Journal of Molecular and Genetic Medicine

Pinzon et al., J Mol Genet Med 2019, 13:1
DOI: 10.4172/1747-0862.1000403

Case Report Open Access

Incidental Finding of Renal Impairment Leading to a Diagnosis of Nephronophthisis

Pinzon MB[1], Chau K[1,3] and Tarafdar S[1,2,3]

[1]Acute Medical Unit, Blacktown Hospital, NSW-2148, Australia
[2]Department of Renal Medicine, Blacktown Hospital NSW-2148, Australia
[3]School of Medicine, Western Sydney University, Sydney, Australia

Abstract

This case report describes the diagnosis of a familial juvenile nephronophthisis in a 17-year-old boy and emphasises on the increasing importance of genetic testing in patients with chronic kidney disease. A 17-year-old Iraqi refugee presented with abdominal pain and was incidentally found to have renal impairment (creatinine 279 µmol/L, urea 12.6 mmol/L, calculated eGFR for age 28 ml/min/1.73 m^2). Urinalysis showed no proteinuria nor haematuria and renal ultrasound and computed tomography revealed small kidneys (left=8.4 cm and right=7.9 cm). The patient's brother had end-stage renal disease and commenced on peritoneal dialysis at the age of 19 with a presumed diagnosis of cystic renal hypodysplasia. Genetic testing revealed homozygous deletion of 2q13 that encompasses *NPHP1* giving a diagnosis of juvenile nephronophthisis. Nephronophthisis is an autosomal recessive disorder characterised by normal to small cystic kidneys and an insidious onset of end-stage renal disease. It is the most common genetic renal disease in the first two decades of life and mortality is related to the complications of renal failure. It is caused by mutations in the NPHP genes, which encode proteins involved in the function of primary cilia, centrosomes and basal bodies. Nephronophthisis may be isolated or part of a syndrome and diagnosis is established by genetic testing.

Keywords: Nephronophthisis; Genetics; Familial renal disease; Chronic renal failure; Chronic tubulointerstitial nephritis

Introduction

This is a case of a 17-year-old male with renal impairment and anaemia that was incidentally found during work up of abdominal pain which was attributed to constipation. The patient had an older brother who had developed end-stage renal disease (ESRD) at the age of 19 and has since been on dialysis. Genetic testing revealed that the patient had juvenile nephronophthisis.

Case Description

AJ is a 17-year-old Iraqi refugee who initially presented to the emergency department with severe intermittent abdominal pain associated with nausea and vomiting, which after appropriate investigations was attributed to constipation. Routine blood tests performed as part of this investigation revealed significant renal impairment and mild anaemia.

The patient was born 2 months preterm but was reportedly a well-baby and was never hospitalised as a child. Past medical history was unremarkable. In particular, there was no history of childhood enuresis, recurrent urinary tract infections or renal calculi. He denied intake of any maintenance or over-the-counter medications and denied tobacco, alcohol and recreational drug use. He had no known drug or food allergies. He also denied chronic NSAID or analgesia use.

The patient has 5 siblings (Figure 1). His 23-year-old brother was diagnosed with cystic renal hypodysplasia at the age of 19 and is currently on ambulatory peritoneal dialysis. His 2-year-old sister was also found to have small kidneys during family screening at 1 ½ year old. His parents deny consanguinity to any degree. His father is 65 years old and has type 2 diabetes mellitus. His mother is 56 years old with no known co-morbidities. His family spent a few years in Turkey as refugees before migrating to Australia in 2011. He is currently in Year 12 and doing well in school.

Physical examination revealed a thin boy without any dysmorphic features. He weighed 48.9 kg and stood at 167 cm tall. BMI was 16.8. He was normotensive at 125/83 mmHg and euvolemic. Cardiovascular, respiratory, abdominal and neurologic examinations were non-contributory.

Initial laboratory investigations are displayed in Table 1. Urine dipstick showed no proteinuria or blood.

CT scan and ultrasound of the kidneys showed slightly small kidneys (left=8.4 cm and right=7.9 cm) with loss of corticomedullary differentiation and increased renal echogenicity. There was also note of 2 cysts in the right kidney measuring up to 6 mm. There was no hydronephrosis, calculus or mass lesion (Figure 2, 3A and 3B).

Due to the normocytic anaemia (haemoglobin 97 g/L, MCV 89 fL) and thrombocytopaenia (platelet count 113 × 10^9/L), the patient was referred to a haematologist. Bone marrow biopsy showed normal numbers of CD117, positive myeloblasts (3%; normal value ≤ 5%), normal granulocyte maturation pattern, normal neutrophil side scatter, normal expression of HLA-DR/CD116 on monocytes and no flow cytometry features of myelodysplastic syndrome.

The brother's diagnosis of cystic renal hypodysplasia with early onset ESRD and the probable kidney disease in his younger sister raised the possibility of a familial disease, so he was referred to a geneticist. An array comparative genomic hybridization (CGH)

***Corresponding author:** Dr. Marlies Bosch Pinzon, Acute Medical Unit, Blacktown Hospital, NSW-2148, Australia, Tel: +610435774132; E-mail: mboschpinzon@gmail.com

Received February 06, 2019; **Accepted** February 18, 2019; **Published** February 25, 2019

Citation: Pinzon MB, Chau K, Tarafdar S (2019) Incidental Finding of Renal Impairment Leading to a Diagnosis of Nephronophthisis. J Mol Genet Med 13: 403 doi:10.4172/1747-0862.1000403

Test	Result	Normal Range
Sodium	137 mmol/L	135 – 145 mmol/L
Potassium	3.6 mmol/L	3.2 – 5.0 mmol/L
Chloride	100 mmol/L	95 – 110 mmol/L
Bicarbonate	29 mmol/L	22 – 32 mmol/L
Anion gap	12 mmol/L	12 – 20 mmol/L
Creatinine	279 umol/L	60 – 110 umol/L
Urea	12.6 mmol/L	3.0 – 7.5 mmol/L
eGFR for age	28 ml/min	1.73 m^2
Bilirubin Total	19 umol/L	</=20 umol/L
Protein	74 g/L	60 – 80 g/L
Albumin	46 g/L	35 – 50 g/L
Total globulin	28 g/L	22 – 39 g/L
ALT	38 U/L	</= 40 U/L
AST	34 U/L	</= 40 U/L
GGT	29 U/L	</= 50 U/L
ALP	310 U/L	60 – 200 U/L
Lipase	238 U/L	</= 400 U/L
C reactive protein	<3 mg/L	</=3 mg/L
Intact parathyroid hormone	107.3 pmol/L	1.6 – 7.5 pmol/L
Corrected calcium	2.06 mmol/L	2.15 – 2.55 mmol/L
Phosphate	1.37 mmol/L	0.75 – 1.50 mmol/L
Haemoglobin	97 g/L	130 – 180 g/L
Haematocrit	0.27 L/L	0.40 – 0.54 L/L
RCC	3.0 x 10^{12}/L	4.2 – 5.3 x 10^{12}/L
WCC	4.5 x 10^9/L	3.7 – 9.5 x 10^9/L
Platelets	113 x 10^9/L	150 – 400 x 10^9/L
MCV	89 fL	77 – 93 fL
MCH	32 pg	24 – 30 pg
MCHC	358 g/L	300 – 350 g/L
RDW	12.1%	11.0 – 15.0 %
Abs Neutrophils	2.1 x 10^9/L	1.7 – 5.7 x 10^9/L
Abs Lymphocytes	1.9 x 10^9/L	1.4 – 3.8 x 10^9/L
Abs Monocytes	0.2 x 10^9/L	0.2 – 1.3 x 10^9/L
Abs Eosinophils	0.2 x 10^9/L	0.1 – 1.0 x 10^9/L
Blood film	**Large platelets**	
Albumin: Creatinine (urine)	33.1 mg/mmol	</= 30 mg/mmol
Urine osmolality	180 mOsm/kg	300 – 900 mOsm/kg

Table 1: Initial laboratory investigations.

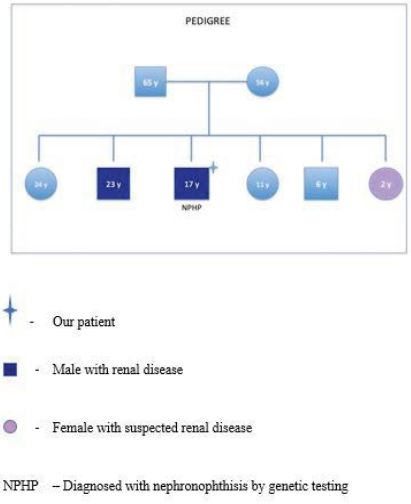

Figure 1: Pedigree showing members of the family affected with renal disease.

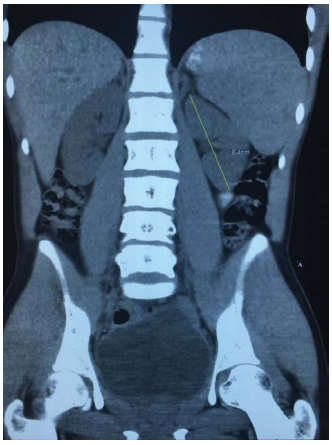

Figure 2: CT scan image showing the left kidney measuring at 8.4cm and the right kidney at 7.9 cm.

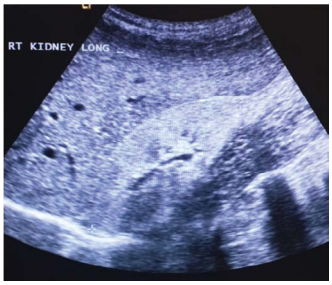

Figure 3A: Right kidney.

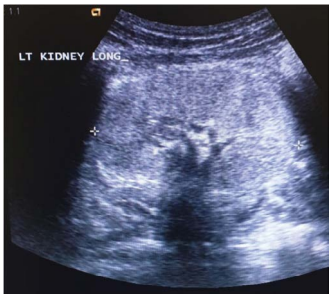

Figure 3B: Left kidney.

analysis of his chromosomes revealed a homozygous deletion of 2q13 that encompasses *NPHP1*.

The patient was therefore diagnosed with juvenile nephronophthisis based on renal impairment detected at the age of 17, a bland urinalysis, small cystic kidneys with loss of corticomedullary differentiation and the identification of the *NPHP1* gene mutation.

Because juvenile nephronophthisis may be associated with Senior-Loken and Joubert syndromes, he underwent a thorough ophthalmological assessment to check for retinal involvement and a brain MRI to look for superior cerebellar peduncle prominence and was found to have none.

Discussion

Nephronophthisis (NPHP) is an autosomal recessive disorder

characterised by normal to small cystic kidneys and an insidious onset of end-stage renal disease (ESRD). It is the most common genetic cause of ESRD in the first 2 decades of life, accounting for 5-15% of ESRD cases. Mortality results from the complications of renal failure. No racial or gender predilection has been identified. Mutations in genes that encode proteins involved in the function of primary cilia, centrosomes and basal bodies account for both renal and extrarenal manifestations. Renal cyst formation results from defects in the ciliary mediated mechanosensory pathways that regulate cell cycle, proliferation and death. Extrarenal manifestations are due to the presence of cilia in almost all cells and tissues in the body [1-6]. The clinical variants infantile, juvenile and adolescent are based on the expected age of onset.

Infantile NPHP would present with ESRD by age 3 or 4. It is very rare and is the most severe form. It is caused by mutations in the NPHP2 and NPHP3 genes. It is characterised by severe hypertension, renal abnormalities with oligohydramnios in prenatal ultrasound by 22 weeks gestation and hyperechogenic kidneys on dedicated renal ultrasound that are normal or small in size with or without renal cysts. Around 80% of patients with infantile nephronophthisis exhibit extrarenal manifestations such as hepatic fibrosis (50%), cardiac valve or septal defects (20%) and recurrent bronchial infections (18%). Because infantile nephronophthisis may be caused by mutations in NPHP2 gene, which encodes the protein inversin, it may also be associated with situs inversus [1-5].

In juvenile nephronophthisis, which is the most common form, ESRD typically develops by age 13. The incidence is approximately 0.13 for 10,000 live births in Finland, whereas in Canada, it is 1 per 50,000 live births and in United States 9 per 8.3 million [6]. The condition involves a mutation in the *NPHP1* gene, but some cases have shown mutations in the NPHP2 gene as well. The *NPHP1* gene encodes the protein nephrocystin-1, which interacts with products of other NPHP genes and is important in maintaining the integrity of the tubular epithelium. Initial symptoms of polyuria and polydipsia manifest at age 4 - 6 years, and typically present as primary enuresis. This is due to tubular dysfunction resulting in impaired urinary concentration and renal wasting. Blood pressures are typically within the normal range. Children and teens with juvenile NPHP may manifest some degree of growth retardation and anaemia secondary to CKD. Renal ultrasonography shows normal to slightly small kidneys with increased echogenicity and loss of corticomedullary differentiation. Renal cysts may be identified as the disease progresses [1-3,5].

Adolescent nephronophthisis progresses to ESRD in late adolescence and young adulthood (median age of 19 years) and is caused by a mutation in the NPHP3 gene. Clinical manifestations are similar to those of the juvenile variant [1-3,5].

Generally, the clinical manifestations are divided into renal and extrarenal. The renal disease is characterised by impaired urinary concentrating ability and tubular dysfunction leading to salt wasting, resulting in symptoms of polyuria and polydipsia. Blood pressure is usually within the normal range due to associated hypovolaemia caused by the tubulointerstitial impairment. Urinalysis is typically bland. As patients develop glomerular sclerosis, proteinuria may be observed. First morning void urine specific gravity may be low due to the impaired urinary concentrating ability in NPHP. Low erythropoietin levels result in anaemia [1-3].

Extrarenal manifestations occur in approximately 20% of patients and are most common in infantile NPHP (80%). These are attributed to the ciliary dysfunction caused by the mutation in the NPHP gene and result in a multisystem disease. Extrarenal manifestations include skeletal defects, neurologic symptoms and ophthalmologic disorders. Children exhibit decreased growth velocity due to chronic dehydration and renal insufficiency. Liver function tests may be deranged if there is concomitant hepatic fibrosis. Ophthalmological examination is done to assess for retinal degeneration [1,3-6].

The majority of patients with *NPHP1* mutation have no extra-renal manifestations [7]. Although renal ultrasound may be a good modality to screen for renal cysts and for ruling out other causes of renal insufficiency, assessing renal size and identifying loss of corticomedullary differentiation, contrast-enhanced thin-section CT scanning is the modality of choice to look for cysts that may be smaller than 0.5 mm in diameter [1].

Diagnosis of nephronophthisis is suggested by characteristic clinical findings and is established by genetic testing. Gene mutation is identified in about 70 percent of patients. The most common gene mutation is homozygous deletion of *NPHP1*, accounting for 21% of cases [8]. If whole exome testing is not available, homozygous or heterozygous *NPHP1* deletion screening should be performed, as this is the most common. If a positive gene test is not exhibited or if genetic testing is not at all available, then renal biopsy may be done to demonstrate chronic tubulointerstitial changes and thickening of tubular basement membrane to suggest nephronophthisis [1,3,5].

Extra renal manifestations associated with nephronophthisis may also be associated with the following syndromes:

1. Senior-Loken syndrome is associated with retinitis pigmentosa [3-6].
2. Joubert syndromes may be associated with developmental delay, neonatal breathing abnormalities, muscular hypotonia, and ataxia. MRI imaging of the brain reveals the characteristic molar tooth sign due to cerebellar vermis aplasia/hypoplasia [3-6].
3. Meckel-Gruber syndrome is a severe form of nephronophthisis where affected patients with occipital encephalocele, polydactyly, liver fibrosis and cystic kidney disease frequently die in the perinatal period [5-8].

Management of nephronophthisis is largely supportive. As it is inevitable that patients with nephronophthisis will ultimately progress to end-stage renal disease, early referral for pre-emptive transplantation should be considered if possible. Outcomes for renal transplant are excellent because tubular injury does not recur in the transplanted kidney [1-8].

Conclusion

This patient's renal impairment had an insidious onset and had no significant symptoms to prompt any consult or investigation in his earlier years. The only clue to a probable diagnosis of renal disease would have been the presence of a similar renal disease in his older brother. Genetic testing on the older brother could have paved the way for an earlier diagnosis in this patient and allowed for closer monitoring and supportive management at an earlier age. Nevertheless, this patient's diagnosis allows renal function testing and genetic screening on other family members.

Acknowledgments

We would like to extend our warmest gratitude to Dr. Michel Tchan, BMedSc MBBS PhD FRACP and Dr. Abir Bhattacharyya FRACP for providing their valuable inputs in arriving at a diagnosis for our patient.

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