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, altra yatan renal veya sistemik bir hastalığın ilk bulgusu olarak görülebildiği için ayrıntı tanışı güç bir bulgu olabilir. Bilinen herhangi bir hastalığ olmayan adolesan bir erkek çocuk poliüri ile başvurdu. Detaylı öyküsünde öğrenme güçlüğü, konuşma bozukluğu, dengesiz yürüş ve balık bulguları ile polidaktili operasyonu yönüyle saptandı. Akıra evliliği olması ve 21 yaşındaki annenin son dönem böbrek hastalığı teşhisi konan bir erkek kardeşinin olması gibi ipuçları altra yatan genetik bir etyolojiye işaret ediyordu. Fizik muayenede pektus excavatum, atipik yüz görünümü, dizartrisi, hipotoni, rotatuar nistagmus, bozulmuş tandem yürüş, retinada hiperpigmente düzensizlikler görüldü. Labotatuar tıbbi kriterleri sonucunda tüberlopatinin eşlik ettiği Evre-4 kronik böbrek hastalığı olduğu gösterildi. Ultrasonografide ise
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 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.
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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.

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

**REFERENCES**

1. Bhasin B, Velez JC. Evaluation of Polyuria: The Roles of Solute Loading and Water Diuresis. Am J Kidney Dis 2016;67:507-11.
2. Simms RJ, Hynes AM, Eley L, Sayer JA. Nephronophthisis: a genetically diverse ciliopathy. Int J Nephrol 2011;2011:527137.
3. Blowey DL, Querfeld U, Geary D, Warady BA, Alon U. Ultrasound findings in juvenile nephronophthisis. Pediatr Nephrol 1996;10:22-4.
4. Watnick T, Germino G. From cilia to cyst. Nat Genet 2003;34:355–6.
5. Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: disease mechanisms of a ciliopathy. J Am Soc Nephrol 2009;20:23–35.

6. Betz R, Rensing C, Otto E, Mincheva A, Zehnder D, Lichter P, et al. Children with ocular motor apraxia type Cogan carry deletions in the gene (NPHP1) for juvenile nephronophthisis. J Pediatr 2000; 136: 828–31.

7. Castori M, Valente EM, Donati MA, Salvi S, Fazzi E, Procopio E, et al. NPHP1 gene deletion is a rare cause of Joubert syndrome related disorders. J Med Genet 2005; 42; e9.

8. Gleeson JG, Keeler LC, Parisi MA, Marsh SE, Chance PF, Glass A, et al. Molar tooth sign of the midbrain- hindbrain junction occurrence in multiple distinct syndromes. Am J Med Genet A 2004;125:125-34.

9. Caridi G, Dagnino M, Rossi A, Valente EM, Bertini E, Fazzi E, et al. Nephronophthisis type 1 deletion syndrome with neurological symptoms: Prevalence and significance of the association. Kidney Int 2006;70:1342-7.

10. Gattone VH, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003;9:1323–6.

11. Tobin JL, Beales PL. Restoration of renal function in zebrafish models of ciliopathies. Pediatr Nephrol 2008;23:2095–9.

12. Leuenroth SJ, Bencivenga N, Igarashi P, Somlo S, Crews CM. Triptolide reduces cystogenesis in a model of ADPKD. J Am Soc Nephrol 2008;19:1659-62.

13. Bukanov NO, Smith LA, Klinger KW, Ledbetter SR, Ibraghimov-Beskrovnaya O. Longlasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. Nature 2006;444:949-52.