

An Adolescent Boy Presented with Polyuria: A Diagnostic Challenge

Adolesan bir Erkek Çocukta Poliüri: Tanısal Güçlük

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ABSTRACT

Polyuria in children may become a diagnostic challenge since it may be seen as presenting symptom of an underlying renal or systemic disease.

An adolescent boy, who did not have any known illness, was presented with polyuria. The detailed history revealed the findings of learning difficulty, speech impairment, unsteady gait and an operation of polydactyly. He had consanguineous parents and a brother who had abruptly diagnosed with the end-stage renal disease at the age of 21. These clues pointed to genetic background. On physical examination, he had pectus excavatum, atypical facial appearance, dysarthria, hypotonia, rotatory nystagmus, impaired tandem walk, hyperpigmented retinal irregularities. Laboratory examinations showed Stage-4 chronic kidney disease accompanied by tubulopathy. Ultrasonography detected cystic lesions on the corticomedullary junction. Thus, the patient had diagnosed Juvenile-Nephronophthisis. During further examinations, Molar Tooth Sign was detected in cranial MRI imaging. All these clinical and radiological findings indicate the spectrum of Joubert-Syndrome-Related-Disorders (JSRD). Genetic analysis of the patient and his brother revealed homozygous NPHP1 deletion. Distinctly from literature, they both had hematological involvement in the form of persistent thrombocytopenia.

Genetic heterogeneity and phenotypic variability of nephronophthisis are major challenges. Although NPHP1 deletions are mostly identified in isolated nephronophthisis, they have also been described in complex ciliopathy syndromes such as JSRD. This case is also specific due to haematological involvement additional to kidney, retina, skeleton, neurological. We think, this case may shed light on future genotype-phenotype studies.

Key Words: Cerebellar diseases, Cystic kidney diseases, Polyuria

ÖZ

Çocuklarda poliüri, altta yatan renal veya sistemik bir hastalığın ilk bulgusu olarak görülebildiği için ayırıcı tanısı güç bir bulgu olabilir.

Bilinen herhangi bir hastalığı olmayan adolesan bir erkek çocuk poliüri ile başvurdu. Detaylı öyküsünde öğrenme güçlüğü, konuşma bozukluğu, dengesiz yürüyüş bulguları ile polidaktili operasyonu öyküsü saptandı. Akraba evliliği olması ve 21 yaşındayken aniden son dönem böbrek hastalığı teşhisi konan bir erkek kardeşinin olması gibi ipuçları altta yatan genetik bir etiyolojiye işaret ediyordu. Fizik muayenede pektus ekskavatum, atipik yüz görünümü, dizartri, hipotoni, rotatuar nistagmus, bozulmuş tandem yürüyüş, retinada hiperpigmente düzensizlikler görüldü. Labotatuvar tetkikleri sonucunda tübülöpatinin eşlik ettiği Evre-4 kronik böbrek hastalığı olduğu gösterildi. Ultrasonografide ise



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kortikomedüller bileşkede kistik lezyonlar saptandı. Böylece hastaya Juvenil nefronofitizis tanısı koyuldu. Ayrıca ileri incelemeler sırasında, kranial MRI görüntülemesinde "Molar Diş Bulgusu" belirlendi. Tüm bu klinik ve radyolojik bulgular, Joubert Sendromu İlişkili Hastalıklar spektrumuna işaret etmekteydi. Olgunun kendisi ve kardeşinde genetik analizinde homozigot NPHP1 delesyonlarını saptandı. Literatürden farklı olarak, vakamızda ve abisinde persistan trombositopeni şeklinde

Nefronofitizisin genetik heterojenliği ve fenotipik değişkenliği tanısız güçlüğe neden olmaktadır. NPHP1 delesyonları çoğunlukla izole nefronofitizisde olmakla birlikte, JSRD gibi siliyopati sendromlarında da tanımlanmıştır. Bu vaka böbrek, retina, iskelet ve nörolojik tutulumlara ek olarak hematolojik tutulumu da olması nedeniyle özgündür. Bu vakanın, gelecekteki genotip-fenotip çalışmalarına ışık tutabileceğini düşünmekteyiz.

Anahtar Kelimeler: Serebellar hastalıklar, Kistik böbrek hastalıkları, Poliüri

INTRODUCTION

Urine output is mainly dependent on two factors; daily solute excretion, and concentration capacity of the nephrons. Disturbances of these factors can lead to excess diuresis, polyuria. It becomes a diagnostic challenge for the physicians as it could be seen as presenting symptom of the underlying renal disease or systemic disease.

We report an adolescent boy presented with polyuria and detected Stage-4 chronic kidney disease (CKD) accompanied with other systemic involvements.

CASE REPORT

A 15-years-old boy presented with frequent urination and excess water intake noticed for the past two weeks. He had no known chronic disease, regular medication, history of head trauma, urinary tract infection. He had consanguineous parents. He had a brother who had been diagnosed with End-Stage (ESKD) kidney disease during a routine control at the age of 21. That family history was indicating genetic background.

On physical examination, his height (1.56 m, SDS -2.1) and weight (43 kg, SDS -2.3) were below 3rd percentile. Blood pressure was normal. He had normal skin turgor, moist oral mucosa, and no oedema. He had an atypical facial appearance with hypertelorism, thick eyebrow and wide mouth. Pectus

excavatum deformity was noted. His family told that his brother with ESKD also had a similar atypical facial appearance and short stature.

On blood analysis, mild metabolic acidosis, normocytic anaemia, hypocalcemia, hyperphosphatemia, high parathyroid levels, high serum creatinine and urea levels were noticed (Table I). 24 hours urine collection revealed that his urine output was 4.2 mL/kg/hour, tubular functional tests were impaired, non-nephrotic range proteinuria was detected. Creatinine clearance was calculated as 24 mL/min (Table II). The patient was considered as Stage-4 CKD.

Further evaluation of chronic kidney disease was continued. Viral serology was unremarkable. Serum complement levels were normal and antinuclear antibody (ANA) was negative. Imaging of urinary tract with ultrasonography showed bilateral small kidneys with Grade-1 hyperechogenicity and small cystic lesions on the corticomedullary junction. According to these clinical, laboratory and imaging findings, we easily diagnosed him as Juvenile Nephronophthisis (NPHP). However, it seems that the diagnosis did not fully cover his clinical situation. So, we decided to deepen the examination.

First of all, his past medical history was further elaborated, and it was found that he was operated at the age of 1 due to postaxial polydactyly of feet. He was always behind his peers in speech and learning abilities. His neurological examination also revealed hypotonia, rotatory nystagmus, impaired tandem walk test. An ophthalmoscopic examination found out hyperpigmented

Table I: Blood results of the case

Blood analysis	Results	Normal Range	Blood analysis	Results	Normal Range
Glucose (mg/dL)	98	70-120	Hemoglobin (g/dL)	10.7 (↓)	13- 16.2
Urea (mg/dL)	106 (↑)	17-43	Hematocrit (%)	30.9 (↓)	37- 47.9
Creatinine (mg/dL)	2.4 (↑)	0.8-1.3	MCV (fL)	87.9	80-97
Uric acid (mg/dL)	7.4 (↑)	3.5-7.2	Leukocyte (x10 ³ /mL)	9.5 /mL	4.2-10.6
Albumin (g/dL)	4.6	3.5-5.2	Platelet (x10 ³ /mL)	155	150-450
Sodium (mmol/L)	144	135-145	C-reactive protein (mg/L)	8.6 (↑)	0-5
Potassium (mmol/L)	4.5	3.5-5.5	Eryth.Sedim. Rate (mm/h)	66 (↑)	0-20
Calcium (mg/dL)	5.0 (↓)	8.5-10.5	25-OH-vitamin D (mg/L)	9.7 (↓)	<12: deficiency
Phosphorus (mg/dL)	8.9 (↑)	2.5-4.5	pH	7.30 (↓)	7.35-7.45
Magnesium (mg/dL)	1.9	1.8-2.6	pCO ₂ (mmHg)	30 (↓)	35-45
Parathormone (ng/L)	470 (↑)	18.5-88	HCO ₃ (mmol/L)	19.8 (↓)	22-26

Table II: Urine results of the case.

Dipstick Urinalysis	Results	Normal Range
pH	5	4.5-6.5
Specific gravity	1005 (↓)	1010-1030
Glucose / Protein	Neg	Neg
Erythrocyte/ Leukocyte	Neg	Neg
Spot Urine Sample *	Results	Calculations
U Creatinine (mg/dL)	38	
U Sodium (mmol/L)	42	FE Na: 2.1 % (†)†
U Potassium (mmol/L)	12	FE K: 19.6 % (†) †
U Phosphorus (mg/dL)	39	TRP: 0.68 ‡
24 hours Urine Sample	Results	Calculations
Volume (mL)	4350 (↓)	Urine output: 4.2 mL/kg/h (†)
U Protein (mg/day)	528	Proteinuria: 16.4 mg/m ² /h (†)
U Creatinine (mg/dL)	23	Creatinine Clearance: 24 mL/min §
U Sodium (mmol/L)	44	
U Potassium (mmol/L)	7	
U Urea Nitrogen(mg/dL)	325	U Osmolarity: 218 mOsm/kg
U Glucose (mg/dL)	Neg	

*The spot urine and blood serum samples were obtained for analysis simultaneously. **Formulas used for the calculations;** †Fractional Excretion of Solute X (FE X) = [Urine X / Urine Cre] / [Serum X / Serum Cre] x 100, ‡Tubular Reabsorption of Phosphate = 1-[(Urine P / Urine Cre) / (Serum P / Serum Cre)], §Creatinine clearance (mL/min) = [Urine Volume in 24 hours (mL) x Urine Cre (mg/dL)] / Serum Cre (mg/dL) x 1440 (min), ||Urine Osmolality (mOsm/kg) = 2 x [Urine Na (mmol/L) + Urine K (mmol/L)] + [Urine Urea Nitrogen (mg/dL) /2.8] + [Urine Glucose (mg/dL) / 18].

retinal irregularities. Echocardiography was normal. In brief, he had retinal, skeletal and neurological involvement addition to renal involvement.

His cranial MR imaging showed Molar Tooth Sign (MTS) (Figure 1). All these findings direct us to Joubert Syndrome-Related Disorders (JSRD). Genetic analysis revealed homozygous whole gene deletion in NPHP1 gene. Genetic testing results of him and his family shown as a pedigree in Figure 2.

On follow-up, he had persistent pancytopenia without a sign of an infection. Bone marrow aspiration showed normocellularity without atypical cell infiltration. Cytogenetic analysis in terms of the myelodysplastic syndrome was normal. After one month, leukopenia and neutropenia were improved, but thrombocytopenia showed a fluctuating course. Also, from medical reports, we learnt that his brother with JSRD had thrombocytopenia with hypoplastic bone marrow.

He progressed to ESKD after four months. Hemodialysis was chosen by his parents as the renal replacement therapy during waiting for cadaveric renal transplantation.

DISCUSSION

Polyuria in children is defined as urine output exceeding 2 L/ m²/day or 4 mL/kg/hour. It can be driven either by solute or water diuresis, or a combination of both. Determining which mechanism causing diuresis could lead the physician to

underlying pathology. Here, we report an adolescent boy presented with polyuria. In our case, polyuria was caused by concentration defect of urine due to CKD. Presentation at adolescence age with CKD, history of consanguineous parents, detection of tubular dysfunction and small kidneys with cystic lesions on corticomedullary junction primarily refer to nephronophthisis (NPHP).

Nephronophthisis is an autosomal recessively inherited chronic interstitial nephritis which is a distinct genetic cause of ESKD in children. The incidence ranges from 1/50.000 to 1/900.000 worldwide (2). Common findings of NPHP are polyuria, polydipsia, nocturia and enuresis due to salt wasting and concentration defect. It is classified as infantile, juvenile and adolescent forms, according to the age of progression to ESKD. The juvenile form is the most common form of the disease with the development of ESKD at a mean age of 13 years. Renal ultrasound may be normal, but parenchymal hyperechogenicity and loss of corticomedullary differentiation are often observed. At later stages, small cysts are present in the medulla and corticomedullary junction (3). Clinical and ultrasonographic findings of our case were suitable for Juvenile NPHP.

Studies have shown that the mutations that cause dysfunction of primary cilia are responsible for the development of NPHP. This leads to the recognition of the disease as a ciliopathy (4). Genetic heterogeneity and phenotypic variability cause the main difficulty in defining ciliopathy disorders. More than twenty genes are defined in NPHP so far. The most common mutation

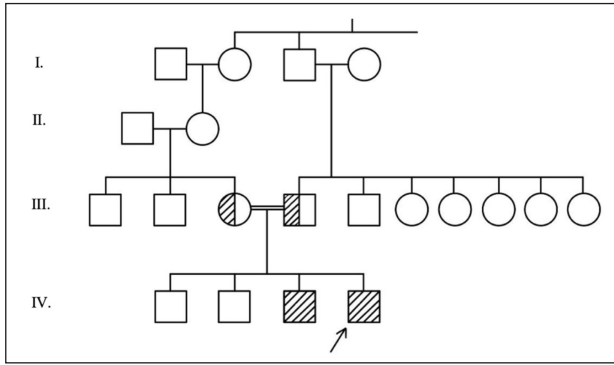


Figure 2: The pedigree of the patient.

detected in approximately 20% of the cases is the NPHP1 gene deletion, as in our case (5).

Nephronophthisis may present as a component of some syndromes and in association with other ciliopathy disorders. Most patients with NPHP1 deletions have no extrarenal findings. However, the mutation is also identified with congenital oculomotor apraxia type Cogan and Senior Loken syndrome and JSRD phenotypes (6,7). Our case had neurological, retinal, renal and skeletal involvements as indicating another ciliopathy component. His cranial MRI showed hypoplasia of cerebellar vermis, elongated, thick superior cerebellar peduncles and abnormally deep interpeduncular fossa. These described features contribute to the radiological view known as the molar tooth sign. Molar tooth sign is seen in Joubert Syndrome and Related Disorders (JSRD) (8). In a case series of 125 nephronophthisis patients, 5 patients (8.9%) with NPHP1 deletion had signs of neurological involvement and just two of them received a diagnosis of JSRD based on molar tooth sign (9).

According to our research, we could not find similar to our case in the literature where NPHP1 deletion and kidney, retina, skeleton, neurological system involvements are all seen together. Besides, the presence of thrombocytopenia, which was not fully explained in the case and his brother, made us think whether the genetic disorder, in this case, is related to a different type of NPHP.

Currently, there is no effective treatment available for NPHP. Supportive treatment for chronic renal failure, renal replacement therapies like dialysis and transplantation are considered according to the stage of kidney disease. Treatments targeted towards the collecting duct may be available for future use. These include vasopressin-2 receptor antagonists, OPC31260, Rapamycin (mTOR inhibitor), triptolide and roscovitine (cyclin-dependent kinase inhibitors) (10-13).

CONCLUSION

A patient presented with polyuria may become a diagnostic challenge. For the correct diagnosis, not just the renal findings,

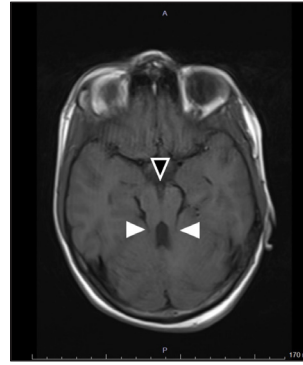


Figure 1: Cranial MRI of the case. Axial T1-weighted image of cranial MR shows the deepened interpeduncular fossa (open arrowhead) and elongated thick superior cerebellar peduncles (thick arrowheads).

but also other systemic manifestations should be defined and evaluated together as in nephronophthisis and related ciliopathies.

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