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Clinical case

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Clinical features of juvenile nephronophthisis in an adolescent girl

Abstract

Nephronophthisis type 1 (juvenile) OMIM 256100 is a rare ciliopathy with autosomal recessive inheritance that is the most common genetic cause of end-stage renal failure in children and young adults. The development of this pathology is based on a mutation in the NPHP1 gene (homozygous or compound heterozygous mutations), which is responsible for the structure and functioning of the nephrocystin-1 protein in the primary cilium. The average age of onset of end-stage renal disease (ESRD) in the juvenile form of nephronophthisis is 13 years. The first clinical symptoms of the disease, such as polyuria and polydipsia, are rarely noticed by adolescents and their parents, which lead to late diagnosis of the disease at the stage of chronic renal failure. The article presents a clinical observation of a 14-year-old patient diagnosed with type 1 nephronophthisis, whose only complaints are polyuria and polydipsia. Our observations demonstrate the nonspecificity of the symptoms of the juvenile form of nephronophthisis, and early detection will help to make a timely diagnosis, begin nephroprotective therapy, and slow down the progression of renal failure.

Keywords: nephronophthisis, chronic renal failure, ciliopathy, nephrocystin, kidney cysts

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Introduction

Juvenile nephronophthisis (NPH) is a genetically heterogeneous disorder representing the most frequent inherited cause of chronic renal failure in children. The gene, NPH1, was recently assigned to the 2q13 region of chromosome 2, which is responsible for approximately 85% of cases mutational mechanism involved in deletions in familial juvenile nephronophthisis.[1,2]

The histological signs of nephronophthisis were first described by Smith C. and Grham J. in 1945 based on the autopsy results of an 8-year-old girl with refractory anemia and renal failure.[3] The term "nephronophthisis" was proposed by Fanconi et al. in 1951, and the NPHP1 gene was identified by F. Hildebrandt et al. in 1997.[2,4] The prevalence of the disease varies from 1 in 50,000 to 1 in 1,000,000 people.[5–7] Three clinical variants of nephronophthisis have been described previously, based on the mean age of onset of ESRD: infantile (1 year), juvenile (13 years), and adult (19 years).[1,8] Cases of the juvenile form have been reported worldwide, with a prevalence of 0.1 to 0.2 per 10,000 live births in Finland and Canada.[5,7] Girls and boys are affected with equal frequency.[9]

More than 20 genes, mutations in which are responsible for the development of nephronophthisis, are known in the literature.[1,9,10] Mutations in the NPHP1 gene are the most common and account for approximately 20% of cases; in 80% of them, there are deletions, and in 30% of patients, the gene remains unknown. Mutations in the corresponding genes lead to disruption of the structure and function of the proteins of the primary cilium (cilia); therefore, nephronophthisis is considered a ciliopathy.[2] Nephronophthisis can manifest itself as a disease with isolated kidney damage, or in combination with extrarenal manifestations, including retinal degeneration, cerebellar ataxia, and liver fibrosis. Extrarenal manifestations are observed in approximately 20% of cases.[1,9,11,12]

Clinical case

We present a clinical case of a 14-year-old girl with manifestations of nephronophthisis type 1 with obesity, anemia, polyuria, and polydipsia.

A 14-year-old girl considered herself healthy until age 9, with urinalysis performed infrequently. She was admitted to the nephrology department with complaints of obesity, increased thirst, and excessive urination. The patient's family history is unknown (data on pregnancy, childbirth, and the neonatal period are missing). Physical, psychomotor, and motor development are age-appropriate. At age 9, complaints of polydipsia and weight gain were first noted; renal function was not assessed. At age 11, azotemia, hyperuricemia, and elevated parathyroid hormone (PTH) levels were detected. On examination, physical development is average, disharmonious due to excess weight (25–50% of height; 75–90% of body weight). Polydipsia is 2.2 L/m2/24 h, and polyuria is 2.4 L/m2/24 h. Blood pressure is normal in single measurements. No extra renal manifestations are noted.

According to laboratory data, a clinical blood test reveals an increase in ESR to 80 mm/h without leukopenia, leukocytosis, or thrombocytopenia. The hemoglobin concentration was 120 g/L (normal 115–160 g/L), erythrocytes 4.2 x 1012/L (normal 3.90–5.50 x 1012/L), transferrin 325 mg/dL (normal 193–421 mg/dL), ferritin 36 ng/mL (normal 11.0–306.8 ng/mL), serum iron 15 µmol/L (normal 10.7–32.2 µmol/L). Hypokalemia 3.3 mmol/L (normal 3.70–5.12 mmol/L), hyperuricemia 0.58 mmol/L (normal 0.15–0.43 mmol/L), and hyperparathyroidism 263.6 pg/mL (normal 16.0–62.0 pg/mL) were detected with a normal vitamin D level of 37.1 ng/mL (normal 14.0–60.0 ng/mL), P and Ca there were no violations. When assessing the acid-base balance, metabolic acidosis was not detected. Urinary syndrome is represented by minimal low molecular weight proteinuria (β2-microglobulin 252 mg/day), there is no microalbuminuria and glucosuria. An increase in fractional excretion of sodium (2.04%), potassium (23.8%) and magnesium (7.3%) was revealed, Ca/Cr - 0.01, tubular reabsorption of phosphates was reduced (TmP/GFR 0.76 mmol/L), osmolality in daily urine was reduced (103 mmol/kg), and the relative density (specific gravity) of urine was 1.001. The level of creatinine in urine was 139 µmol/l. Glomerular filtration rate was 37.9 ml/min/1.73 m2, which corresponds to chronic kidney disease C3.

Ultrasound examination revealed an increase in the volume of both kidneys (right kidney >97‰, left kidney >97‰), parenchyma

of increased echogenicity, impaired cortico medullary differentiation; a moderate number of cysts were found in the parenchyma of both kidneys, on the right, up to 1.4×1.0 cm in size; on the left, up to 1.0×0.7 cm (Figure 1).

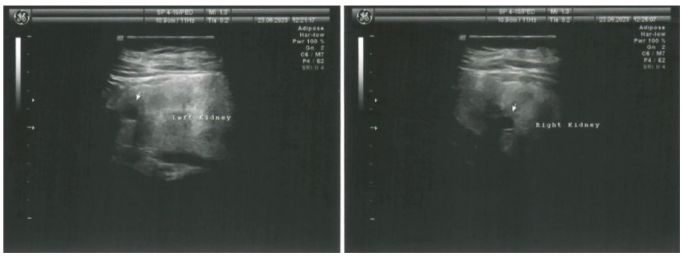

Figure 1 Ultrasound of the kidneys of a patient with nephronophthisis type 1.

X-ray examination of the hands and shins revealed signs of osteoporosis (Bernard-Laval index 0.34). To exclude pathology of the hypothalamic-pituitary region, magnetic resonance imaging of the brain was performed in a child with polyuria: no data confirming organic damage were found. In addition, the patient underwent an ophthalmological examination, the results of which revealed moderate myopia and reverse myopic astigmatism. Due to hyperuricemia, decreased renal function, and the presence of kidney cysts, autosomal dominant tubule interstitial kidney disease (ADTKD)-(UMOD gene?) is suggested.

Given low-molecular proteinuria, hypokalemia, hypophosphaturia, and increased fractional excretion of sodium and potassium in the urine, the girl was diagnosed with incomplete Fanconi syndrome, and therefore, a molecular genetic study was performed - whole-exome sequencing. Informed consent was obtained from the child's legal representative for the examination and description of the patient. Based on the results of the coverage (redundancy) analysis of the sequenced genes, data were obtained in favor of the presence of a homozygous deletion of a segment of chromosome 2 with approximate boundaries of 110855110–110970403 bp and a size of about 115 thousand bp, encompassing the NPHP1 gene (Table 1).

Table 1 Results of a molecular genetic study of a patient, 14 years old

Gene	Associated disease	DNA Alteration (Protein Alteration)	Zygosity (Inheritance pattern)	Allele frequency
NPHP1	Nephronophthisis 1, Juvenile (OMIM #256100)	2:g(?_110097534)_(110212826_?) del	Homozygote (recessive)	0,001798

Thus, based on clinical and anamnestic data, laboratory and instrumental examination results, in particular molecular genetic testing, the child was diagnosed with nephronophthisis type 1 (juvenile form) due to a mutation in the NPHP1 gene.

Given signs of stable arterial hypertension based on 24-hour blood pressure monitoring, therapy with the angiotensin-converting enzyme inhibitor enalapril at a dose of 0.11 mg/kg/day was initiated for nephroprotective and antihypertensive purposes. Due to the identified hyperuricemia, therapy with allopurinol at a dose of 300 mg/day was initiated, and a potassium supplement was prescribed to correct electrolyte imbalances (hypokalemia). Against the background of therapy carried out over 6 months, positive dynamics were noted in the form of stabilization of the filtration function of the kidneys (GFR CKID U25 - 40.1 ml/min/1.73 m^2), elimination of electrolyte disturbances (potassium levels increased to 3.8 mmol/l), and normalization of uric acid levels (0.32 mmol/L).

Discussion

Nephronophthisis is the most common genetic cause of end-stage renal disease in young adults. According to various researchers, nephronophthisis accounts for approximately 2.4% of cases of end-stage renal disease in children in the United States; studies conducted in Europe have revealed a higher incidence of 15%.[13] The development of juvenile nephronophthisis is underpinned by the occurrence of homozygous or compound heterozygous mutations in the NPHP1 gene, localized on the long arm of chromosome 2 - 2q13 (Figure 2).[5]

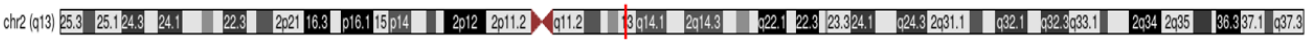

Figure 2 Localization of the *NPHP1* gene on chromosome 2.

The NPHP1 gene is responsible for the structure and function of the nephrocystin-1 protein, which is a component of the ciliary apparatus; it is expressed in primary cilia, basal bodies, and centrosomes. The primary cilium is an organelle located on the surface of most cells and functions as a cellular sensor. In the kidney, cilia protrude into the lumen of the renal tubules from the surface of epithelial cells and facilitate interactions between cells and the environment.[14,15] Mutations in the NPHP1 gene are believed to alter ciliary function by disrupting intra- and intercellular signaling pathways, which leads to impaired epithelial cell differentiation and the subsequent development of renal cysts.[1,2]

In the juvenile variant of nephronophthisis, the kidneys are normal in size or have a wrinkled appearance with small corticomedullary cysts (less than 1.5 cm), interstitial fibrosis, and tubular atrophy with thickened and multilayered basement membranes. The glomeruli are often not damaged, but as the disease progresses, severe periglomerular sclerosis is possible.[9,16]

In 20% of cases, extrarenal manifestations are associated with a defect in this NPHP1 gene and have been described in patients with Senior–Loken syndrome, which is characterized by concomitant manifestation of retinitis pigmentosa with severe visual loss; and in patients with Joubert syndrome, characterized by hypoplasia of the cerebellar vermis leading to ataxia, muscle hypotonia, and motor developmental delay (Figure 3).[1,9,10,12,17]

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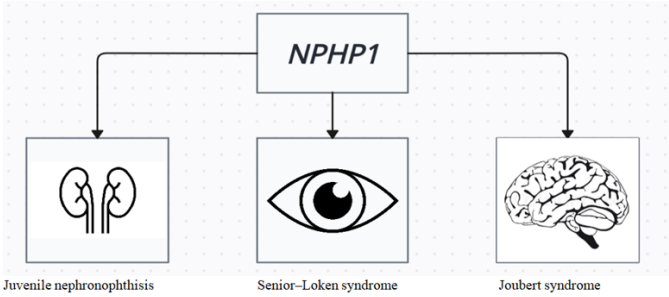

Figure 3 Mutations in the NPHP1 gene: nephronophthisis and associated syndromes.

It is difficult for nephrologists to establish the correct diagnosis due to the non-specificity of symptoms, and nephronophthisis is often diagnosed by chance at the stage of chronic renal failure. Clinical symptoms of the disease, such as polyuria, polydipsia, and obesity, do not always indicate nephronophthisis. In the case we presented, these complaints first appeared at the age of 9 years. As a rule, the reason for an in-depth examination of patients is treatment-resistant anemia associated with impaired erythropoietin synthesis and/or delayed physical development.[18] The girl did not have these symptoms at the time of examination. In nephronophthisis, as a rule, mild tubular proteinuria and glucosuria can be observed, which was observed in our patient.[8] Considering that polyuria-polydipsia syndrome is often the only clinical symptom of nephronophthisis, this condition requires careful differential diagnosis with diseases such as primary polydipsia and diabetes insipidus.[19–24]

Conclusion

Nephronophthisis is a common genetic cause of end-stage chronic renal failure in children and young adults. Based on our observations, we can conclude that nephronophthisis symptoms, such as polyuria and polydipsia, are specific and require renal function testing, a clinical blood test, and ophthalmological screening for retinopathy. Molecular genetic testing is currently recognized as the method of choice for diagnosis, as it allows for the identification of genes responsible for the development of nephronophthisis in 50–70% of cases. Early diagnosis of nephronophthisis, based on the results of clinical genetic testing, provides a personalized approach to patient care and correction of the clinical manifestations of chronic kidney disease. Specific therapy for this disease has not yet been developed.[1,9] The patient was started on nephroprotective therapy, which resulted in stabilization of renal function.

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Conflict of interest

The authors of this article confirmed the absence conflict of interests, financial or any other support which should be reported.

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