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CASE REPORTS / *OLGU SUNUMLARI*

Importance of Recognising Dysmorphic Features: Trichorhinophalangeal Syndrome

Dismorfik Özellikleri Tanımanın Önemi: Trikorinofalangeal Sendrom

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ABSTRACT

Trichorhinophalangeal syndrome is a rare disease caused by variations in the TRPS1 gene. The disease is characterized by slowly growing hair/nail and skeletal malformations, including brachydactyly and cone-shaped epiphysis. Hip problems are frequently observed, and musculoskeletal pain associated with hypermobility may also occur. Recognition of dysmorphic features associated with this rare disease may lead to prompt diagnosis and improved care of these patients. Herein, we present a paediatric case with longstanding complaints diagnosed with the trichorhinophalangeal syndrome.

Keywords: Brachydactyly, Cone-Shaped Epiphysis, Hypermobility, Legg-Calve-Perthes, Mitral Valve Prolapse, Trichorhinophalangeal Syndrome

ÖZ

Trikorhinofalangeal sendrom, TRPS1 genindeki mutasyonların neden olduğu nadir bir hastalıktır. Hastalık, koni şeklindeki epifiz ve brakidaktiliyi içeren iskelet malformasyonları ve yavaş büyüyen saç ve tırnak ile karakterizedir. Kalça problemleri sıklıkla gözlenir ve hipermobiliteye bağlı kas-iskelet ağrıları da ortaya çıkabilir. Bu nadir hastalıkla ilişkili dismorfik özelliklerin tanınması, bu hastaların hızlı teşhis edilmesini ve daha iyi izlenmesini sağlayabilir. Burada uzun süredir şikayetleri olan ve trikorinofalangeal sendrom tanısı alan bir pediatrik olguyu sunuyoruz.

Anahtar Kelimeler: Brakidaktili, Hipermobilite, Trikorinofalangeal Sendrom

INTRODUCTION

Musculoskeletal complaints are common in children with joint hypermobility. Syndromes associated with this condition had to be kept in mind, especially in patients with dysmorphic features. Marfan syndrome and Ehlers-Danlos syndrome are well-known causes of joint hypermobility syndromes leading to musculoskeletal complaints [1]. Besides these well-known diseases, trichorhinophalangeal syndrome (TRPS) is a rare autosomal dominant disease and is characterized by hypermobility, musculoskeletal complaints, and dysmorphic features [2]. Three different types of TRPS were described: TRPS type I (OMIM #190350), TRPS type II (OMIM #150230), also known as Langer Giedion syndrome (LGS), and TRPS type III (OMIM #190351). The characteristic features of TRPS type I include sparse scalp hair, a rounded nose, a long flat philtrum, and a thin upper lip. Individuals with TRPS type I often have short stature and skeletal abnormalities, including cone-shaped epiphyses in the fingers and toes. TRPS type II is clinically differentiated from TRPS types I and III by the presence of exostoses, distinct facial features, and occasional intellectual disability, and is associated with continuous gene deletions of *EXT1* and *RAD21* [3]. Individuals with TRPS type III have features similar to those with type I, but additionally often have brachydactyly and are generally shorter in stature [4].

Herein, we present a TRPS case with musculoskeletal complaints caused by a de novo variation in the *TRPS1* gene.

CASE REPORT

An 11-year-old girl with a four-year history of joint pain in her ankles, wrists, and hips applied to our Department of Paediatric

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Rheumatology. She did not describe any swelling or stiffness in any joint and had no history of fever or weight loss. Besides joint pains, she had complaints of slowly growing hair and nails with a small appearance of hands and feet. She had been evaluated several times by outpatient clinics of dermatology, paediatric endocrinology, and paediatric gastroenterology in different hospitals for 4 years, but had not been diagnosed. She was the first child of non-consanguineous parents and was born at full term. Her motor and cognitive development were normal. She had been diagnosed with Legg-Calve Perthes disease about three years ago, but no specific treatment had not been recommended. Her height was 140 cm with a -0.79 standard deviation score (SDS), and her weight was 37 kg with a -0.16 SDS. Her intelligence appeared normal. Physical examination revealed thin and sparse hairs, eyebrows, and eyelashes. The nose was broad and pear-shaped, with a moderately long philtrum. Short and stubby hands with lateral deviations and deformations of the interphalangeal joints and brachydactyly were observed. Also, her feet were small for her age with brachydactyly (Figure 1). Joint hypermobility in bilateral thumbs, wrists, ankles, knees, and elbows was observed, and the Beighton score was calculated as 6. Otherwise, her physical examination was unremarkable. X-ray of both hands showed cone-shaped epiphyses of the middle phalanges. Besides, symphalangism was observed in the bilateral fifth proximal interphalangeal joints (Figure 2). Laboratory evaluation revealed a normal range of blood cell counts with a normal peripheral blood smear investigation. C-reactive protein and erythrocyte sedimentation rates were within normal ranges, and antinuclear antibody and rheumatoid factor were negative. The echocardiographic examination performed due to dysmorphic features and hypermobility revealed mitral valve prolapse (MVP).

Based on dysmorphic physical and radiological findings, variation in the *TRPS1* gene was suspected. Genetic analysis revealed heterozygous c.3253A>C/p.(Met1085Leu) variation that showed the TRPS type I. The variant analyses in both parents revealed normal results, indicating a de novo occurrence in our patient.

DISCUSSION

Trichorhinophalangeal Syndrome is caused by the variations in the *TRPS1* gene mapped to 8q24.1 with or without continuous gene deletions of *RAD21* and *EXT1*. To date, different variations in chromosome 8q24 were reported to be linked to TRPS [2-3]. Although TRPS is inherited with an autosomal dominant pattern, in our case, the disease was caused by a novel de novo missense variation. *TRPS1* gene encodes a zinc-finger transcription factor and has a role in kidney and hair follicle development, epithelial-mesenchymal transition, and contributes to bone formation and mineralization [2,5].

Characteristic features of TRPS include short stature, sparse, fair, and slowly growing hair, distinctive facial features with large prominent ears, rarefaction of lateral eyebrows, pear-shaped nasal tip, high philtrum, and thin upper lip [2]. Our case had most of the characteristic features of the disease. In most cases, affected individuals exhibit skeletal abnormalities, including brachydactyly and clinodactyly, short metacarpals, phalanges and metatarsals, and hip joint malformations. Similar

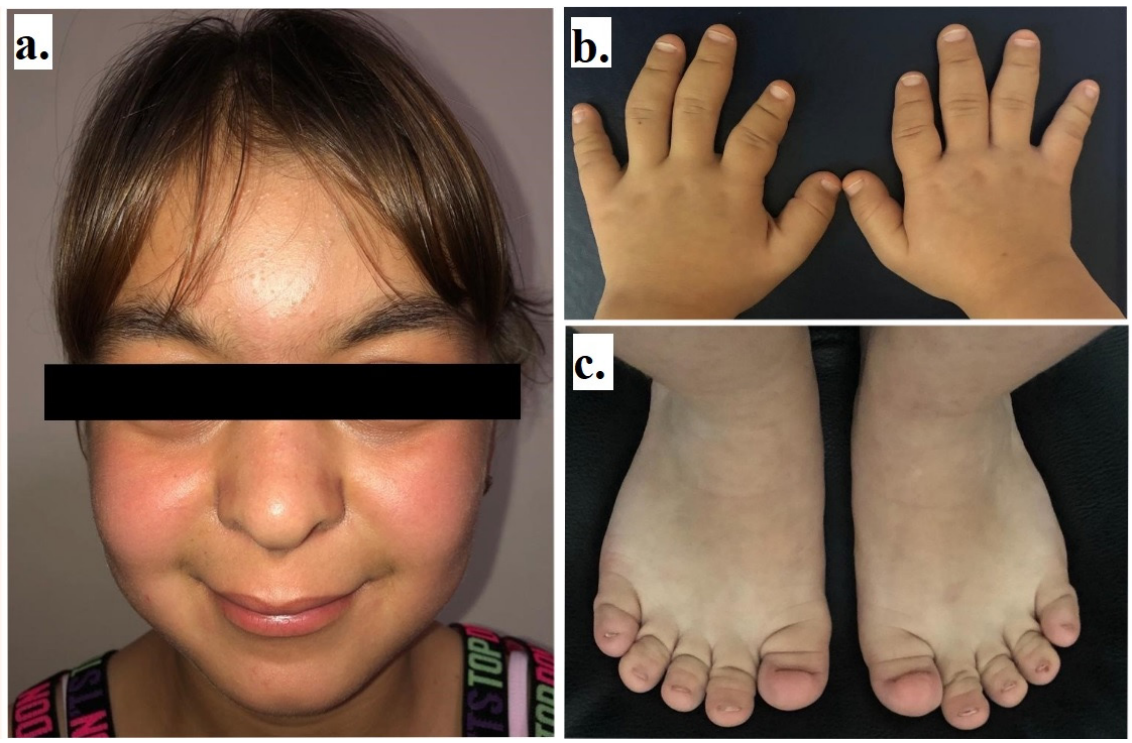

Figure 1: The common skeletal findings of our patient are: a. pear-shaped nose, long philtrum, and thin upper lip b. small hand with brachydactyly and lateral deviations in fingers c. small feet with short phalanges.

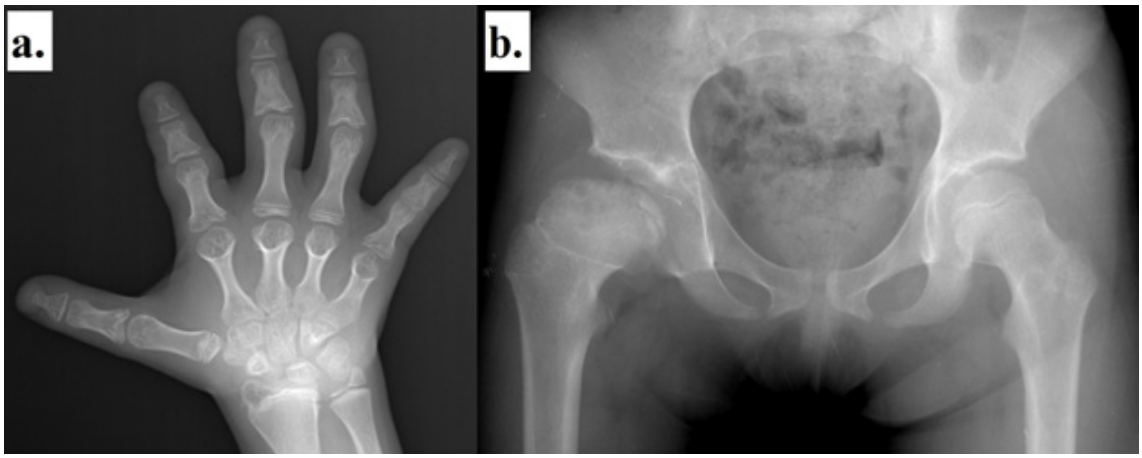

Figure 2: Radiographic examination of our patient reveals a. characteristic appearance of cone-shaped epiphyses and symphalangism in the fifth proximal interphalangeal joint b. Legg-Calve-Perthes disease in the right hip.

to ours, patients may show joint hyper-extensibility [7].

The radiological investigation in these patients revealed cone-shaped epiphyses of the middle and proximal phalanges and severe generalized shortening of all phalanges, metacarpals, and metatarsal bones [2]. Patients with TRPS frequently have hip deformities and secondary joint degeneration, characterized by joint space narrowing and subchondral sclerosis [8]. The long-term morbidity of TRPS is due to the early osteoarthritis-like changes with marked epiphyseal involvement, which affect the large joints, especially the hips [2]. Our case presented with Legg-Calve-Perthes disease as a clinical feature of TRPS as well. In addition to skeletal malformations, cardiac and urinary abnormalities have been reported in association with the disease [2,9]. Our case had MVP as a cardiac manifestation of TRPS.

CONCLUSION

Trichorhinophalangeal syndrome is a rare disease and often remains undiagnosed. Despite our patient having the characteristic features of TRPS, the ultimate final diagnosis was relatively late. Awareness of dysmorphic features may help in a quick diagnosis. Early recognition of TRPS is important to improve morbidity and avoided unnecessary investigations, and receive genetic counselling and information on growth, learning, orthopaedic, and cosmetic issues to patients and parents.

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