

Trichorhinophalangeal syndrome type 1: a novel variant and Perthes-like hip changes as first manifestation

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ABSTRACT

We report a case of Trichorhinophalangeal syndrome type I (TRPS1) in a 16-year-old boy who was referred due to painless finger deformities over the last year. Legg-Calvé-Perthes disease (LGP) had been diagnosed at age 7 and required surgical treatment at age 12. Parents were healthy and non-consanguineous; there was family history of pectus carinatum of maternal lineage. On examination the patient presented a bulbous nose, thin and sparse scalp hair; pectus carinatum; clinodactyly of the first and fifth fingers and hard painless swelling of all of the proximal interphalangeal joints; brachydactyly of the toes. Laboratory tests were unremarkable and radiographic studies revealed distinctive abnormalities of the hands (e.g., epiphyseal coning). This diagnosis was confirmed by gene sequencing, which identified in heterozygosity a pathogenic variant c.124G>T (p.Glu42Ter) in the exon 3 of the TRPS1 gene.

The diagnosis of TRPS1 may be suspected upon identification of characteristic physical features, a compatible clinical history and imaging findings.

Keywords: TRPS1 gene; Trichorhinophalangeal syndrome type I; Legg-calvé-perthes disease.

A 16-year-old caucasian boy was referred to a pediatric rheumatology clinic for suspected juvenile idiopathic arthritis (JIA). He reported painless finger deformities over the last year, denied functional impairment, morning stiffness, nocturnal pains and other joint or sys-

temic complaints.

Legg-Calvé-Perthes disease (LGP) (Figure 1) had been diagnosed at age 7 and required surgical treatment at age 12. Parents were healthy and non-consanguineous; there was family history of pectus carinatum in the maternal lineage.

Physical examination revealed characteristic facial features with rounded bulbous nose, thickened helix of the auricle, thin and sparse scalp hair (the patient declined having his photograph taken); pectus carinatum (Figure 2); clinodactyly of the first and fifth fingers and hard painless swelling of all of the proximal interphalangeal joints; brachydactyly of the toes; thin nails of fingers and toes. Normal height (50th percentile for height, according to WHO child growth standards).

Laboratorial workup was unremarkable (including blood count, erythrocyte sedimentation rate and C-Re-

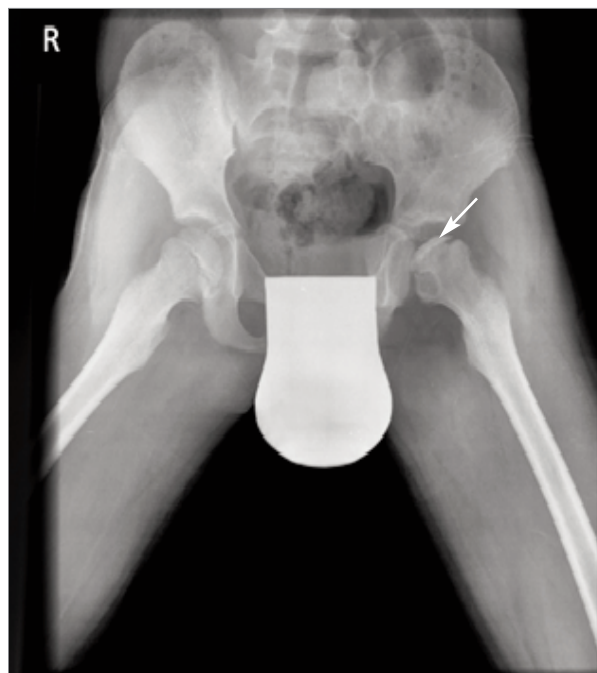


FIGURE 1. Left capital femoral epiphysal osteonecrosis.

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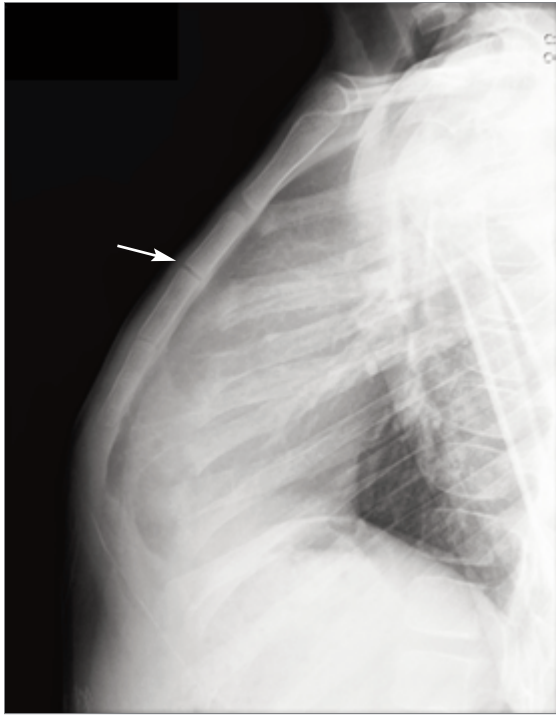


FIGURE 2. Pectus Carinatum visible in the thoracic radiograph

active Protein, endocrine and immunologic studies). Hand radiographic studies demonstrated abnormal “cone-shaped” bones in the middle phalanges - epi-

physeal coning (Figures 3 and 4), compatible with Trichorhinophalangeal syndrome type I (TRPS1).

Genetic study identified a novel variant c.124G> T (p.Glu42Ter) in the exon 3 of the *TRPS1* gene. This nonsense variant introduces a premature stop codon at the position 42 which is expected to lead to the loss of function of TRPS1 protein by nonsense-mediated decay (NMD). This variant was not described in the literature or in databases (gnomAD) and *in silico* analyses predict this variant as pathogenic. Furthermore, the c.124G> T variant is classified as pathogenic according to ACMG criteria supporting the suspected diagnosis of TRPS1 in our patient^{1,2}.

The TRPS1 is a rare genetic disorder with an autosomal dominant inheritance caused by pathogenic variants in the *TRPS1* gene and characterized by craniofacial abnormalities and disturbances in formation and maturation of bone matrix. It includes thin, sparse scalp hair, unusual facial features, abnormalities of the fingers and/or toes, and multiple abnormalities of bone epiphyses (skeletal dysplasia), especially in hands and feet. LGP-like hip dysplasia may be present; in this case it preceded hand and feet changes^{3,4}. In individuals with mild symptoms, a diagnosis may be easily missed or go unreported.

Patients may present to the rheumatologist at different ages, evoking differential diagnosis such as

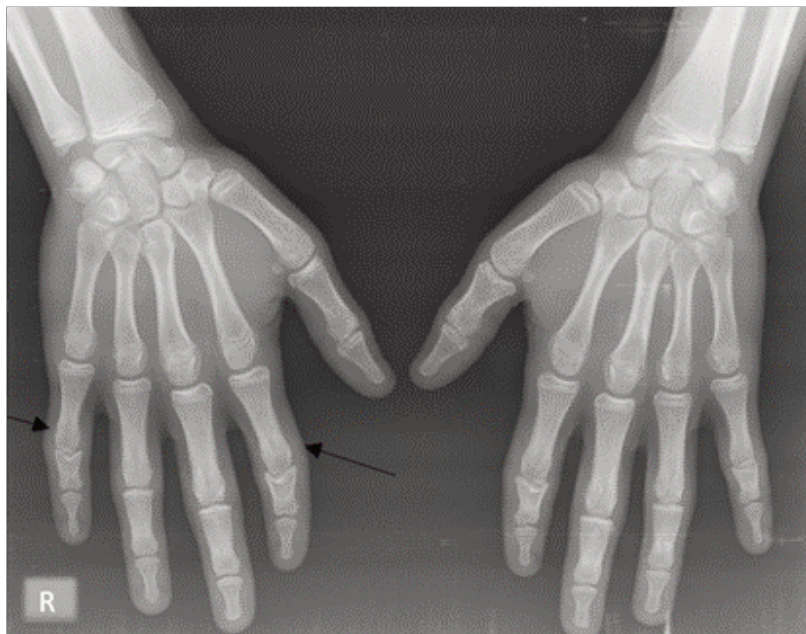


FIGURE 3. Clinodactyly and abnormal “cone-shaped” bones in the middle phalanges (epiphyseal coning)



FIGURE 4. Clinodactyly and abnormal “cone-shaped” bones in the middle phalanges (epiphyseal coning)

skeletal dysplasias, LGP or JIA. Besides changes of the hands and feet, degeneration of the hip joint may be a serious consequence due to the potential for early functional impairment⁵.

Diagnosis requires a thorough patient history, detailed clinical evaluation, and radiographic studies that reveal distinctive abnormalities of the hands and feet. Also, the presence of Perthes-like hip changes can be a valuable clue for diagnosis.

The clinical diagnosis is confirmed by molecular genetic testing with the identification of a pathogenic variant in the *TRPS1* gene.

Treatment is often supportive and multidisciplinary, with a focus on genetic counselling^{3,4,5}.

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