Juvenile nephronophthisis and dysthyroidism: a rare association

Fateme Shamekhi Amiri¹ · Ariana Kariminejad²

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Abstract Nephronophthisis, an autosomal recessive kidney disease, represents the most frequent genetic cause of end-stage kidney disease in the first three decades of life. A 27-year-old male was presented with gait imbalance, severe pruritus since 10 days prior time of admission. In past medical history, he had bilateral cataract, torsional nystagmus, and bilateral optic nerve atrophy since 2 years of age. He was also mentioned history of multinodular goiter with dysfunctional thyroid state since 2 years before admission. At admission bilateral blindness, torsional nystagmus, asymmetric thyromegaly with nodularity was found in physical examination. Laboratory tests showed elevated urea and creatinine (200, 10.7 mg/dl), hypomagnesemia (1.1 mEq/l), decreased thyroid stimulating hormone (<0.004 mIU/l). Ophthalmologist consultation confirmed retinitis pigmentosa. Renal sonography showed small-sized kidneys. Brain magnetic resonance imaging did not reveal molar tooth sign. Genetic testing performed and a large homozygous deletion at the NPHP1 gene locus was found. The patient was diagnosed with juvenile nephronophthisis and consideration of dysthyroidism as extrarenal manifestation of nephronophthisis is suggested in this case. Furthermore, loss of function mutation in SLC41A1 gene that leads to magnesium depletion must be noted in patients with suspected to nephronophthisis.

Keywords Magnesium depletion · Nephronophthisis · Nystagmus · Retinitis pigmentosa · Thyroid dysfunction

Introduction

Senior-Løken syndrome (SLS) is an autosomal recessive disease characterized by development of a retinitis pigmentosa (RP) or Leber congenital amaurosis (LCA)-like retinal dystrophy, medullary cystic kidney disease and nephronophthisis (NPHP). Mutations in several genes (called nephrocystins) have been shown to cause SLS. Nephronophthisis is characterized by a chronic tubulointerstitial nephritis that progress to terminal renal failure during the second decade (juvenile form) or before the age of 5 years (infantile form). In the juvenile form, a urine concentration defect starts during the first decade, and progressive deterioration of renal function is observed into the following years [1]. We present a patient of juvenile nephronophthisis with dysthyroidism as extrarenal manifestation and resulting or associated magnesium depletion in nephronophthisis.

Case report

A 27-year-old male presented with gait problems, severe pruritus since 10 days prior time of admission. In medical history, he is a case of bilateral cataract, torsional nystagmus, and bilateral optic nerve atrophy since 2 years of age and was diagnosed as Leber's congenital amaurosis by ophthalmologist.

The patient had visited by endocrinologist 2 years before admission on nephrology ward due to hypofunctioning state of thyroid gland and started levothyroxine for him. At the

✉ Fateme Shamekhi Amiri
fa.shamekhi@gmail.com

¹ Division of Nephrology, Imam khomeini hospital, Faculty of medicine, National University of Tehran Medical Sciences, Tehran, Iran

² Shahrak of Gharb (Qods) pathologic and genetic center, Tehran, Iran

same time, the patient had pancytopenia/bicytopenia and normal renal function. Few several months later he found hyperfunctioning thyroid state, gait problems, severe pruritus, elevated serum urea and creatinin levels that started hemodialysis for him. In family history, his father grandparents were relative. Furthermore, his parents are first-degree cousins and asymptomatic except history of hypothyroidism in his mother. Also his brother was developed intestinal obstruction in postnatal period and then dilated cardiomyopathy and hypothyroidism were detected in him. For this reason, levothyroxin was started for him, but he was expired at the 5 years old. His sister is asymptomatic carrier and unaffected. On admission, in physical examination he was well-developed, undernourished young male, stable normal blood pressure. Eye examination showed pale conjunctiva, bilateral blindness, and torsional nystagmus. In neck detected asymmetric thyromegaly with nodularity and neck sonography confirmed it. Cardiac examination was normal except grade II over VI (GII/VI) systolic murmur in apex and left lower sternal border (LLSB). In abdominal examination, there was no hepatosplenomegaly.

The patient was alert and oriented to time, place and person and had decreased deep tendon reflexes in neurological examination. Skin was pale, dry and scaly and there was diffuse, patchy and brownish discoloration in back. Laboratory analysis revealed pancytopenia (WBC: $3.2 \times 10^3/\mu\text{l}$, Hb: 7.6 g/dl, plt: $130 \times 10^3/\mu\text{l}$), elevated serum urea and creatinine (200, 10.7 mg/dl), adequate urinary output, serum Na^+ and K^+ were normal (Na^+ : 138 mEq/l, K^+ : 4.8 mEq/l). Hypocalcemia, hypomagnesaemia and hyperphosphatemia and hyperuricemia were detected (Ca^{2+} : 5 mg/dl, Alb: 5.1 g/dl, Pi: 5.9 mg/dl, Mg^{2+} : 1.1 mEq/l, uric acid : 7.2 mg/dl). Thyroid function test showed elevated serum FT4 (54 pmol/l), FT3 (23 pmol/l), decreased TSH (<0.004 mIU/l). In urinalysis, microscopic hematuria (RBC: 10–12/hpf) and proteinuria (1+) were detected (Table 1). Renal sonography revealed small-sized kidneys [right kidney: 83 mm, left kidney: 84 mm (normal kidney size: 85–130 mm)] without cyst formation. Brain magnetic resonance imaging (MRI) did not reveal molar tooth sign (MTS) but was in favor of mild brain atrophy and small arachnoid cyst. Upper gastrointestinal endoscopy showed chronic gastritis. Echocardiography was performed and detected 1+ mitral regurgitation. In direct ophthalmoscopy by ophthalmologist bilateral cataract, pigmentary changes as bony spicule in peripheral retina (retinitis pigmentosa) with optic nerve atrophy and vascular attenuation were observed. Gene analysis with deoxyribonucleic acid (DNA) extraction from blood samples through whole exome sequencing based copy number variant (CNV) plus polymerase chain reaction/gel electrophoresis analysis revealed a large homozygous deletion at the NPHP1 gene locus (Fig. 1). The patient underwent hemodialysis and

then performed kidney transplantation for him 3.5 years ago. Currently, kidney allograft function is acceptable with serum creatinin of 1.4 mg per dl.

Discussion

Senior-Løken syndrome (SLS) is an autosomal recessive disease. A combination of RP or LCA and nephronophthisis develops in patients with SLS. The inspiration for the term nephronophthisis (ancient Greek for kidney/nephron decline) came from the observation that in contrast to more frequent cystic kidney disease such as autosomal dominant polycystic kidney disease, the kidney size in NPHP patients is often small [2]. Three clinical forms of NPHP have been distinguished by onset of end-stage kidney disease (ESKD): infantile, juvenile and adolescent NPHP which manifests with ESKD at the median ages of 1, 13 and 19 years old, respectively [3–5]. Initial symptoms are relatively mild and consist of polyuria, polydipsia with regular fluid intake at nighttime, secondary enuresis and anemia. At an average of 9 years of age, a slightly raised serum creatinin is noted, before invariably developing within a few years. Renal sonography reveals increased echogenicity. Later, cysts appear at the corticomedullary junction. Kidneys are normal or slightly decreased in size. Renal histology reveals a characteristic triade of tubular basement membrane disruption, tubular interstitial nephropathy and corticomedullary cyst. In nephronophthisis, cysts arise from the corticomedullary junction of kidneys. In humans, cilia are found on almost every cell in the body, and they can be broadly categorized into motile and nonmotile cilia, but not both. Gene products of some of the NPHP genes are found in the cilia of other organs. Mutations of these genes result in the non-renal manifestations of NPHP, such as retinitis pigmentosa, which occurs in 20% of all genes of NPHP. Chaki et al., in a study, evaluated a worldwide cohort of 440 patients from 365 families with NPHP-related ciliopathies, in whom both disease-causing alleles were identified. Analysis of genotype–phenotype correlation in NPHP1 revealed extrarenal manifestations in 55 families: specifically, 24 had central nervous system defects (oculomotor apraxia type cogan, mental retardation, locomotive disorders, cerebrovascular accident, developmental delay, porencephaly, hydrocephalus, and epileptic seizure) and 27 had eye involvement (tapetoretinal degeneration, optic nerve atrophy, and pigmented fundus). Two families exhibited liver fibrosis and two had heart anomalies (hypertrophic non-obstructive cardiomyopathy and aortic stenosis) [6].

Our patient presented with thyroid disease as if hypothyroid functional state was detected first and then thyroid showed increased function with multinodular thyroid on ultrasonography. Endocrine abnormalities as thyroid

Table 1 Laboratory findings of patient with nephronophthisis

Parameters (reference range)	14/Sep/2009	23/Nov/2009	21/Jan/2010	21/Apr/2010	3/Apr/2011	2012	2016
Fasting blood sugar (60–110)	83 mg/dl				96 mg/dl		
Serum urea (15–45)					200 mg/dl		
Serum creatinin (0.7–1.3)	0.7 mg/dl				10.7 mg/dl		1.4 mg/dl
Serum sodium (135–145)					138 mEq/l		
Serum potassium (3.5–5.5)					4.8 mEq/l		
Serum calcium (8.5–10.5)	9.3 mg/dl				6.6 mg/dl	8.4 mg/dl	
Serum phosphorous (2.5–5)	4.5 mg/dl				5.5 mg/dl	3.2 mg/dl	
Serum magnesium (1.5–2.05)					1.1 mEq/l	1.5 mEq/l	
Serum uric acid (2.5–6.2)					7.2 mg/dl		7.6 mg/dl
Alkaline phosphatase (68–279)	448 U/l				423 U/l		
Thyroxin, free (FT4)	1.5 pmol/l	0.8 pmol/l	18.9 pmol/l	9.9 pmol/l	51 pmol/l	11.6 pmol/l	
Triiodothyronin, free (FT3)	5.2 pmol/l	4 pmol/l	3 pmol/l	3.6 pmol/l	23 pmol/l	4.1 pmol/l	
Thyroid-stimulating hormone (TSH)	0.5 mIU/l	>20 mIU/l	<0.3 mIU/l	1.6 mIU/l	<0.004 mIU/l	0.2 mIU/l	
Triiodothyronin resin uptake (T3RU)			42.8				
White blood cell count [WBC (4–10 × 10 ³ /μl)]	6.1 × 10 ³ /μl	3.5 × 10 ³ /μl			3.4 × 10 ³ /μl		
Hemoglobin [Hb(13.2–16.5)]	9.9 (g/dl)	9.7 (g/dl)			7.2 g/dl		
Platelets (140–450 × 10 ³ /μl)	112 × 10 ³ /μl	148 × 10 ³ /μl			171 × 10 ³ /μl		
Mean corpuscular volume [MCV (82–102)]	77 fL						
Mean corpuscular concentration [MCH (27–33)]	25 pg						
Neutrophil	47%						
Lymphocyte	51%						
Reticulocyte percent		0.4%					
Serum Iron, total (60–170)	55 μg/dl				100 μg/dl		
Iron binding capacity, total [TIBC (250–450)]	328 μg/dl				420 μg/dl		
Ferritin	160 ng/ml				1080 ng/ml		
TSAT	16.7%				23%		
Albumin					5.1 g/dl	3.4 g/dl	
Erythrocyte sedimentation rate (ESR)	5 mm/h				39 mm/h		
C-reactive protein (CRP)					Negative		
Triglycerides (35–175)					65 mg/dl		
Cholesterol, Total (<200)					89 mg/dl		
Low-density lipoprotein cholesterol [LDL-C (105)]					40 mg/dl		
Alanine aminotransferase [ALT (<31)]					19 U/l		
Aspartate aminotransferase [AST (<31)]					24 U/l		
Total bilirubin (0.1–1.2)					0.5 mg/dl		
Direct bilirubin (0–0.4)					0.2 mg/dl		
Lactate dehydrogenase [LDH (<530)]					386 U/l		
Total CPK (<196)					73 U/l		
Stool examination	NI				NI		
Intact parathyroid hormone [iPTH (150–300)]					260 pg/ml	740 pg/ml	
25(OH) vit D ₃ [30–100]					45.5 ng/ml		
Urine protein, dipstick					1+		
Urine red blood cell					12–14/hpf		
Urine white blood cell					4–5/hpf		
Urine blood					3+		

Table 1 (continued)

Parameters (reference range)	14/Sep/2009	23/Nov/2009	21/Jan/2010	21/Apr/2010	3/Apr/2011	2012	2016
PH					7.35		
PCO ₂					26 mmHg		
HCO ₃ ⁻ (total CO ₂ content)					14.5(15.7) mEq/l		

Nl normal, *hpf* high power field

Fig. 1 Characteristics of gene analysis. GRCh 37, genome reference consortium human reference 37

hormone deficiency have found in joubert syndrome related disorders (JSRD), but thyroid disorders have not been mentioned as extrarenal manifestations of NPHP in the literature review so far [7, 8]. The reasons for this hypothesis are that we know primary cilia are present on a wide variety of cell types such as the bile duct, the kidney tubule, the pancreas, the thyroid, smooth muscle cells, neurons, fibroblasts, and chondrocytes [9] and furthermore they were first observed in the renal epithelium and thyroid gland [10, 11], perhaps association between NPHP and thyroid disorders can be illustrated via this observation. In children with recessive mutations in the 1, 2, 3 and 4 genes, retinitis pigmentosa occurs in approximately 10% of all affected families without any obvious genotype/phenotype correlation. The early onset type seems to represent a form of Leber's congenital amaurosis, because children exhibit coarse nystagmus and/or blindness at birth or develop these symptoms within the first 2 years of life [12]. Our patient showed bicytopenia/pancytopenia with low reticulocyte count percent on laboratory investigations. It appears that

Vit B12 deficiency causes this problem. Furthermore, clinical picture of optic neuropathy associated with Vit B12 deficiency shows similarity to that of leber's hereditary optic neuropathy.

On admission, hypomagnesemia despite uremic syndrome was detected in our patient. Magnesium deficiency may be caused by extrarenal causes and renal magnesium wasting. Salt-losing tubulointerstitial nephropathy and primary magnesium-wasting disorders can be considered in this patient. Although hypomagnesemia occasionally complicates nonoliguric acute tubular necrosis associated with nephrotoxic drugs, but hypokalemia is accompanied with these conditions. Recently Kolisek et al. has reported that the human solute carrier family 41, anion exchanger, member 1 [SLC41A1 (mapped on chromosome 1q 31–32)] encodes for the Na⁺/Mg²⁺ exchanger 4 [13] and gain of function mutation of SLC41A1 is associated with Parkinson's disease [14]. But in study by Hurd et al., whole-exome capture revealed a homozygous splice acceptor site mutation in the renal Mg²⁺ transporter SLC41A1. This mutation

Fig. 2 Proposed algorithm for diagnosis of juvenile nephronophthisis and genotype–phenotype correlation in NPHP1 gene deletion. *Cogan SX* cogan syndrome, *ESKD* end-stage kidney disease, *JS* Joubert syndrome, *JS-OR* Joubert syndrome-oculorenal, *JS-R* Joubert syndrome-renal, *JSRD* Joubert syndrome and related disorders, *MTS* molar tooth sign, *NPHP* nephronophthisis, *RP* retinitis pigmentosa, *SLS* senior-Löken syndrome. *Asterisk* shows homozygous deletion of NPHP1 gene

resulted in skipping of exon 6 of SLC41A1, resulting in an in-frame deletion of a transmembrane helix. Transfection of cells with wild-type or mutant SLC41A1 revealed that deletion of exon 6 completely blocks the Mg^{2+} transport function of SLC41A1. Furthermore, in normal human kidney tissue, endogenous SLC41A1 specifically localized to renal tubules situated at the corticomedullary boundary, consistent with the region of cystogenesis observed in NPHP and related ciliopathies. Last, morpholino-mediated knockdown of SLC41A1 expression in zebrafish resulted in ventral body curvature, hydrocephalus, and cystic kidneys, similar to the effects of knocking down other NPHP genes. Moreover, downstream of the NPHP-protein/ciliary network is considered in regulation of the SLC41A1 transporter regulation. Taken together, these data suggest that defects in the maintenance of renal Mg^{2+} homeostasis may

lead to tubular defects that result in a phenotype similar to NPHP, but no correlation between SLC41A1 mutation and NPHP 1 disorder phenotype has been found in literature review so far [15]. Unfortunately, SLC41A1 mutation has not been checked at our patient. In order to establish a clinical diagnosis of NPHP, a detailed history, clinical examination including looking for extrarenal associations (abnormal eye movement, retinopathy, ataxia, polydactyly and cardiac malformations) is required. A detailed family history must be taken both to facilitate diagnosis and to highlight other individuals who should be invited for review.

Appropriate investigation including renal and liver function tests, urine concentration ability, renal and hepatic ultrasound and cerebral imaging if clinically indicated and must be referred to an ophthalmologist. After genetic counselling by geneticist, blood may be sent for genetic testing

(Fig. 2) [16]. Gene analysis (with emphasis on the variants within 23 genes known to be involved in nephronophthisis and related ciliopathies) in this case revealed homozygous NPHP 1 gene deletion that is similar with NPHP 1 associated JSRD, but previous different studies demonstrated the presence of MTS on cerebral imagings in all of the cases of NPHP 1 associated JSRD [17–21]. Although, study by Maria et al. revealed MTS in 85% cases of pure joubert syndrome with 13% of these showing additional malformations, patients without the MTS had other mimicking conditions such as neocerebellar dysgenesis, isolated vermian atrophy, cerebellar aplasia, and cystic dilation of the cisterna magna [22]. Currently there is no effective prophylaxis or treatment available for NPHP other than supportive treatment once chronic renal failure has developed, and dialysis and transplantation for terminal renal failure. Successful renal transplantations have been performed in patients with juvenile nephronophthisis, without the recurrence of the disease in the transplanted organ. An important future challenge will be the development of therapies that capitalizes on what we have learnt about the biology of NPHP and other cystic disease of the kidney [23]. Currently, next generation sequencing (NGS) that is also known as massively parallel sequencing and clinical perspectives is mostly used for research purposes in order to identify novel disease genes and to gain more insights into genotype–phenotype correlations in a time and cost effective effort. Although NGS will improve diagnosis, prognosis and genetic counseling for patients in daily clinical practice, there are also challenges for the implementation of this technology in DNA diagnostics. The power of NGS has proven itself in research laboratories, and in the coming years this technology will be implemented in DNA diagnostics laboratories throughout the world. Whereas disease genes are currently stepwise the Sanger sequenced in diagnostics based on an educated guess at the best candidate gene, whereby clinical phenotype, mutation frequency, and ethnic origin are considered, unbiased mutation screening through NGS is expected to be much more effective [24–26]. Whole exome resequencing establishes an efficient, non-invasive approach towards early detection and causation-based diagnosis of recessive disease genes [27]. To the best of our knowledge, this is the first report of thyroid disorder as extrarenal manifestation of nephronophthisis. Furthermore, loss of function mutation in SLC41A1 gene must be considered in nephronophthisis and related ciliopathies.

Conclusion

Diagnosis of nephronophthisis must be considered in patients presenting with renal failure and ocular involvement. Molecular study can play a very useful role

in confirmation of diagnosis. Once the diagnosis of nephronophthisis has been made, complete work-up must be done in order to identify extra-renal disorders. The presented case suggests thyroid dysfunction as extra-renal manifestation of nephronophthisis. Furthermore, loss of function mutation in SLC41A1 gene that leads to magnesium depletion must be noted in patients with suspected to nephronophthisis and nephronophthisis-related ciliopathies. Finally, kindred must be investigated for early detection of nephronophthisis.

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Compliance with ethical standards

This article does not contain any studies with animals performed by any of the authors.

Conflict of interest The authors declare no conflict of interests.

Informed consent Informed consent was obtained from all individual participants included in the study.

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