations related to hereditary cystic kidney disease. Since the dizygotic twins were exposed to similar environmental factors, genetic factors may have influenced their clinical course more strongly than environmental factors.

Key words: nephronophthisis, dizygotic twins, *NPHP1* gene mutation, chronic kidney disease

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Introduction

Nephronophthisis (NPH) is an autosomal recessive cystic kidney disease, with most afflicted patients developing end-stage kidney disease (ESKD) in the first two decades of life. More than 20 genes have been reported to be involved in the development of NPH (1). These genes encode proteins related to the functions of the primary cilia, basal bodies, and centrosomes. Mutations in *NPHP1*, which encodes nephrocystin 1, account for approximately 20% of NPH cases and are the most common mutation in juvenile NPH.

The initial symptoms of juvenile NPH include polyuria, polydipsia, and secondary enuresis caused by an impaired urinary-concentrating ability and sodium wasting due to tubular dysfunction. Patients with juvenile NPH develop ESKD at a median age of 13 years old. Extrarenal lesions are present in 10-20% of cases, including retinitis pigmentosa, olfactory dysfunction, hearing abnormalities, situs inversus, liver fibrosis, musculoskeletal abnormalities, and facial abnormalities. Some symptoms concurrent with NPH include Senior-Loken syndrome, Joubert syndrome, and Meckel-Gruber syndrome.

NPH is occasionally diagnosed based on clinical manifestations and kidney biopsy findings. The main histological findings in NPH include tubular atrophy with thickened tubular basement membranes, tubular diverticulum and florets, interstitial fibrosis and chronic inflammation, cysts at the corticomedullary junction and in the medulla, and periglomerular fibrosis (1, 2).

We herein report the findings of two cases of NPH with differing clinical courses in a pair of dizygotic twins with a homozygous full-gene deletion of *NPHP1*.

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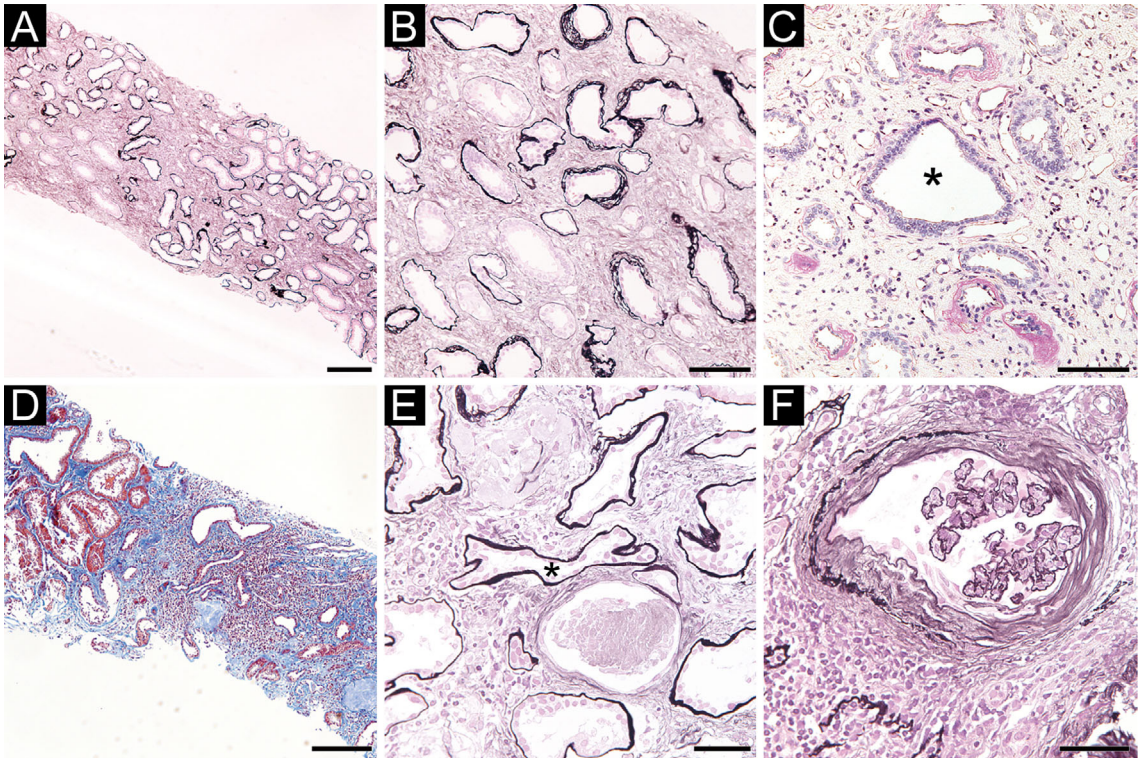

Figure 1. **Representative histopathologic findings of a kidney biopsy. A-C: Case 1, at 14 years old. The tubulointerstitium shows extensive fibrosis with dilated tubules (A, silver staining; original magnification, 40×). The tubular basement membrane is thinned or thickened with multiple layers (B, silver staining; original magnification, 100×). In the medulla, cystic changes in the collecting ducts can be observed (C, asterisk, periodic acid-Schiff staining; original magnification, 100×). D-F: Case 2, at 22 years old. The tubulointerstitium demonstrates mononuclear inflammation and atrophy and dilation of the distal tubules. The proximal tubules are also dilated and damaged (D, Masson's trichrome staining; original magnification, 40×). Irregular branching is observed in some distal tubules (E, asterisk, silver staining; original magnification, 200×). This glomerulus is collapsed with a multi-layered Bowman's capsule (F, silver staining; original magnification, 200×). Scale bars represent 200 μm (A and D), 100 μm (B and C), and 50 μm (E and F).**

Case Report

A Japanese boy (Case 1) was clinically diagnosed with NPH at 14 years old. He had presented with polyuria, polydipsia, and enuresis from approximately 5 years old. Growth impairment had been apparent from 8 years old [height, 121.5 cm (mean -1.0 standard deviations (SD) compared with that noted in the average Japanese population (3)); body weight, 15.9 kg (-2.0 SD)]. At 12 years old, he showed slight kidney insufficiency [serum creatinine (sCr), 1.2 mg/dL; adolescent estimated glomerular filtration rate (eGFR) (4), 40.3 mL/min/1.73 m^2], hyposthenuria (urine specific gravity, 1.004; urine osmolality, 204 mOsm/kg H_2O) without hematuria or proteinuria, and slight anemia (hemoglobin, 11.7 g/dL). The results of the water restriction test and administration of vasopressin indicated nephrogenic diabetes insipidus; however, thiazide diuretics did not improve his condition. The patient did not show retinitis pigmentosa, ataxia, situs inversus, or mental retardation; however, he was short statured [height, 131.1 cm (-2.5 SD); body weight, 24 kg (under -2.0 SD)]. His kidney dysfunction gradually progressed to an sCr level of 1.64 mg/dL, eGFR of 36.3 mL/min/1.73 m^2, bicarbonate level of 23.0 mmol/L, and hemoglobin level of 10.7 g/dL at 14 years old.

An ultrasound study showed hyperechogenicity of the kidneys but did not reveal apparent kidney cysts. A kidney biopsy revealed extensive tubulointerstitial fibrosis, thinning and thickening of the tubular basement membrane, and cystic changes in the collecting ducts (Fig. 1A-C), which were compatible with NPH. Among 36 glomeruli, 14 were globally sclerosed without arteriosclerosis and arteriolosclerosis. The patient developed ESKD and received living kidney transplantation from his father at 17 years old.

In contrast to the above findings, the patient's dizygotic twin sister (Case 2) did not show any apparent kidney insufficiency or anemia (sCr, 0.64 mg/dL; eGFR, 86.2 mL/min/1.73 m^2; urine specific gravity, 1.019; hemoglobin, 12.5 g/dL) at 14 years old. Kidney insufficiency was not apparent at 19 years old [sCr, 0.81 mg/dL; eGFR (5), 77.5 mL/min/1.73 m^2]; however, her kidney function decreased (sCr, 1.30 mg/dL; eGFR, 44.0 mL/min/1.73 m^2) without hematuria or

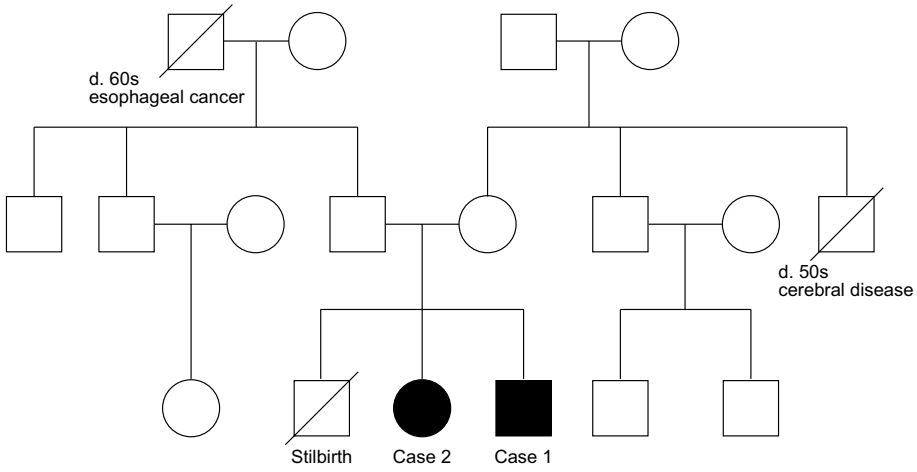

Figure 2. Three-generation pedigree.

proteinuria at 22 years old. Although she did not show significant polydipsia or polyuria, hyposthenuria was observed (urine specific gravity, 1.001; urine osmolality, 225 mOsm/kg H_2O). She showed mild anemia (hemoglobin, 10.6 g/dL) and had no metabolic acidosis (bicarbonate, 24.2 mmol/L). She had a slightly short stature [height, 152.5 cm (-1.1 SD)] and high-pitched hearing impairment but did not show other extrarenal manifestations of NPH. She had no medical history of hypertension, diabetes mellitus, or medication use.

Abdominal magnetic resonance imaging revealed more than five small kidney cysts at the corticomedullary junction in both kidneys. A kidney biopsy revealed tubulointerstitial damage in approximately 40% of the cortex, with dilated tubules accompanied by irregular thickening and meandering of the tubular basement membrane (Fig. 1D-F). Three of seven glomeruli were globally sclerosed. Other glomeruli showed periglomerular fibrosis, some of which had collapsed. Arterio- or arteriolosclerosis was not observed. These findings are compatible with NPH.

In this study of dizygotic twins, there was no family history of NPH or consanguineous marriage (Fig. 2). The patients had lived together until 20 years old and attended the same schools until 15 years old. The patient in Case 1 played baseball as an extracurricular activity from 6-12 years old, whereas the patient in Case 2 enjoyed arts and handicrafts.

The twins underwent genetic testing using capture-based next-generation sequencing for 69 genes related to hereditary cystic kidney disease (6, 7) at 22 years old, which revealed a homozygous full gene deletion of *NPHP1* in both patients. The *NPHP1* deletion was validated by polymerase chain reaction, leading to a genetic diagnosis of NPH. In addition, heterozygous missense variants of *PKHD1* (p.Arg 2667Lys) and *BBS1* (p.Ile238Val) were detected in Case 1, and heterozygous missense variants of *PKHD1* (p.Arg2667 Lys), *BBS2* (p.Met645Thr), and *IFT172* (p.Met560Val) were detected in Case 2.

The kidney function in Case 2 had declined gradually (sCr, 1.90 mg/dL; eGFR, 28.2 mL/min/1.73 m^2) at 25 years old.

Discussion

We encountered two cases of NPH in dizygotic twins with a homozygous *NPHP1* full-gene deletion who showed different clinical courses. To our knowledge, this is the first report describing NPH in dizygotic twins. The brother (Case 1) developed ESKD at 17 years old, whereas the sister (Case 2) showed a slower progression of kidney dysfunction, despite both having *NPHP1* full-gene deletion and having spent most of their lives together.

A previous case report from China of twins with a homozygous *NPHP1* deletion demonstrated a similar progression of kidney dysfunction (8), although siblings with *NPHP1* deletion often show different phenotypes and different clinical courses (9, 10). The contributing factors to the phenotypic variance are yet to be elucidated. However, the influence of modifier genes and environmental factors, such as diet, water consumption, and salt intake, is expected to be involved.

In the present cases, since the dizygotic twins spent most of their lives together, the influence of genetic factors, including sex differences, on their clinical course may have been stronger than that of environmental factors. Although the genetic and environmental aspects in dizygotic twins are similar to those in non-twin siblings, both patients had the same environment at home and school at the same ages during the progression of kidney insufficiency in Case 1. Therefore, the impact of environmental factors on the status of these dizygotic twins is likely far smaller than that in non-twin siblings. Regarding genetic factors, among the cystic kidney disease-related gene mutations, point mutations in *PKHD1* (Cases 1 and 2), *BBS1* (Case 1), *BBS2* (Case 2), and *IFT172* (Case 2) were also detected. Mutations in these genes are associated with autosomal recessive polycystic kidney disease, Bardet-Biedl syndrome (BBS), and Joubert syndrome. Although these are autosomal recessive diseases, heterozygous point mutations in the genes may have had

some effect on the homozygous *NPHP1* mutation (11). ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) reported that the mutation of *IFT172* (p.Met560Val) is "likely benign," while that of *BBS2* (p.Met645Thr) is of "uncertain significance" but had no data regarding the *BBS1* mutation (p.Ile238Val). BBS proteins, including *BBS1* and *BBS2*, form a BBSome complex. NPHP-associated proteins are linked to the regulation of BBSome integrity and trafficking (12, 13). In addition, recent data have suggested that copy-number variants contribute to BBS (14). Thus, heterozygous point mutations in *BBS1* and *BBS2* in addition to *NPHP1* full-gene deletion might have had some impact on the clinical courses in the present cases. Since limited genes were studied in both cases, undetected gene mutations may have affected the clinical courses. In addition, the influence of some environmental factors, such as the amount of exercise, diet, and the drinking of fluids cannot be completely ruled out.

Cases of NPH with *NPHP1* gene mutations that show ESKD development in adulthood have rarely been reported (9-11, 15). However, slowly progressive NPH, such as that observed in Case 2, may be underdiagnosed. The patient in Case 2 would not have been diagnosed with NPH without a family history of NPH. Genetic testing of 5,606 patients with adult-onset ESKD revealed homozygous *NPHP1* deletions in 26 patients (0.5%), of whom only 3 (0.05%) had been diagnosed with NPH before genetic testing (16). Thus, a genetic analysis is recommended in adult patients with chronic tubulointerstitial nephropathy of unknown causes and unknown genetic backgrounds.

In summary, we report the findings of two cases of NPH in dizygotic twins with a homozygous *NPHP1* full-gene deletion who showed different clinical courses. Although the influence of environmental factors cannot be ruled out, since the twins spent most of their lives together, the influence of genetic factors on their clinical course may have been stronger than that of environmental factors.

The case report was written in compliance with the Declaration of Helsinki. Written informed consent for the publication of this report was obtained from the patients.

The authors state that they have no Conflict of Interest (COI).

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