

Case Report

Nephronophthisis in 11-year-old female presented with anemia

Ammar M. A. Algburi, M.D.*

Al-Yarmouk Teaching Hospital, Baghdad, Iraq.

Here we report a case of nephronophthisis in an 11-year-old child with known case of mental retardation, positive family history of renal failure, having pallor that is not responding to treatment with history of polyuria, polydipsia and retinal hypoplasia.

Keywords: Nephronophthisis (NPHP); child; anemia; renal failure.

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Introduction

Nephronophthisis (NPHP) is a rare autosomal recessive cystic kidney disease (figure-1) and a leading genetic cause of renal failure in children and young adults that's histologically characterized by interstitial fibrosis and corticomedullary cysts replacing normal renal tissue. The median age of NPHP induced renal failure in children is 13 years. The incidence of NPHP varies worldwide and ranges from 1 in 900,000 to 1 in 50,000. [1] The paucity of this disease and its presentation in mentally retarded female child prompted this case report.

Case presentation

An 11-year-old female child admitted to our hospital as her mother stated that she was complaining from pallor for one-month duration. She is a known case of mental retardation presented with history of pallor for one-month duration of progressive onset that's not associated with fever, blood loss, skin rash or change in color of urine. The family consulted a primary health care center where iron syrup was prescribed to her but her condition deteriorated by the development of poor feeding and decrease in her activity based on which the family consulted a private clinic where investigations revealed increase in renal function indices. Afterwards, her doctor referred her to our hospital where she was admitted to our nephrology unit because of history of polyuria. On admission, she had history of polyuria, about 11 time/day, started 5 months ago

and associated with polydipsia and enuresis. There was no history of hematuria or dysuria. History and examination of other systems was unremarkable. In regards to vaccination, she completed her vaccinations since the age of 4 years according to her schedule and BCG scar is present at left forearm. However, she had history of developmental delay, sitting at age of one year, walking at age of 3.5 years, speaking one word at age of 2 years. speaking in 2 to 3 word-sentences at the age of 5 years, she got sphincter control at age of 8 years, she did not attend neither kindergarten nor school because of her mental retardation.

The past medical history revealed previous admission to the hospital for Transient Tachypnea of Newborn (TTN) in neonatal period and at age of 5 years, her family consulted an ophthalmologist who diagnosed her with bilateral retinal hypoplasia. Family history revealed that she has two cousins who are known cases of cerebral palsy and both of them died due to renal failure. On examination, her weight: 34 kg (on 25th centile), height:135 cm (on 10th centile). Vital signs were all normal with normal blood pressure.

General examination revealed only mild leg edema. On Abdominal examination, there was no abdominal distention, organomegaly, palpable mass or shifting dullness. Neurological examination, she was alert with dysarthric speech, she had left eye movement limitation (left oculomotor apraxia), she had vertical nystagmus in all directions. On fundoscopy, there was pale retina. Other cranial nerves were intact. Tone was decreased in four limbs, power was +4 in upper and lower limbs bilaterally,

* Correspondence: Ammar M. A. Algburi, Al-Yarmouk Teaching Hospital, Baghdad, Iraq. E-mail: dr.lami2020@gmail.com

reflexes were normal in upper and lower limbs bilaterally, coordination in upper and lower limbs with ataxic gait. sensory examination was normal, and impaired

Blood and urine investigations: Table. 1

Table. 1 Blood and urine indices.

Blood index	value	Normal range
White blood cells (W.B.C)	6.5 *10 ⁹ /l with normal differentiation	4-10 x 10 ⁹ /L
Packed cell volume (P.C.V)	24 %	35-45% for females
Platelets (Plt)	239*10 ⁹ /l	150-400 x 10 ⁹ /L
Serum sodium (s.Na)	132 mmol/l	135-145 mmol/L
Serum potassium (s.K)	4.3 mmol/l	3.5-5 mmol/L
Serum calcium (s.Ca)	0.7 mmol/l	2-2.6 mmol/L
Serum phosphate (s.PO4)	2.6 mmol/l	0.8-1.5 mmol/L
Random blood sugar	4.6 mmol/l	3.9-5.6 mmol/L
Blood urea nitrogen	27 mmol/l	2.9-7.1 mmol/L
Serum creatinine	356 µmol/L	61.9-115 µmol/L
Prothrombin time (PT)	13 seconds	11-14 sec
Partial thromboplastin time (PTT)	29.8 seconds	20-40 sec
General Urine Examination		
Specific gravity	1000	1001-1035
W.B.C.	4-6/hpf	≤2-5 WBCs/hpf
R.B.C	nill	≤2 RBCs/hpf
Albumin	nill	nill
Blood film	Normochromic normocytic anemia with normal W.B.C. and Plt.	

Table. 2 Genetics defects underlying NPHP, associated features and other clinical phenotypes [3]

Gene (protein)	Chromosome	NPHP type	Clinical features associated with NPHP	Other clinical phenotypes
NPHP1 (nephrocystin-1)	2q13	NPHP	Mild JS, mild RP, Cogan	JS
NPHP2/INVS (inversin)	9q31	Infantile NPHP	RP, liver fibrosis, situs inversus, hypertension, VSD	
NPHP3 (nephrocystin-3)	3q22	NPHP, Infantile NPHP	Liver fibrosis, RP, situs inversus	MKS
NPHP4 (nephrocystin-4 or nephroretinin)	1p36	NPHP	Cogan, RP	
NPHP5/IQCB1(nephrocystin-5)	3q21	NPHP	Severe RP	
NPHP6/CEP290(nephrocystin-6/ CEP290)	12q21	NPHP	JS, severe RP	Isolated RP, JS, MKS, BBS
NPHP7/GLIS2 (GLIS2)	16p	NPHP		
NPHP8/RPGRIP1L(RPGRIP1L)	16q	NPHP	JS	JS, MKS
NPHP9/NEK8 (NEK8)	17q11	NPHP, Infantile NPHP		
AHI1 (Joubertin/AHI1)	6q23	NPHP	JS, RP	JS

JS, Joubert syndrome type B; RP, retinitis pigmentosa; Cogan, oculomotor apraxia type Cogan; MKS, Meckel–Gruber syndrome; VSD, ventricular septal defect.

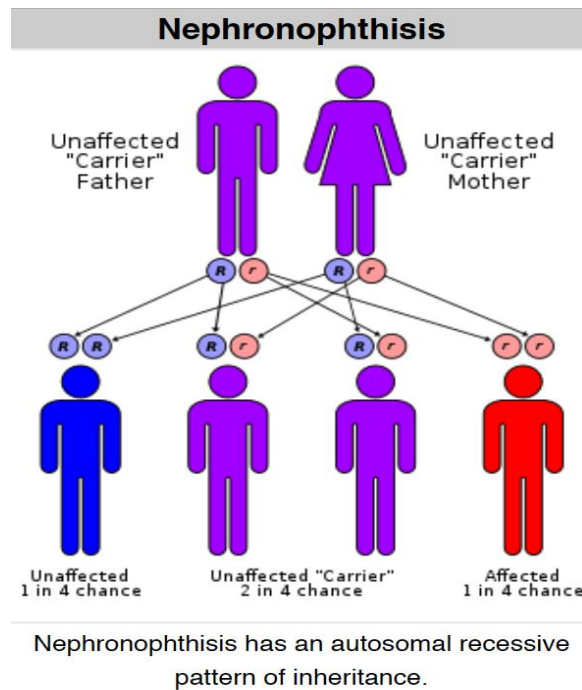


Fig.1 genetic inheritance of Nephronophthisis

Table.3 Extra renal manifestations associated with NPHP [3]

Eye/retinal disease
Isolated oculomotor apraxia
Retinitis pigmentosa
Coloboma
Nystagmus
Ptosis
Neurological disease
Learning difficulties
Cerebellar ataxia with vermis hypoplasia
Hypopituitarism
Encephalocele
Liver disease
Elevation of hepatic enzymes
Fibrosis, biliary duct proliferation
Skeletal
Phalangeal cone-shaped epiphyses
Short ribs
Postaxial polydactyly
Skeletal dysplasia
Others
Situs inversus
Cardiac malformations
Bronchiectasis
Situs inversus
Cardiac malformations
Bronchiectasis

Discussion

Nephronophthisis (NPHP) is a cause of autosomal recessive cystic kidney disease as well as renal fibrosis and end-stage kidney failure that typically affects young adults and children.[2] Many of the genes have been described as the cause of this hereditary disease and many of which are expressed on the in centromeres and primary cilia, rendering he disease to be as ciliopathy disease (table-2). [3] The histopathological features of the disease consist of corticomedullary cysts, atrophy, and interstitial fibrosis that reflect clinically as reduced GFR and loss of tubular function in the range of polyuria, polydipsia, secondary enuresis and growth retardation in children and eventually

Imaging investigation:

Chest X-Ray:

normal

Abdominal Ultrasound:

right kidney length 9.3 cm

Left kidney length 9 cm

Increase in echogenicity with ill-defined corticomedullary junction

Picture suggestive of parenchymal renal disease.

Abdominal CT scan:

Right kidney shoe normal size and position of 9.2 cm

Left kidney shows normal size of and position 9.1 cm

Both kidneys show no evidence of cysts or calcification

Differential diagnosis:

Neurogenic bladder lead to CRF.

Nephronophthisis.

Polycystic kidney disease.

Diagnosis and treatment: The patient was diagnosed with nephronophthisis and was given the followi2ng treatment:

Hemodialysis

Folic acid tab 5 mg/day

Vitamin D3 1000 IU/day

Calcium carbonate tab 500 mg/day

Ferrous syrup 40 mg * 2/day

Epirax (erythropoietin) vial 400 IU/wk

end stage renal disease ESRD. [4] The widely used classification of the disease is based upon age of ESRD onset as infantile, that causes ESRD around the age of 1; juvenile and adolescent that cause ESRD around the ages of 13 and 19 respectively. The Juvenile form is the classical one which is characterized by polyuria and polydipsia symptoms and often anemia in patients within the first decade of life. Progressive loss of kidney function leads to ESRD at a median age of 13 years while other forms are rare. [5]

NPHP is characterized by inability to concentrate urine early in life that is responsible for polyuria and polydipsia. The disease may be easily misdiagnosed, as there is typically no severe hypertension, very little or no

proteinuria. Besides extensive investigations of renal function, clinical phenotyping should also encompass a full neurological screening to assess for cerebellar signs and funduscopy to assess for retinal degeneration.

A formal ophthalmological examination is advised. The role of renal biopsy in diagnosing NPHP should be limited to cases that are hard to be differentiated from other diseases. In most cases, a histopathological diagnosis should be preceded by a molecular genetic diagnostic approach, because genetic screening allows for early diagnosis and prevents complications of renal biopsy. NPHP1 mutations and deletions are the most frequent genetic cause of NPHP and may be screened for using standard PCR assays. [6]

NPHP should be considered in any child who presents with the following characteristics:

- Polyuria due to decreased concentrating ability with a relatively normal urinalysis and reduced urinary sodium conservation

- Progressive chronic kidney disease with a normal blood pressure

- Ultrasonography demonstrates normal or slightly decreased in size kidneys for age with increased echogenicity with loss of corticomedullary junction. There is no dilation of the urinary tract, and renal cysts are not typically identified on the initial ultrasound examination but may appear at a late stage of the disease. The diagnosis is also supported by the presence of associated extrarenal manifestations (table-3).

Various theories behind the pathogenesis of the NPHP have been described. The very early hypotheses stated that this disease was caused by some unknown nephrotoxic agent or an enzyme defect. [7] The finding of tubular basement membrane thickening led to a basement membrane hypothesis for the pathogenesis of NPHP. Later, the hypothesis that described NPHP as a ciliopathy emerged. [8] This hypothesis is strongly supported by multiple gene discoveries in NPHP with many of which are coding for the components of the cilia. A study that links between NPHP and cilia found that INVS mutations cause infantile NPHP and that the encoded protein inversin interacts with nephrocystin-1 and β -tubulin, co-localizing with them to the primary cilia of renal tubular cells. [9]

The treatment of NPHP is mainly supportive. Control of blood pressure and correction of water and electrolyte

imbalances are priorities in affected children and young adults. Management of children in the early stage of the disease without renal impairment is focused upon replacing their ongoing water needs to prevent episodes of hypovolemia. Patients with NPHP uniformly progress to ESRD. Renal transplantation is the preferred therapy in patients with ESRD. However, management of complications arising from progressive renal failure such as anemia, symptoms of uremia and fluid overload are important alongside preparation for future renal replacement therapy.

In conclusion, we diagnosed this patient as having NPHP disease given the positive family history of renal failure, history of pallor that is not responding to iron treatment alone, history of polyuria, polydipsia and retinal hypoplasia, in addition to imaging and blood tests results. The patient had inability to conserve sodium because of defect of tubules leading to polyuria and polydipsia. The anemia is attributed to a deficiency of erythropoietin production by failing kidneys. She had no hypertension as nephronophthisis is a salt-losing nephropathy.

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Conflict of Interest

none.

References

1. Simms RJ, Hynes AM, Eley L, Sayer JA. Nephronophthisis: a genetically diverse ciliopathy. *Int J Nephrol*. 2011;2011:527137.
2. Delous M, Baala L, Salomon R, Laclef C, Vierkotten J, Tory K, et al. The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. *Nat Genet*. 2007;39(7):875-81.
3. Simms RJ, Eley L, Sayer JA. Nephronophthisis. *Eur J Hum Genet*. 2009;17(4):406-16.
4. Krishnan R, Eley L, Sayer JA. Urinary concentration defects and mechanisms underlying nephronophthisis. *Kidney Blood Press Res*. 2008;31(3):152-62.
5. Hildebrandt F, Strahm B, Nothwang HG, Gretz N, Schnieders

B, Singh-Sawhney I, et al. Molecular genetic identification of families with juvenile nephronophthisis type 1: rate of progression to renal failure. APN Study Group. Arbeitsgemeinschaft für Padiatrische Nephrologie. *Kidney Int.* 1997;51(1):261-9.

6. Otto EA, Helou J, Allen SJ, O'Toole JF, Wise EL, Ashraf S, et al. Mutation analysis in nephronophthisis using a combined approach of homozygosity mapping, CEL I endonuclease cleavage, and direct sequencing. *Hum Mutat.* 2008;29(3):418-26.

7. Waldherr R, Lennert T, Weber HP, Fodisch HJ, Scharer K. The nephronophthisis complex. A clinicopathologic study in children. *Virchows Arch A Pathol Anat Histol.* 1982;394(3):235-54.

8. Watnick T, Germino G. From cilia to cyst. *Nat Genet.* 34. United States 2003. p. 355-6.

9. Otto EA, Schermer B, Obara T, O'Toole JF, Hiller KS, Mueller

AM, et al. Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat Genet.* 2003;34(4):413-20.



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