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Case Report / Olgu Sunumu

A Case Report of Familial HDR Syndrome

Ailesel HDR Sendromu: Bir Olgu Sunumu

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Abstract

HDR Syndrome is a rare disease that is inherited autosomal dominantly characterized by a triad of hypoparathyroidism, sensorineural hearing impairment and renal dysplasia. This syndrome is caused by haploinsufficiency of GATA3 gene. We report a family in which two sisters and the father diagnosed with HDR Syndrome because of having hypoparathyroidism and sensorineural deafness. One of these patients had an arachnoid cyst in the left temporal region and cerebellar tonsillar ectopy. The father had horseshoe kidney. A heterozygous GATA3 gene variant (NM_001002295.1 c.1099C>T (p.R367X)) were showed in the sisters. By presenting this case, the clinical and genetic features of HDR Syndrome are reviewed.

Keywords: Hypoparathyroidism; deafness, renal dysplasia; HDR Syndrome

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Özet

HDR Sendromu, hipoparatiroidizm, sensörinöral işitme bozukluğu ve böbrek displazisi triadı ile karakterize, nadir görülen otozomal dominant geçişli bir hastalıktır. Bu sendrom, GATA3 geninin haplo yetersizliğinden kaynaklanır. Burada iki kız kardeşte ve babalarında hipoparatiroidizm ve sensörinöral sağırlık saptanması nedeniyle HDR Sendromu tanısı konulan bir aile sunulmuştur. Kardeşlerden birinde sol temporal bölgede araknoid kist ve serebellar tonsiller ektopi, babada at nalı böbrek vardı. Her iki kız kardeşte heterozigot GATA3 gene varyantı (NM_001002295.1 c.1099C> T (p.R367X)) saptandı. Bu olgu sunularak HDR Sendromunun klinik ve genetik özellikleri gözden geçirilmiştir.

Anahtar Kelimeler: Hipoparatiroidi; sağırlık; renal displazi; HDR Sendromu

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1. Introduction

HDR Syndrome (OMIM 146255), a rare disease that is inherited autosomal dominantly, characterized by a triad of hypoparathyroidism (HP), sensorineural hearing impairment and renal dysplasia (1-13). Barakat et al (1) first defined the HDR Syndrome in two male siblings who had nephrosis, HP and hearing impairment in 1977. It is also called as Barakat Syndrome. The patients with HDR syndrome reported by Barakat et al. (1) died from kidney failure in early childhood. At autopsy, the parathyroid glands were absent in one of whom, and hypoplastic in the other these patients.

HDR Syndrome is caused by haploinsufficiency of *GATA3* gene located on chromosome 10p14-10pter. *GATA3* gene encodes GATA binding zinc finger transcription factors that are essential in the development of mainly parathyroid glands, the inner ear and kidneys and also central nervous system and thymus during the embryonic period. This gene variants are resulted in many malformations in different systems. HDR Syndrome is a genetically and clinically heterogenous disorder. HDR Syndrome is caused by many different *GATA3* intragenic variants and distal 10p deletions involving *GATA3* gen*e* region (2-9,10,11).

We report a family with HDR Syndrome in which we demonstrated a heterozygous *GATA3* gen*e* NM_001002295.1 c.1099C>T (p.R367X) variant.

2. Case Presentation

A 12-year-old girl (Case 1) had been referred to our clinic because her serum calcium level was 7.1 mg/dl during the complaint of tetanic spasms and numbness in the hands. She was born with a birth weight of 4000 g at 40 gestational weeks by a normal vaginal delivery after an unremarkable pregnancy. The patient had a history of convulsion when she was 2.5 years old. Her serum calcium level was normal at that time and magnetic resonance imaging had been revealed a 4x4 cm arachnoid cyst in the left temporal region and cerebellar tonsillar ectopy. She had received phenobarbital therapy for four years after that convulsion. She has been using hearing aids since the age of 3 years.

Physical examination of the patient revealed that body weight: 45 kg (25-50 p.), height: 157 cm (50-75 p.), no facial dysmorphism. Systemic examinations and neuromotor development were in normal limits.

In the laboratory analysis, serum calcium: 5.93 (8.6-10.2) mg/dl, phosphorus: 5.7 (2.7-4.5) mg/dl, alkaline phosphatase: 517 (0-270) U/L, magnesium: 0.9 (0.65-1.05) mmol/l, parathormone: 47 (15-65) pg/ml, BUN: 3.8 mg/dl, creatinine: 0.4 mg/dl. Urinalysis was normal. Echocardiography was normal. Any structural renal abnormalities were not detected with ultrasonography (USG). Oral calcitriol and calcium treatment were started for HP.

In her family history, there was no consanguinity between father and mother. Her 16-year-old sister (Case 2) was being followed up with a diagnosis of HP in our clinic since she was 8 years old. She had admitted with the complaint of tetanic spasms in the hands. She had been suffering from intermittent muscle aches. This sister was born 4100 g at term by an uncomplicated vaginal delivery. She had also hearing impairment and had been using hearing aids since the age of 2. She had no facial dysmorphism. Her growth and neuromotor development were normal. Her renal function tests and urinalysis were within normal limits. Echocardiography and renal USG was normal. She was using oral calcium and calcitriol therapy for HP since the diagnosis.

The father had hearing impairment and was also using hearing aids since childhood. Due to the similar clinical presentations of both siblings and the father, underlying genetic causes were reviewed and HDR Syndrome was considered. The both parents were investigated for HDR Syndrome. HP and horseshoe kidney were determined in the father. Treatment for HP was started to him. The mother did not have any sign of HDR Syndrome.

Informed consent from the children and parents was obtained prior to the genetic analysis. Targeted next generation sequencing of the related *GATA3* gene (INTERGEN Laboratory) showed that previously defined a heterozygous *GATA3* gene pathogenic variant NM_001002295.1 C.1099C>T (p.R367X) in these both sisters (Figure 1). Genetic analysis was not done in the father.

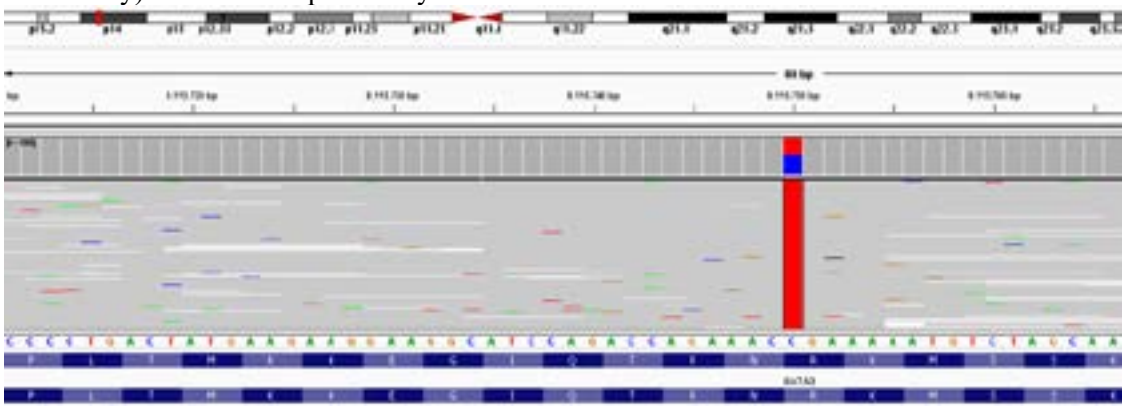

Figure 1. Picture of genetic analysis of Case 1

One of the sisters has been following and receiving treatment of HP for 6 years and one for 14 years. Despite receiving treatment, the drug dose had been adjusted because asymptomatic hypocalcemia varying between 6.6-7.4 mg/dl was found in some routine controls in Case 2 and no additional pathology was observed during their routine controls.

3. Discussion

HDR Syndrome is characterized by HP, sensory neural deafness and renal dysplasia (1-12). This triad of the syndrome is determined in the most patients with HDR Syndrome. The father of our patients had all three phenotypic characteristics. On the other hand, a wide spectrum of genotypic and phenotypic variations has been reported in this syndrome. HP and hearing impairment were identified in our two patients. Some cases who had only two main findings of the syndrome have been also reported as in our two patients (2,4,5).

The age of onset of HP is variable. History of tetanic spasms and convulsions due to hypocalcemia present in the most of the patients. There are reports of severe hypocalcemia observed during the neonatal period (2). Asymptomatic hypocalcemia is also determined in children (2,5,6). Both of our patients presented with the complaint of tetanic spasms in the hands in early childhood. Asymptomatic HP was diagnosed in the father.

Bilaterally, mild to-moderate-severe sensorineural hearing impairment have been observed in the most of patients with HDR Syndrome (1-3,5-12). Fukami et al. (2) reported a four-year-old case of HDR Syndrome with HP and renal pelvic duplication. But he did not have hearing loss. A frame ship mutation in the *GATA 3* gene was determined in this patient. The case with HDR Syndrome reported by Döneray et al. (4) had a p.R367X variant in the *GATA3* gene and showed no deafness. All of our patients had hearing impairment.

Quite variable renal pathologies have been reported in patients with HDR Syndrome such as renal agenesis, renal hypoplasia and dysplasia, , renal ectopy, proteinuria, hematuria, nephrosis, renal tubular acidosis, renal cyst, pelvic duplication, pelvic and horseshoe kidney (1,2,4-9, 11). Horseshoe kidney was detected in our patient's father. However, there are some patients with HDR Syndrome without any both structural and functional renal abnormalities as in our sisters (5,10). These patients should be monitored for impaired renal function that may develop in the future.

Some developmental anomalies of the other systems have been reported in this syndrome

such as dysmorphic facial features, vagina and uterus abnormalities, VSD, pyloric stenosis, clinodactyly, pectus excavatum, scoliosis, central nervous system abnormalities; autism, delayed, psychomotor development, extrapyramidal signs, hemimegalencephaly (8-11). One of our patients had cerebellar tonsillar ectopy and an arachnoid cyst in the left temporal region.

The HDR Syndrome is genetically heterogenous disorder. *GATA3* gene encodes GATA binding zinc finger transcription factors that are essential in the development of mainly parathyroid glands, the inner ear and kidneys and also central nervous system and thymus during the embryonic period (3). Many different intragenic *GATA3* mutations and deletions of 10p have been reported in patients with HDR Syndrome (2-9,10,11). DiGeorge Syndrome is one of the main causes of congenital HP caused by the deletions at chromosome 22q11.2. On the other hand, distal 10p deletions (10p13-10p14) involving *GATA3* gene defined as second DiGeorge region result in the HDR Syndrome and as well as congenital heart defects, immune deficiency, facial dysmorphism. This clinical picture is called as DiGeorge like Syndrome (2,3). Fukami et al. (2) had reported a case with 10p15 deletion presenting all characteristics of the HDR Syndrome and as well as congenital cardiac defects, facial dysmorphism and T-cell immune deficiency. On the other hand, Fukai et al. (12) identified a de novo 10p deletion in a case of DiGeorge Syndrome with facial dysmorphisim, severe progressive renal failure, intellectual disabilities and also findings of HDR Syndrome (HP and deafness) and a deletion in the 22q11 region had been demonstrated in this patient previously. These authors pointed out that 22qdeletion and HDR Syndrome could be found together in a patient. Our patients had no facial dysmorphism and congenital cardiac defect. Genetic analysis revealed a previously defined heterozygous *GATA3* gene NM_001002295.1 c.1099C>T (p.R367X) variant in our both patients.

Murayo et al. (6) reported a case of HDR syndrome that developed type 1 diabetes. They stated that *GATA3* haploinsufficiency has been shown to have a role in lymphocyte development and functions before. So they suggested that there might be a relationship between the development of diabetes and *GATA3* haploinsufficiency in the HDR Syndrome. Our patients did not have any immunological abnormalities or history or clinical finding of any autoimmune disease.
The earliest finding observed in all of our patients was deafness. Patients with familial congenital deafness should be investigated for asymptomatic hypocalcemia/HP as in HDR Syndrome. The patients with HDR Syndrome also should be monitored for some other clinical abnormalities may develop later during their treatment and follow-up.

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