Case Report

A Family with Five Siblings Affected with Nephronophthisis

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ABSTRACT. Nephronophthisis is an autosomal recessive disease that leads to end-stage renal disease. These days, molecular genetic analysis is used pre-emptively for making a definitive diagnosis in patients who have clinical and radiological data suggestive of the disease. Herein, we are reporting a 12-year-old girl who was genetically diagnosed to have juvenile nephronophthisis, which explained the mystery of the chronic kidney disease in her four affected siblings.

Introduction

Nephronophthisis is a genetic disease that leads to end-stage renal disease (ESRD). It is characterized by polyuria and polydipsia. The prevalence of nephronophthisis in Jordan is not known. Genetic testing leads to a definitive diagnosis.¹ We herewith present a 12-year-old girl with a strong family history of ESRD in her family who had renal impairment and in whom genetic analysis revealed the diagnosis of nephronophthisis.

Case Report

A 12-year-old girl presented to the pediatric nephrology clinic with vomiting and abdominal pain of few weeks duration along with increased thirst and nocturia. Her height was 151 cm (at the 50th centile) and her weight was 39 kg (between 25th and 50th centile). Blood pressure was 90/60 mm Hg. On physical examination, no abnormalities were detected; detailed ophthalmological assessment was also normal. Laboratory results showed a serum creatinine of 224 µmol/L, urea of 16 mmol/L, sodium of 140 mmol/L, potassium of 3.8 mmol/L, calcium of 1.5 mmol/L, phosphate of 1.75 mmol/L and hemoglobin of 9.5 g/L. The parathyroid hormone level was 625.7 pg/mL (normal up to 54 pg/mL) and urine osmolality was 131 milli osmoles. Urine analysis and liver function tests did not show any abnormality.

Family history revealed that the patient had an older brother who died at the age of six years from renal failure of unknown etiology. He was on peritoneal dialysis for a year before his death. His kidney biopsy showed interstitial fibrosis and tubular atrophy.

The study patient has two other brothers and one
sister who underwent kidney transplantation. An elder brother aged 28 years was diagnosed to have renal impairment at the age of 10 years and his renal function deteriorated with time. He was put on hemodialysis for a few months and subsequently underwent a living unrelated donor transplantation at the age of 13 years; presently, he has normal graft function 15 years post-transplant (Figure 1).

The eldest sister of the study patient is 27 years old at the time of reporting. She was diagnosed to have renal impairment at the age of ten years and was on peritoneal dialysis for nine months. Subsequently, she underwent living unrelated donor transplantation at the age of 11 years. Currently, 16 years post-transplant, her graft function is normal. Her younger brother is now 19 years. He had renal impairment at the age of seven years. He underwent a preemptive kidney transplant, the donor being his father at the age of 14 years. Currently, five years post-transplant, he has stable graft function. One brother, who is now 29 years, has been reported as healthy. Her parents are first-degree cousins.

Our patient underwent a renal ultrasound that revealed bilateral small echogenic kidneys. The family refused a kidney biopsy. Genetic testing of nephronophthisis gene NPHP1 was performed and showed a homozygous deletion in the NPHP1 gene confirming the diagnosis of JN. She is now being followed-up regularly at the clinic and her last serum creatinine was 265 umol/L, with an estimated glomerular filtration rate (GFR) of 25 mL/min/1.73 m² (chronic kidney disease stage IV). Currently, she is on anti-hypertensive medications, erythropoietin, phosphate binders, iron supplements and calcitriol. The family has opted for pre-emptive kidney transplantation in the future.

Discussion

Nephronophthisis is an autosomal recessive disorder characterized by chronic tubulointerstitial nephritis progressing to ESRD. It was first described in 1951 by Fanconi. There are three types according to the age of onset: Infantile, juvenile and adolescent forms.

The prevalence of nephronophthisis in Jordan is not known. A retrospective study from Jordan regarding etiology of chronic renal failure in 202 patients revealed that 3.96% had nephronophthisis. More than 300 cases of nephronophthisis have been published in the literature thus far.

JN is the most common type; children present around the age of seven years with polyuria and
polydipsia secondary to reduced urinary concentrating ability demonstrating low urine osmolality and progressing to renal failure by the age of 13 years. Renal ultrasound usually reveals normal-sized kidneys with increased echogenicity and loss of corticomедullary differentiation. Cysts may be seen at later stages.

Light microscopy usually shows interstitial fibrosis and tubular damage in the form of tubular atrophy and tubular basement membrane anomalies such as thickening and disintegration of the basement membranes.

Eleven different genes have been identified in JN. The most frequent of these gene mutations is homozygous deletion of NPHP1, which causes approximately 20% of cases. Other mutations contribute to less than 3% each. NPHP1 is one of the earliest genes identified in 1993 on chromosome 2q13 by positional cloning in consanguineous families. Homerzygous deletions of 250 kb in this gene was detected in 70% of cases of nephronophthisis in 1997.

A cohort of 20 Egyptian children with nephronophthisis were studied and homozygous deletion in NPHP1 gene was indentified in 29.4% of patients, and this is similar to what has been reported from the Western countries.

The NPHP1 gene encodes a protein called nephrocystin that is present at the cell–cell junction and the cell–matrix interface, suggesting important functions in the tubular epithelium. It is also localized at the primary cilialike proteins.

Extra-renal symptoms are seen in 10–20% of cases, and these include retinitis pigmentosa (Senior–Loken syndrome), cerebellar ataxia in Joubert syndrome, bone anomalies, mental retardation and liver fibrosis.

The majority of patients with NPHP1 mutation have no extra-renal symptoms, although moderate forms of retinal degeneration and Joubert syndrome have been reported in some cases. Medullary cystic kidney disease has similar clinical features and pathology to JN, but has an autosomal dominant pattern of inheritance and leads to renal failure at the age of 50 years.

Our patient had a history of polyuria and progressive familial renal disease. She was diagnosed by genetic analysis that revealed homozygous deletion of NPHP1, indicating that her parents were carriers. This family was quite unlucky to have five affected members. The high rate of consanguinity in Jordan increases the prevalence of such inherited autosomal recessive diseases.

To the best of our knowledge, this is the first case report from Jordan where genetic testing confirmed the diagnosis of JN. Also, genetic analysis will enable prenatal diagnosis in subsequent siblings. In conclusion, based on clinical and radiological findings, JN can be diagnosed by genetic studies.

References
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