An Uncommon Presentation of HDR Syndrome: Distal Renal Tubular Acidosis in a Patient with Sjögren's Syndrome

HDR Sendromunun Nadir Bir Başvuru Şekli: Sjogren Sendromlu Bir Hastada Distal Renal Tübüler Asidoz

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ABSTRACT

HDR syndrome is an autosomal dominant disorder characterized by hypoparathyroidism, sensorineural deafness and renal dysplasia. Haploinsufficiency of GATA3 on chromosome 10p15 is implicated in the pathogenesis of the syndrome. It may manifest itself with clinical features other than the classical triad. Here we report a case of HDR syndrome with concomitant Sjögren's syndrome in a 33-year-old who female presented with distal renal tubular acidosis (dRTA).

KEY WORDS: HDR Syndrome, Distal renal tubular acidosis, Sjögren's Syndrome

ÖZ

HDR sendromu Hipoparatroidism, sağırlık ve renal disgenesizle karakterize otomozal dominant geçişli genetik bir hastalıktır. Hastalığın patogenezinden 10p15 kromozomundaki GATA3 bozukluğu sorumlu tutulmaktadır. HDR sendromu klasik triadının dışında nadirde olsa farklı klinik bulgularla başvurabilir. Burada 33 yaşında, distal renal tübüler asidozla başvuran HDR sendromuna eşlik eden sjogren sendromlu bir olgu sunulmaktadır.

ANAHTAR SÖZCÜKLER: HDR Sendromu, Distal renal tübüler asidoz, Sjögren Sendromu

HDR syndrome is an autosomal dominant disorder characterized by hypoparathyroidism, sensorineural deafness and renal dysplasia (1). Haploinsufficiency of GATA3 on chromosome 10p15 is implicated in the pathogenesis of the syndrome (2,3). Approximately two thirds of the patients present with the classic triad of hypoparathyroidism, sensorineural deafness and renal dysgenesis (4). Frequently associated renal and urinary abnormalities include cystic kidney disease, renal dys-, hypo- or aplasia, pelvicalyceal deformity, vesicoureteral reflux, renal scarring, proteinuria, and hematuria (1,4). Tubular dysfunctions such as nephrocalcinosis and renal tubular asidosis, on the other hand, are quite rare (5).

Sjogren's Syndrome (SS) is a progressive systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands (6,7). Autoimmunity, viral infections, and genetic factors play a role in the pathogenesis of this disorder (6,7). In the literature, there are reports of various autoimmune and genetic disorders that accompany HDR syndrome including autoimmune polyendocrine syndromes, Hirschsprung's Disease, DiGeorge Syndrome, and diseases with central nervous system involvement (5, 8-10). A common genetic pathway and/or the regulatory effect of GATA3 on lymphocyte functions are incriminated in the pathogenesis. Association with SS, however, is unknown. Here, we describe a case of HDR syndrome accompanied by SS, admitting to hospital with clinical manifestations of dRTA.

CASE

A 33-year-old female patient presented to the hospital with complaints of fatigue and generalized pain especially localized

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in hip and waist area. She was referred to the nephrology department due to hypokalemia and metabolic acidosis found on the laboratory examination. Her medical history revealed hearing loss and SS. Her medication included corticosteroid and NSAII treatment for 18 months. Her vital signs were in the normal range. She had limited range of motion in hip and the physical examination was otherwise normal. Laboratory studies revealed the following data: serum urea: 34 mg/dL, serum creatinine: 1.2 mg/dL, serum sodium (Na):136 mmol/L, serum chloride (CL) 118 mmol/L, serum potassium (K):2.81 mmol/L, venous blood gas analysis was as follows: pH: 7.26, pco2: 28.7, HCO3:13 mmol/L, anion gap: 5. Laboratory data are listed in the Table I. Serum PTH level was low in repeated tests. Urinalysis revealed a urine pH of 6.5 and microscopy was normal. She had a creatinine clearance of 35 mL/min in 24-hour urine collection. Urinary protein excretion was 443 mg/day whereas calcium excretion was 521 mg/day (Normal range; 100-300).

The patient was diagnosed with distal renal tubular acidosis (dRTA) and started on potassium citrate 3x1/day and sodium bicarbonate 1500 mg/day. Sonographic examination showed multifocal hyperechogenicity in the periphery of the renal pyramids as well as in the corticomedullary junction that was consistent with nephrocalcinosis. A plain radiograph revealed increase in opacity in bilateral kidneys (Figure 1). Other laboratory tests as thyroid function tests, pituitary hormones were also in normal range. Antinuclear antibody titer was 1/360 positive with a homogeneous pattern, anti-dsDNA antibody was negative, and Anti-Ro (SSA) antibody was positive.

Computed tomography scan of the pelvis revealed reduced bone density as well as multiple fracture lines in sacrum and bilateral femur necks were seen. Audiology assessment showed bilateral mild sensorineural hearing loss. Based on clinical manifestations and laboratory evaluations the patient was diagnosed as HDR syndrome associated with distal RTA. Genetic analysis was not performed. The patient was discharged in good clinical condition with an outpatient follow up recommendation.

Table I: Laboratory data of our patient.

Test	Measured level	Normal range
Hemoglobin	12.4	11-16
White blood cells (10^3/µl)	4480	4.000-10.000
Platelet (10^3/µl)	221.000	150.000-400.000
Erythrocyte sedimentation rate	14	
C-Reactive Protein	0.3	0.0-0.34
Blood Urea Nitrogen (mg/dL)	34	10-50
Serum Creatinine(mg/dL)	1.2	0.5-0.9
Serum Calcium (mg/dL)	8.1	8.1-10.7
Serum Phosphor (mg/dL)	3.1	2.6-4.5
Serum Sodium (mEq/L)	136	137-146
Serum Potassium (mEq/L)	2.81	3.5-5.2
Serum Chloride (mEq/L)	118	97-108
Total Protein (gr/dL)	6.8	6.6-8.8
Serum Albumin (g/dL)	3.8	3.5-5.5
Alkaline phosphatase (U/L)	350	35-105
Parathyroid hormone (PTH) (pg/mL)	9.1	15-88
Blood pH	7.26	7.35-7.45
Blood pCO2 (mmHg)	28.7	
Blood HCO3 (mmol/L)	13	22-26
Anion gap (mEq/L)	5	<11

DISCUSSION

HDR syndrome is a genetically inherited disorder in the pathogenesis in which haploinsufficiency of glutamyl amidotransferase-subunit A (GATA) on chromosome 10p15 plays an important role. Mutations in different locations of

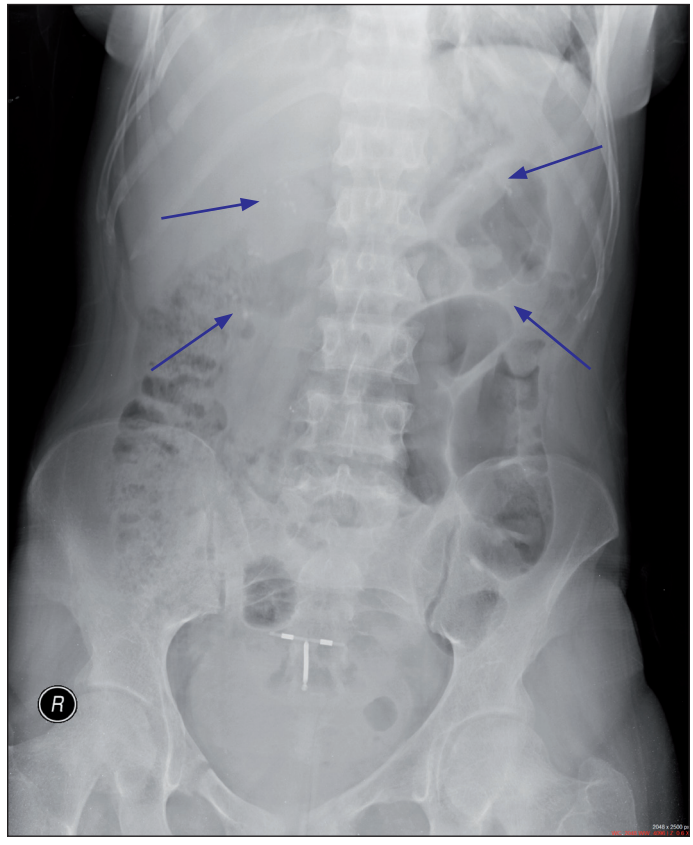

Figure 1: *Plain radiograph of the patient demonstrating increased opacity in the kidneys.*

GATA3 gene are reported in association with the HDR syndrome (1-3). GATA3 is shown in various studies to have a role in the development of multiple organs including parathyroid glands, inner ear, and kidney, as well as in the thymus and central nervous system (4).

The classic triad, not surprisingly, consists of hypoparathyroidism (parathyroid dysgenesis), sensorineural deafness (the degree of hearing loss, which is usually bilateral, may range from mild to severe), and renal disease. Genetically inherited disorders such as Hirschsprung's Disease, or DiGeorge Syndrome may accompany HDR syndrome through a similar genetic mechanism (8-10). A case of HDR syndrome was described by Muroya et al in a 3-year-old patient associated with type I Diabetes Mellitus (11). The patient was reported to have a heterozygous mutation in GATA3 gene that might have an effect on the functions of lymphocytes leading to an autoimmune destruction of β cells. In another case report by Taslipinar et al., a patient with autoimmune polyglandular syndrome type 3 (i.e, autoimmune thyroiditis, hypergonadotropic hypogonadotropism) was reported to have concomitant HDR syndrome (5). Sjögren's Syndrome is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. Both environmental and genetic factors may contribute to the pathogenesis (6,7). Although a genetic analysis was not performed in our patient, we consider a similar genetic mechanism is likely to be responsible for the association of HDR syndrome with SS.

Different types of renal involvement, if present, observed with HDR syndrome include cystic kidney disease, pelvicalyceal deformity, renal hypo- or aplasia, vesioureteral reflux, renal scarring, proteinuria, and hematuria (4). Distal renal tubular acidosis and bilateral nephrocalcinosis were present in our patient. Distal renal tubular acidosis is a tubular transport defect characterized by inability to secrete hydrogen ions resulting with metabolic acidosis (non-anion gap), hypokalemia, and hypercalcuria (i.e., nephrocalcinosis) (12). Distal renal tubular acidosis may accompany SS in which the renal involvement occurs due to a decrease in H+-ATPase in the intercalated cells of cortical collecting tubules of distal nephron (13). Distal renal tubular acidosis, however may also be hereditary. A case was reported by Taslipinar et al in a patient with HDR syndrome accompanying hereditary dRTA (5). In our patient, dRTA may either be secondary to SS or a component of HDR syndrome.

In summary, a case of HDR syndrome is presented here in a patient with SS history who admitted with clinical manifestations of dRTA. It should be remembered that HDR syndrome may manifest itself with clinical features other than the classical triad and may be associated with autoimmmune and/or genetic disorders.

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