Chronic Kidney Disease in a Boy with Enuresis: The Diagnosis Behind the Smile

Enürezis ile Başvuran Erkek Çocukta Kronik Böbrek Hastalığı: Gülümsemenin Ardındaki Tanı

Belde KASAP DEMİR[1]
Robert HALL[2]
William G NEWMAN[2]

1 İzmir Katip Çelebi University, Faculty of Medicine, Department of Pediatric Nephrology, İzmir, Turkey
2 University of Manchester, Manchester Centre for Genomic Medicine, Manchester, England

ABSTRACT

A 13-year-old boy was admitted with enuresis. He had no history of urinary tract infection, daytime incontinence or fecal incontinence. Previously performed ultrasound had revealed bilateral hydroureteronephrosis and trabeculated bladder. Voiding cystoureterography had detected multiple diverticuli without reflux. Renal scan had revealed reduced uptake with multiple renal scarring and diuretic renogram had shown bilateral obstruction. Urodynamic evaluation had revealed non-compliant hyperactive bladder and significant residual volume. Laboratory tests had been consistent with chronic kidney disease and he had been referred to our clinic. On admission, he was diagnosed with urofacial syndrome, due to the grimacing expression while trying to smile on physical examination, and the diagnosis was further confirmed by genetic analysis during follow-up. This case was reported to increase the awareness of physicians about this rare cause of chronic kidney disease as early diagnosis is mandatory. Asking the patient to smile would easily lead to the diagnosis.

KEY WORDS: Urofacial syndrome, Chronic kidney disease, Enuresis, Children

ÖZ

On üç yaşında erkek olgu geceleri idrar kaçırma şikayeti ile başvurdu. Geçirilmiş idrar yolu enfeksiyonu, gündüz idrar kaçırma ya da dışkı kaçırma gibi şikayetlerinin olmadığını belirtti. Başvuru öncesi yapılan ultrasonografisinde bilateral hidroüreteronefrozunun olduğu ve mesanesinin trabeküle olduğu görüldü. İşeme sistoüretrogramında reflüsünün olmadığı ancak çoklu divertiküllerinin olduğu gözlendi. Diüretik renogramında bilateral obstrüksiyonu izlendi. Ürodinamik değerlendirmede kompliyansı düşük hiperaktif mesanesinin olduğu ve anlamlı miktarda rezidüel idrarının kaldığı görüldü. Laboratuvar testlerinin kronik böbrek hastalığı ile uyumlu olması üzerine olgu kliniğimize yönlendirildi. Başvurusunda olgunun fizik bakısında gülmeye çalışırken yüzünde gelişen ağlama/buruşma ifadesi nedeni ile ürofasyal sendrom tanısı aldı ve izleminde tanısı genetik olarak doğrulandı. Olgu, erken tanının önemli olduğu son dönem böbrek yetmezliğinin nadir nedenlerinden olan ürofasyal sendrom konusunda hekimlerin farkındalığını arttırmak amacı ile sunulmuştur. Hastadan sadece gülümsemesini istemek kolaylıkla tanıya götürmektedir.

ANAHTAR SÖZCÜKLER: Ürofasyal sendrom, Böbrek yetmezliği, Enürezis, Çocuk

INTRODUCTION

Urofacial syndrome (UFS), also known as Ochoa syndrome, is a rare autosomal recessive disorder characterized by non-neurogenic bladder dysfunction (BD) associated with an inverted facial expression (1,2). Early recognition is mandatory to prevent further damage to the kidneys (1-3). We report an adolescent boy with UFS, who had severe renal damage due to delayed diagnosis.

CASE SUMMARY

A 13-year-old boy was admitted to clinic with enuresis. He denied any previous urinary tract infection, daytime incontinence or any history of constipation. His parents were third-degree cousins. He had been detected in another clinic and

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Correspondence Address:
Belde KASAP DEMİR
İzmir Katip Çelebi Üniversitesi, Tıp Fakültesi, Çocuk Nefroloji Bilim Dalı, İzmir, Turkey
Phone : +90 532 503 46 75
E-mail : beldekasap@gmail.com

the radiological tests were as follows: Renal ultrasonography revealed bilateral increased kidney sizes, renal echogenicities, severe bilateral hydronephrosis and tortuous ureters. Renal parenchymal thickness was 6 mm in the left kidney. Bladder wall was severely thickened, trabeculated, and there were several diverticuli. Voiding cystoureterography revealed no reflux, but confirmed the trabeculated bladder and multiple diverticuli with a maximum diameter of 4 cm (Figure 1). Dimercaptosuccinic acid (DMSA) scan demonstrated bilateral multiple cortical defective areas with a differential count of 67% for the right and 33% for the left kidney (Figure 2). Diuretic renogram showed bilateral obstruction. Urodynamic evaluation revealed poorly compliant hyperactive bladder with high voiding pressures and significant residual volume with dyssynergia. He was then referred when laboratory findings showed high levels of urea and creatinine.

On admission, the height was 165 cm (75-90 centile) and weight 47 kg (25-50 centile). The blood pressure was 100/70 mm Hg (95 centile: 129/83 mm Hg). The abdomen was soft, there was no hair tuft or bony defect on the lower back. Deep tendon reflexes and the rest of his physical examination were normal. However, it was noticed that he was grimacing when he attempted to smile (Figure 3).

Complete blood cell count on admission was normal. Urinalysis revealed pH 6, specific gravity 1010, protein (-) with few leukocytes on microscopic examination. Other laboratory findings were as follows: blood pH 7.29, pCO_2 34 mm Hg, HCO3 16 mmol/L, urea 95 mg/dL, serum creatinine 3.34 mg/dL, sodium 134 mmol/L, potassium 4.9 mmol/L, uric acid 6.9 mg/dL, calcium 7.5 mg/dL, phosphorus 5.4 mg/dL, alkaline phosphatase 367 U/L, parathyroid hormone 139.3 pg/mL (normal 12-65), 25 (OH) vitamin D 18.5 ng/mL (normal 10-80). Fractional sodium excretion was 7.6% (normal<1%), fractional potassium excretion was 49.4% (normal<15%), tubular phosphorus reabsorption was 75% (normal>80%), calcium excretion was 1.92 mg/kg/d (normal<4), protein excretion was 9.6 mg/m^2/h (normal<4). Glomerular filtration rate (GFR) calculated according to the Schwartz formula was 34.6 ml/min/1.73 m^2 and creatinine clearance calculated using 24 hour collected urine was 14 mL/min/1.73 m^2. When the radiographic and laboratory findings were evaluated together with the grimacing gesture, he was thought to have chronic kidney disease due to UFS.

In this patient, we identified a homozygous nonsense mutation [c.429T>A, p.(Y143*)] in exon2 of the *HPSE2* gene (2). Both parents were, as expected, heterozygous for the mutation (Figure 3). He was started on antibiotic prophylaxis, anticholinergics and clean intermittent catheterization.

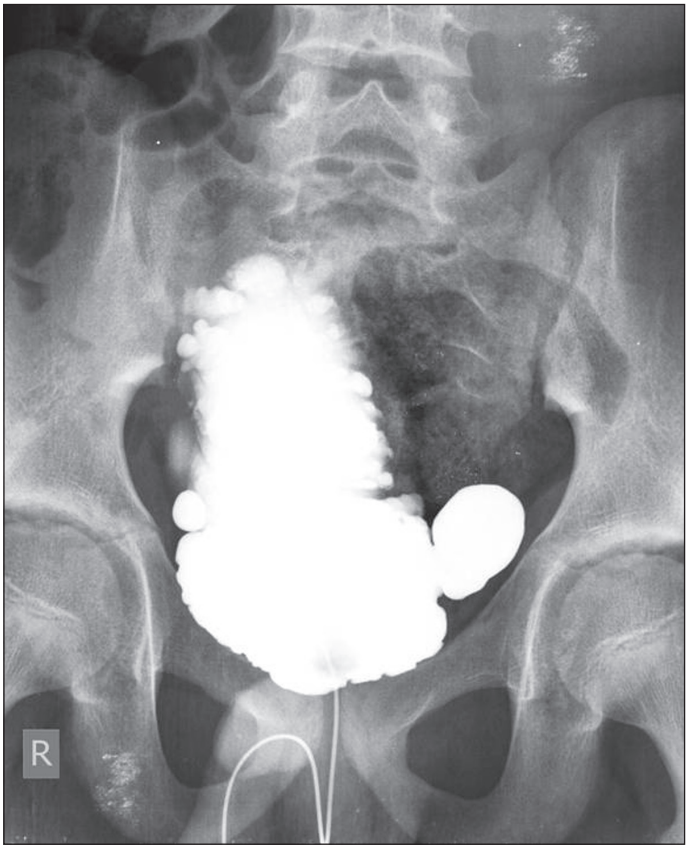

Figure 1: *Voiding cystoureterography revealing neurogenic bladder with trabeculation and multiple diverticuli.*

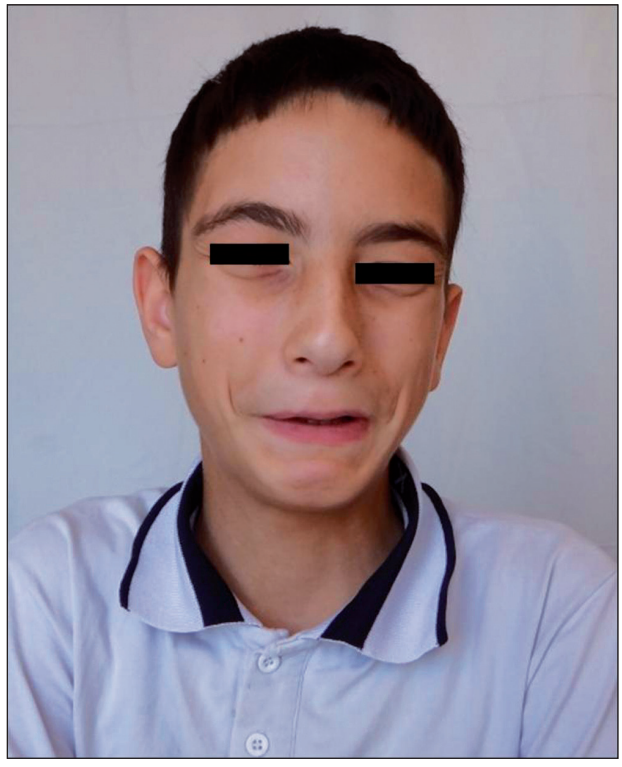

Figure 2: *Characteristic inversion of facial expression appearing when the patient was asked to smile.*

DISCUSSION

Urofacial syndrome is the association of a non-neurogenic BD with a typical facial expression, which may lead to renal damage if left untreated (4). Facial expression is normal at rest, the patient has grimacing when attempted to smile and has no suffering expression but normal facial expression while crying (5). It has been hypothesized that this genetic disorder causes a simultaneous effect both in "laughing and crying centers" and the "micturition center", which have close proximity in upper pons (5). Some others proposed that two separate lesions affecting facial nerve nucleus and sacral cord motor nuclei innervating the external sphincter were responsible (6). The most recent studies in animal models indicate a peripheral autonomic neuropathy for BD in UFS (7,8).

It is reported that UFS is an autosomal recessive disease and patients with Ochoa Syndrome usually have a genetic background (5). Thus, a positive family history should also alert the physicians. Our patient had no relative with a similar problem but his parents were third-degree cousins.

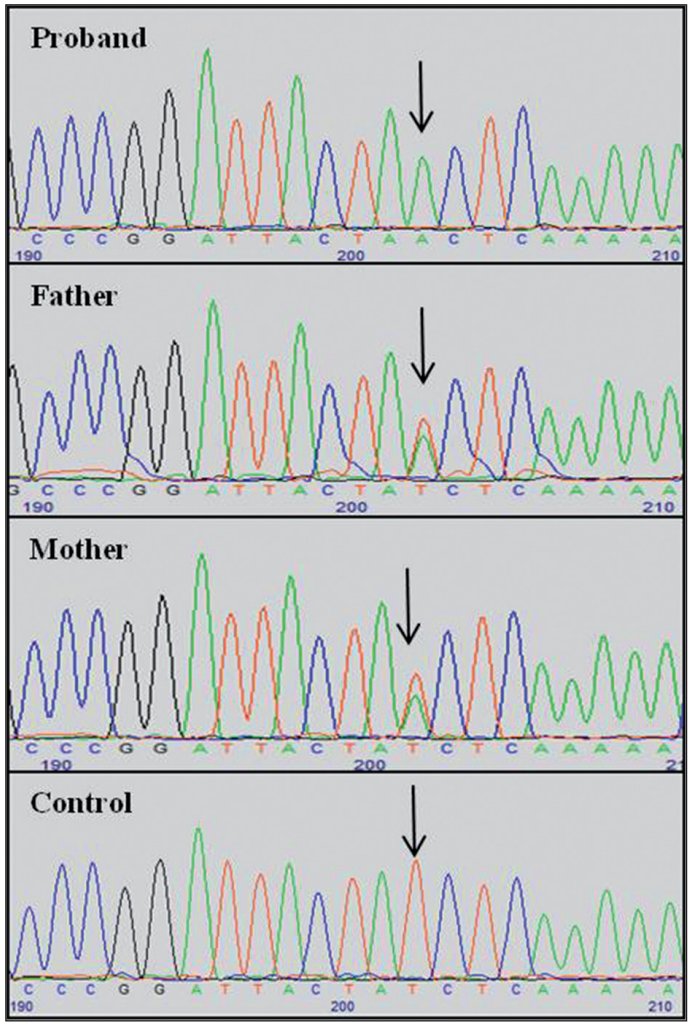

Figure 3: *Sequence traces shows homozygous c.429T>A (p.Tyr143*) in exon 2 of HPSE2. Sequencing of exon 2 in both parents was carried out to confirm they were both heterozygotes.*

Mutations have been detected in several families with UFS. Initially, two different groups defined the same biallelic mutation in *HPSE2 (chromosome 10q24.2)* gene and published their studies on the same journal at the same time (1,3). Afterwards, biallelic *LRIG2 (chromosome 1p13.2)* mutations were identified in UFS patients (2). However, there are still some UFS families the members of which had none of these mutations. In addition, some family members with the same mutation may have no grimacing but BD or may have no BD but just characteristic grimacing while their siblings have full-blown UFS in some series (3,9).

Patients with *HPSE2* mutations have been classified as "UFS1" and those with *LRIG2* mutations has been classified as "UFS2" (10). Both *HPSE2* and *LRIG2* transcripts were detected in nerve trunks invading the first trimester bladder (2,3,11). The exact biological function of HPSE2 and LRIG2 is not clear, but it was hypothesized that both proteins play a key role in the regulatory network of bladder function (11).

The nonsense mutation in *HPSE2* gene of our patient has been formerly defined in two Turkish brothers (8). They both had large trabeculated bladder without VUR and one also had high Scr as in our patient. Aydogdu et al. reported 16 and 19 year old brothers with UFS, presenting with elevated sCr levels in their series (9). Five of nine cases reported by Varlam and Dippell had CRF and one had end-stage kidney disease (12). It was noted that patients diagnosed at school age or later generally exhibit a greater degree of kidney damage (5).

Cases with UFS usually have urgency, urge incontinence, enuresis, recurrent urinary tract infections due to dysfunctional bladder and residual urine in addition to dysfunctional elimination findings including constipation and encopresis (4,5,13). The interesting point in our patient was that although he had severe pathological urinary tract features leading to chronic renal failure, he had no complaints other than enuresis. Thus, although rare, it is reasonable to consider UFS in patients presenting with enuresis and seek for the characteristic inversion of facial expression with smiling. In addition, our case emphasizes the importance of urinary system ultrasonography in the evaluation of patients with enuresis (14).

In conclusion, UFS should be considered in patients with dysfunctional voiding, even in those with only enuresis, particularly in countries where consanguineous marriages are customary. Asking the patient to smile can facilitate early diagnosis, prevent unnecessary interventions and upper tract damage and the diagnosis may be confirmed by genetic testing.

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