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Tricho-rhino-phalangeal syndrome: a rare case of disharmonious short stature

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Abstract

Tricho-rhino-phalangeal syndrome (TRPS) is a genetic disease characterized by craniofacial and skeletal malformations including short stature, brachydactyly, with ulnar or radial deviation of the fingers, clinodactyly and early joint dysplasia, especially of the hips. The most remarkable craniofacial features are slow growing, sparse and brittle hair, pear-shaped nose with a bulbous tip, flat philtrum with thin upper lip, micrognatia and large low-set ears. The radiological hallmarks include cone-shaped phalangeal epiphyses, typical of all TRPS patients, but usually not present until 2 years of age, while bone exostoses appear only in TRPS II individuals. Management is primarily supportive. We describe a case of a male child with disharmonious short stature, affected by TRPS I. The diagnosis was established on the basis of clinical features and genetic testing.

Key Words: disharmonious short stature; genetic disorder; skeletal malformations; tricho-rhino-phalangeal syndrome .

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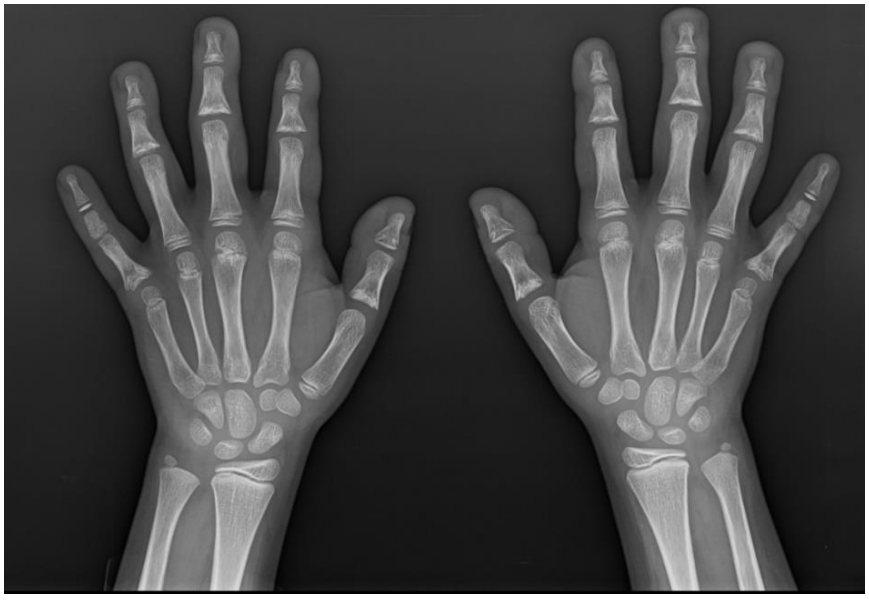
Introduction

Trichorhinophalangeal syndrome (TRPS) is a rare autosomal dominant disorder distinguished by typical craniofacial and skeletal abnormalities, including short stature, brachydactyly, with ulnar or radial deviation of the fingers, clinodactyly and early onset joint dysplasia, especially of hips. The most distinctive facial features are slow growing, sparse and brittle hair, pear -shaped nose with a tip, flat philtrum with thin upper lip, micrognatia and large low set ears. To date, in literature, more than one hundred cases have been described. This syndrome includes the following forms: TRPS I (caused by a heterozygous pathogenic variant in the TRPS1 gene) and TRPS II, also named Langer-Giedion syndrome (caused by a contiguous 8q23.3q24.11 gene deletion that includes TRPS1, RAD21, and EXT1) (1).Some authors have suggested the existence of one more subtype, TRPS III, also due to a sequence variant in TRPS1 and characterized by a higher growth impairment and more severe skeletal deformities (2).

Case presentation

A 11-years-8-months-old caucasian boy came to our pediatric endocrinology out-patients clinic, in order to investigate his short stature. He was the second child of nonconsanguineous parents and was born at full term, adequate for gestational age: birth length 48 cm (−1,3 SD); birth weight 3,800 kg (0,73 SD). The developmental milestones of the child were normal. No intellectual impairment was noticed in either the child or the parents. Mother height was 151,7 cm, father height was 183 cm (Target height 173,85 cm -0,42SD). Maternal grandmother short stature was reported. At the time of presentation, his auxological features were: height 129,10 cm (-2,58 SD) weight 29,40 kg (-0,53 SD), arm span 129 cm, SH/H 0,54, bone age 9 years; his Tanner pubertal stage was G2P1 (testicular volume 4cc). Clinical examination showed dysmorphic features including, a large pear-shaped nose with hypoplastic alae nasi, a long flat philtrum with thin upper vermillion border, large ears, pectus excavatum, and also cubitus valgus. Examination of the oral cavity did not show abnormalities. Moreover, the extremities examination revealed brachydactyly of hands and feet, in association with radial deviation of third and fourth fingers and syndactyly of second and third toes. Celiac disease, pseudohypoparathyroidism, rickets, hypothyroidism, GH deficiency were excluded. Radiological examination reported lack of epiphysial nuclei of middle phalanges in the second, third, fourth and fifth fingers and of the proximal phalanges in the first and fifth fingers, in both hands. Brachydactyly of both feet and hands was also confirmed. In addition, the epiphyses presented a characteristic cone-shaped appearance (Fig1, Fig. 2).

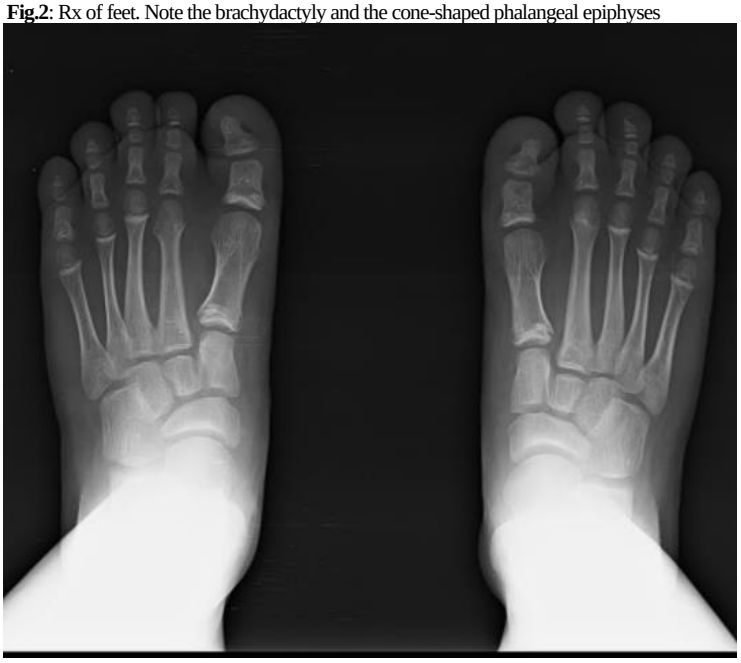
Fig.1 Rx of hands. Note the characteristic cone-shaped appearance of the epiphyses. Note the brachydactyly and the absence of epiphysial nuclei of proximal and middle phalanges.



Indeed spine and limbs radiographs were normal. The child did not complain of reduced mobility or

severe joint pain. Furthermore, BMD Z-score using DXA was performed, revealing reduced BMD of L1-L4. We did not perform abdominal ultrasound or echocardiogram yet. In order to investigate the genetic causes of disharmonious short stature, genomic imbalances and variants in the pseudoautosomal gene SHOX were excluded. Next Generation Sequencing–based analysis was performed on a NovaSeq6000 (Illumina) platform, in order to investigate a multigene panels of skeletal dysplasias. The analysis revealed the heterozygous variant NM_014112: c.2795C>T, (p.Ala932Val) in the TRPS1 gene, which is located on chromosome 8 (8q24.12). This variant is known to be pathogenetic for a rare clinical condition named Tricho-rhino-phalangeal syndrome type 1. Evaluation of the parents by genetic testing is ongoing, in order to detect whether it is a de novo pathogenetic variant.

Fig.2: Rx of feet. Note the brachydactyly and the cone-shaped phalangeal epiphyses



Discussion

Tricho-rhino-phalangeal syndrome type I (TRPSI) is a genetic disorder related to a heterozygous pathogenic variant (missense, nonsense, small deletions) in TRPS1 gene, located on chromosome 8 (8q23.3) . TRPS1 encodes a zinc-finger transcription factor, that appears to be implicated in the proliferation and apoptosis of chondrocyte and perichondrium and in hair follicles proliferation (3-6). Tricho-rhino-phalangeal syndrome type II (TRPS II) is caused by a contiguous gene deletion on chromosome 8q23.3q24.11 involving TRPS, EXT1, and RAD21, EXT1 is located distal to TRPS1, and its deletion is involved in the presence of bone exostoses in TRPS II patients. RAD21 is located between TRPS1 and EXT1, and its haploinsufficiency, may lead to more severe features in TRPS II, resembling Cornelia de Lange syndrome. To date more than 130 pathogenic variants in TRPS1 have been reported. The prevalence of this syndrome is very low (0,2-1 for 100.000), and in most cases is probably underestimated (2). The diagnosis is suggested by the presence of a few recognizable

phenotypic traits, including fine, sparse, and slow-growing hair with an unusually blond hair color, thick and broad eyebrows in the medial and distal part, a long flat philtrum with thin upper lip, micrognatia and large prominent low-set ears. However, the most typical facial sign, in all forms, is the pear-shaped nose, with a broad tip, underdeveloped alae, and occasionally a broad septum. Dystrophic nails, microdontia, malocclusion and supernumerary teeth can also be counted among the ectodermal features. In some studies, it has been shown that TRPS1 gene is also involved in tooth development (7). The clinical picture is completed by skeletal anomalies, including short stature, shortening of the metacarpals and metatarsals, and brachydactyly with ulnar or radial deviation (2; 3). TRPS II differs from TRPS I due to the presence of multiple bone exostoses and an increased risk for a mild to moderate intellectual disability. Instead TRPS III is considered as a variant of the TRPS I spectrum, characterized by a higher impairment of growth. The typical radiological findings, such as the cone-shaped epiphyses, and (in TRPS II individuals) the multiple bone exostoses, are essential for the diagnosis. Short stature is common in all TRPS patients, especially in those with nonsense/frameshit variants. Impaired growth is more remarkable postnatally than prenatally, and the height usually falls below −2 SD, as in our patient. Body weight and head circumference are usually normal. Although not frequently, a growth hormone deficiency could be detected: in these cases a GH treatment may be considered, even if medical literature reports variable effects (3; 4; 8). In our case we found no alteration in GH secretion and therefore GH therapy. was not indicated. Moreover, there is demonstration that TRPS1 gene is expressed in inner organs such as heart, lungs, gut, kidneys, and other tissues in the course of embryonic development (9). Cardiac malformations, despite being uncommon, may be present, ranging from minor anomalies (persistent ductus arteriosus, persistent foramen ovale, bicuspid aortic valves, mitral valve regurgitation) to severe problems (aortic stenosis and anomalous venous return). Renal anomalies (hydronephrosis, unilateral underdeveloped kidney, and vesicoureteral reflux) were detected in literature, and rarely, they could progress into chronic renal insufficiency (3;4; 9). The most important manifestation affects, above all, the large joints, especially the hips, but also the small joints. Patients usually experience pain and decreased mobility since adolescence. The hip dysplasia is a frequent radiological finding, present in more than 70% of patients, that is similar to Legg-Carvè-Perthes disease; most patients require hip prothesis implant earlier than 30 years of age. Osteopenia can be reported in all TRPS forms, but is apparently more frequent in TRPS II patients, and may lead to increased risk of bone fracture. (10,11). In medical literature is reported another very rare manifestation affecting bones, which is a benign, non-neoplastic lesion histologically characterized by a benign fibroblastic proliferation (non ossifying fibroma), that is described in the metaphyseal region of the long bones, and could be responsible of an higher risk of fractures (12). We did not report this clinical feature in our patient. Management is mainly supportive,: in case of joint pain, analgesics can be used, while

physiotherapy could be required to prevent joint dysplasia. In TRPS II resection of bone exostoses should be practiced only in symptomatic patients (3).

Conclusion

Herein we reported a case of disharmonic short stature due to TRPS. This condition can present a wide clinical spectrum and has an important impact on patients and their families. Therefore this disease, once identified, requires a regular clinical follow up. Multidisciplinary approach is essential, and a psychological support can also be indicated.

Conflicts of interest: The authors declare no conflict of interest.

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