Olgu Sunumu / Case Report

A Novel In-Frame Type Deletion in CHST3 Gene in A Patient with Spondyloepiphyseal Dysplasia

Spondiloepifizyal Displazisi Olan Bir Hastada CHST3 Geninde Yeni İn-frame Tip Delesyon

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Abstract

Spondyloepiphyseal Dysplasia (SED) accompanying with congenital joint dislocations; is a genetic disease with different subtypes that progress with multiple dislocations. It occurs due to a mutation in the CHST3 gene. This syndrome requires long and cascading surgeries, which presents with short-bodied dwarfism, joint dislocations and range of motion (ROM) limitations (knee, hip, elbow). In this case report, we describe an in frame type deletion reported for the first time. We also included the step-by-step surgery program applied to the patient and its results.

Key Words: CHST3, chondrodysplasia, spondyloepiphyseal dysplasia, recessive larsen syndrome

Öz

Konjenital eklem çıkıklarının eşlik ettiği Spondiloepifizyal Displazi (SED); multipl çıkıklarla seyreden farklı alt tipleri bulunan genetik bir hastalıktır. CHST3 geninde mutasyon nedeniyle meydana gelir. Kısa gövdeli cücelik, eklem çıkıkları veya eklem hareket kısıtlılıklarıyla (diz,kalça,dirsek) ortaya çıkan uzun ve basamaklı cerrahiler gerektiren bir sendromdur. Bu vaka raporunda ilk kez bildirilen in frame tip bir delesyonu tanımladık. Hastaya uygulanan basamaklı cerrahi programı ve sonuçlarını da ekledik.

Anahtar Kelimeler: CHST3, kondrodisplazi, spondiloepifizyal displazi, resesif larsen sendromu

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Introduction

SED is an autosomal recessive skeletal dysplasia caused by a mutation in the CHST3 gene (on chromosome 10q22.1). CHST3 is the only gene with pathogenic variants that cause associated skeletal dysplasias. This gene encodes Chondroitin 6-O sulfotransferase. This enzyme regulates proteoglycan sulfation in the extracellular cartilage matrix (1,2). It has been reported that it causes severe chondrodysplasia and progressive spinal damage as a result of loss of function (3). In almost all CHST3 mutations; there are congenital dislocations or limitation of ROM (specific knee, hip and elbow). The most common joint involvement is knee, elbow and hip. Most patients have vertebral irregularities and disc space narrowing. Apart from these, kyphosis, scoliosis, clubfoot are found in half of the patients (4,5). Therefore, if the patient has short stature, knee, elbow and hip dislocations without typical facial appearance, vertebral irregularities (kyphosis, scoliosis) and clubfoot, the diagnosis might be chondrodysplasia CHST3 type with congenital dislocations (6).

Case Report

A 17-day-old boy was admitted to our outpatient clinic due to multipl extremity deformities. The mother was 35 years old, the father was 46 years old. They had a cousin marriage. They had 4 children (2 girls, 2 boys) and our patient was their last child. Our patient had bilateral hip dislocation, bilateral knee dislocation and bilateral pes equinovarus deformities. The first child at the age of 12 also had bilateral hip and knee dislocations. The father of the mother has hip dislocation and her brother has bilateral hip dislocation. According to taken information from family, her brother has 3 children and all three have bilateral hip and knee dislocations and bilateral clubfoot. There is no history of deformity on the paternal side. The birth of the patient at term and normal spontanous vajinal delivery. The birth took place in a private health institution. She had no history of drugs or radiation during her pregnancy. Pregnancy follow-up was done regularly and deformities were detected by USG at 3 months of pregnancy. The family was informed about the deformities, and the choice of curettage was asked to the family. The family did not accept.

The physical examination of the patient revealed bilateral hip dislocation with Ortolani test + and there was a genu recurvatum deformity in his bilateral knees with no flexion and bilateral clubfoot deformity. Height of the patient was within normal limits, hearing test was normal. The result of the pediatric consultation was normal in terms of system examinations.

Radiological images revealed bilateral hip dislocations, bilateral knee dislocations and bilateral bifid humerus. On dysmorphic examination, long philtrum, broad forehead, small and low ears, and short neck were noted. (Figure 1)

After evaluating the current clinical findings, a CHST3 full gene sequence analysis was performed with the consent of the family. As a result of whole gene sequencing analysis, CHST3 (NM_004273) homozygous c.1131_1142delGCCGCTGCAGAA (p.P378_K381del) variant was detected by next generation sequencing analysis. The variant detected was confirmed by Sanger analysis. (Figure 2) It was determined that both parents were heterozygous for the related variant. Our patient was diagnosed SED with congenital joint dislocations, considering the heterozygous parents, the absence of the relevant variant in healthy individuals, the pathogenic evaluation reports of in-silico prediction tools, the evaluation of American College of Medical Genetics and Genomics (ACMG) criteria as PM2, PM4 and PP3, and appropriate clinical findings. The mutation detected is an in-frame deletion in the CHST3 gene, which has been reported for the first time to date, as far as it can be evaluated in the printed literature.

Surgical treatment was planned for the patient and obtained pediatric and anesthesia consultations. Bilateral hip closed reduction with adductor tenotomy was performed in the 2nd month. Bilateral quadriceps tenotomy was performed in the same session. After surgery, the hips were reduced and the knees were flexed up to 90 degrees. During the pelvic cast, the hip molding was in the human position, the knees were at 90 degrees and the feet were dynamic, so the ankle was cast at 10 degrees of dorsiflexion and 45-50 degrees of abduction.

After 8 weeks, the patient's cast was removed under anesthesia. The hips were unstable. Knee movements were 90-100 degrees of flexion. Ankles were dorsiflexed to 15-20 degrees bilaterally, and the foot varus was corrected. The plaster was renewed in the same way. After six weeks, his cast was removed from the outpatient clinic, and a control examination was performed. Bilateral hips were stable, both knees were flexed to 100 degrees, and foot examination was within desired limits (14th week). He was followed up for 3 months full time with Dennis-Brown orthosis. In the following 3 months, he was asked to wear it only during sleep, and she was called for control at intervals of 4-6 weeks.

In the examination of the 46-month-old patient, the bilateral hips were reduced and their range of movements were within natural limits. Bilateral knee flexion ranges from 120-130 degrees. The knees were limited in approximately 20 degrees of flexion. The bilateral patella was deviated laterally. The patient was able to sit, crawl, and stand with support.

The findings obtained in the preoperative radiological examination; Bifid humerus and rhizome in the upper extremity, irregularity in the distal femur and proximal tibial epiphyses in the lower extremities, flattening of the vertebral bodies, irregularity in the articular surfaces (especially in the lumbar region), decrease in the joint space distance, and increase in the interpedicular distance were observed. There was mild scoliosis with left opening and lumbar and cervical kyphosis.

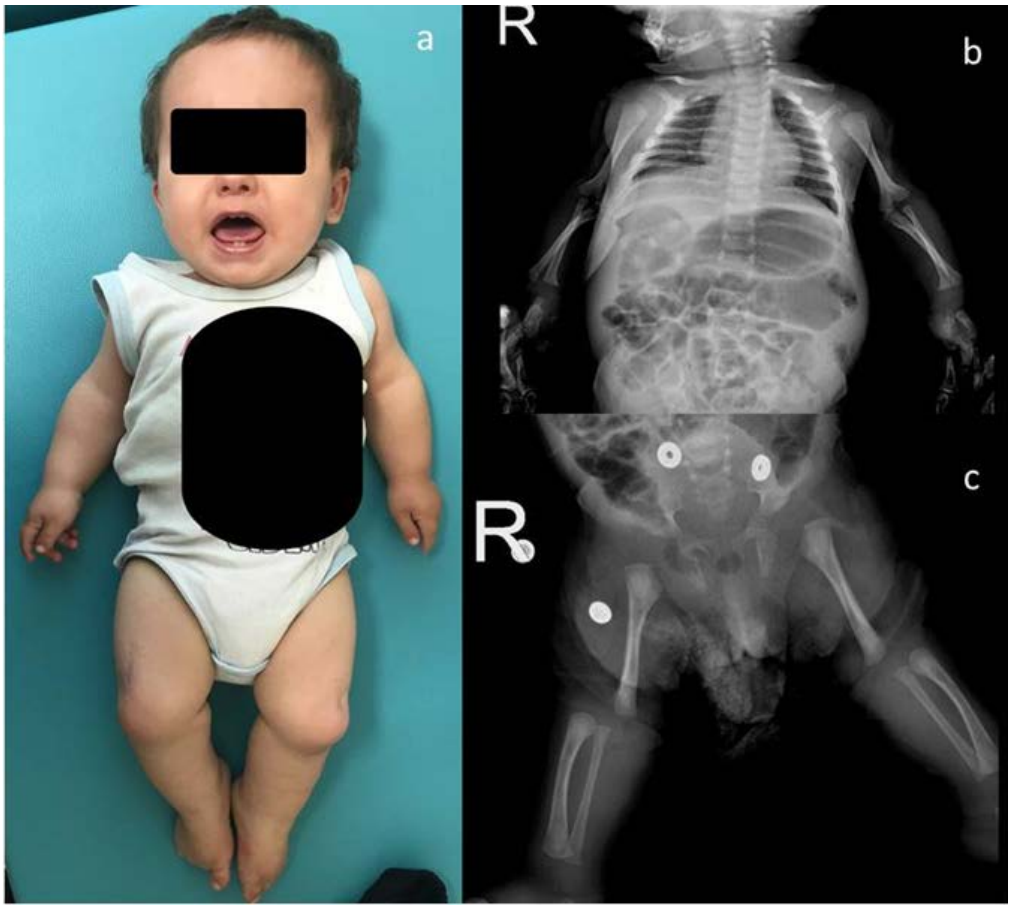

Figure 1: a) Clinical appearence of the patient b) Radiological images of upper extremity and the trunk c) Radiological images of lower extremity

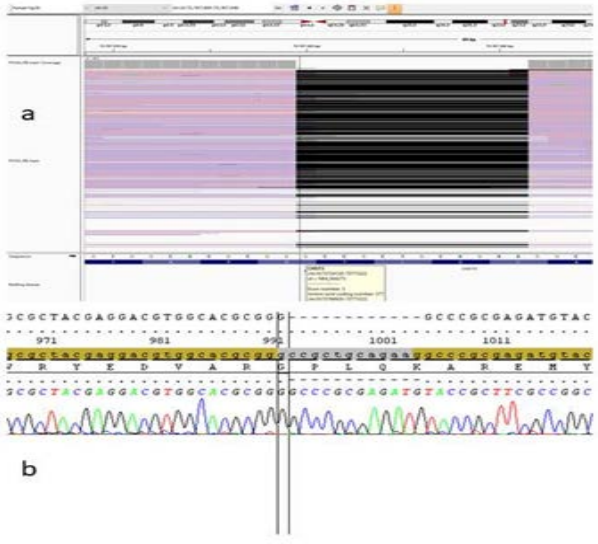

Figure 2. Genetic analysis of CHTS3 gene,
a) Next generation sequencing image for the mutation, b) Sanger confirmation image

As a result of the pediatric consultation, the physical examination of the patient was within natural limits. His height was normal, his hearing was normal, and he had no heart problems. The patient's pes equinovarus recovered completely. Bilateral lateral release and medial plication were performed for patella dislocation. In the follow-up examination, it was observed that patella reduction was achieved, but bilateral knee dislocation continued. When the patient was 51 months old, femoral shortening osteotomy was performed bilaterally for knee reduction. The follow-up of the patient continues. The consent of the family was taken for the patient's photographs and clinical data in order to education and scientific publication.

Discussion

We described a novel in-frame type deletion in the CHST3 gene mutation in this report. Spondyloepiphyseal Dysplasia is a rare condition due to the mutation of this gene. CHST3 gene mutation shows autosomal recessive inheritance and encodes the enzyme chondroitin 6-0 sulfotransferase. The enzyme is involved in proteoglycan sulfation in the extracellular cartilage matrix. As a result of loss of function causes progressive spondylodysplasia in early childhood (3). In the patients' clinic, normal bone age, short stature at birth, rhizomelic shortness of the extremities (proximal shortness of the femur and humerus), multiple joint dislocations (knee, hip and elbow), joint mobility limitation,

clubfoot are frequently observed. Kyphosis (especially cervical), often scoliosis may develop. Cardiac anomalies may occur (minor heart valve dysplasia). Generally mental status, vision and hearing are normal. Although infrequently tooth anomalies (microdontia, delayed teething), inguinal hernia, gastric volvulus, pectus deformity have been reported. Radiologically, progressive spondyloepiphyseal dysplasia with joint anomalies; Mild dysplasia in generalized small epiphyses, delayed ossification of femoral head and neck epiphyses, coxa valga are observed. Premature osteoarthritis can be observed. Spinal anomalies, increases interpedicular distance between T2-L1 or L2, platyspondyl (flattened vertebral body), coronal cleft throughout the lumbar region. Other rare skeletal findings; camptodactyly (PIP flexion deformity), mild brachydactyly, short metacarpals (2,7,8). Diagnosis is made by characteristic clinical and radiological findings and becomes certain with molecular genetic testing. The phenotype was first described in 9 individuals from 2 families in Oman (3,9). CHST3-associated skeletal dysplasia is autosomal recessive. Each sibling is affected by 25%. 50% carriers are asymptomatic, 25% are unaffected. There is no genotype-phenotype correlation. The phenotype shows a homogeneous picture regardless of CHST3 variants (2). It is most often confused with Larsen Syndrome which is characterized by multiple joint dislocations and differed from SED with dysmorphic facial appearance (forward protruding forehead, nasal depression, malar flattening, orbital width), spatulate thumb, accelerated carpal ossification, cleft palate, hearing loss (1,10).

Surgical correction is the only treatment modality for abnormal joint structures in SED. However, it often provides partial improvement, multiple procedures are needed. Physical therapy is not effective. High-grade joint-loading activities and obesity should be avoided (2).

In this case, we considered the diagnosis of the patient as SED clinically and radiologically and confirmed it with genetic examination. We started step-by-step conservative and surgical procedures appropriate for the age of our patient. As a result of genetic analysis, we found that our patient, in whom we detected a CHST3 gene mutation, had an in-frame deletion in the CHST3 gene, which has been reported for the first time. We think that it can be a reference in terms of diagnosis and surgical follow-up.

Informed Consent: *Written informed consent was obtained from the patient's first-degree relatives for this case report.*

Author Contributions:

Concept: B.V.Ç., S.S.

Literature Review: B.V.Ç., E.G.

Design : B.V.Ç.

Data acquisition: B.V.Ç., E.G.

Analysis and interpretation: B.V.Ç., E.G., S.S.

Writing manuscript: B.V.Ç.

Critical revision of manuscript: B.V.Ç., E.G.

Conflict of Interest: *The authors have no conflicts of interest to declare.*

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