Ana Isabel Díaz Cano[a,*], Ana Esplugues[b]

[a] *Hospital Universitario San Agustín, Servicio de Salud del Principado de Asturias, Avilés, Asturias, Spain*
[b] *Facultat d' Infermeria i Podologia, Universitat de València, Unidad Mixta de Investigación en Epidemiología, Ambiente y Salud, FISABIO - Universitat Jaume I - Universitat de València, CIBERESP, Valencia, Spain*

* Corresponding author.
E-mail address: anarkanda@hotmail.com (A.I. Díaz Cano).

https://doi.org/10.1016/j.anpede.2023.06.021

Trichorhinophalangeal syndrome: A diagnosis accessible to the pediatrician at first sight☆

Síndrome tricorrinofalángico: un diagnóstico de visu al alcance del pediatra

Dear Editor:

Trichorhinophalangeal syndrome (TRPS) is an infrequent autosomal dominant syndrome with a high penetrance and variable expressivity caused by a change in the *TRPS1* gene. Its clinical presentation is characterised by abnormalities of the hair (sparse scalp hair, lateral thinning of the brows) and nails (ungual dystrophy), mild facial dysmorphism (bulbous tip of the nose, long and flat philtrum, thin upper lip and protruding ears) and skeletal abnormalities (short stature, brachydactyly, phalangeal deviation, cone-shaped epiphyses at the phalanges, hip dysplasia and osteopenia). It is classified into two types: TRPS I (OMIM # 190350), caused by pathogenic variants of the *TRPS1* gene; and TRPS II (OMIM # 150230), caused by the deletion of contiguous genes in chromosome 8 (including *TRPS1* and *EXT1*), which is also associated with osteochondroma and intellectual disability.[1–3]

In this article, we present the cases of several members of a family who received a diagnosis of TRPS stemming from the evaluation of a boy aged 6 years for growth delay and certain dysmorphic features. In the index case, the main findings of the physical examination were a height of 108.8 cm (height z score, −2.68), a body mass index (BMI) of 13.52 kg/m^2 (10th percentile), with normal body proportions and a height velocity 5.1 cm/year. He had fair, thin and sparse hair, thinning of the tail of the eyebrows and brittle nails. Other salient features were the triangular shape of the face, bulging forehead, long and flat philtrum, thin upper lip and large and retroverted ears. In the extremities, there was clinodactyly of the fifth toe and abnormally proximal position of the first toe joints. The patient also exhibited joint hypermobility, with flexible flatfoot and a scoliotic posture in the absence of abnormal vertebral rotation. He had been born to term with a birth weight of 2690 g (7th percentile) and a birth length of 49 cm (28th percentile) and had a personal history of mild global developmental delay and adenoidectomy for treatment of adenoid hypertrophy.

There was no history of consanguinity in the family. The salient findings of the family history were maternal short stature (147.2 cm; <1st percentile; height z score, −2.83) associated with a phenotype similar to that of the patient. The father's height was normal (175 cm; 36th percentile). On interviewing the mother, she reported that there were several members of her family with short stature and similar facial features.

Hormone levels (IGF1, IGFBP3 and thyroid hormones) were normal, and the patient tested negative for markers of coeliac disease. His bone age was delayed by 3 years and the epiphyses of several phalanges were cone-shaped (Fig. 1). Genetic testing with next generation sequencing (NGS) panel of genes involved in bone dysplasias detected a heterozygous pathogenic variant in the *TRPS1* gene (c.333delC, p.Ser112Profs*7, NM_014112), confirming the diagnosis of TRPS type I.

We performed cascade testing in the mother's family, with participation of the mother and 3 male uncles (Fig. 1). Table 1 presents the findings of the history-taking, examination and genetic testing of the family. Both the mother and two of the uncles had a compatible phenotype, and all were found to have the same pathogenic variant of the *TRPS1* gene as the boy, which was not present in the uncle with few compatible features. We observed phenotypic variability within the family (previously reported in the literature[2]), although they shared, to a varying extent, hair and nail abnormalities, the characteristic facial features and the skeletal changes.

Thus, the diagnosis of TRPS is feasible for paediatricians, as it can be reached with the information obtained in the history-taking and physical examination and supported by plain radiography, which allows visualization of the cone-shaped phalangeal epiphyses characteristic of this disease, after which targeted gene sequencing can confirm the presence of changes in the *TRPS1* gene.

Most of the morbidity in these patients is determined by osteoarticular changes, in the form of osteoarthritis with an early onset (chiefly involving the hips, but also other large joints and the hands), abnormalities in joint mobility, articular pain and phalangeal deviation, so early diagnosis of the syndrome makes it possible to manage these complications from an earlier stage. The syndrome is not usually associated with intellectual disability and, when the latter is present,

DOI of refers to article: https://doi.org/10.1016/j.anpedi.2023.07.010
☆ Previous meeting: this report was presented at the 36th National Congress of the Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria (SEPEAP); October 20–22, 2022; Alicante, Spain.

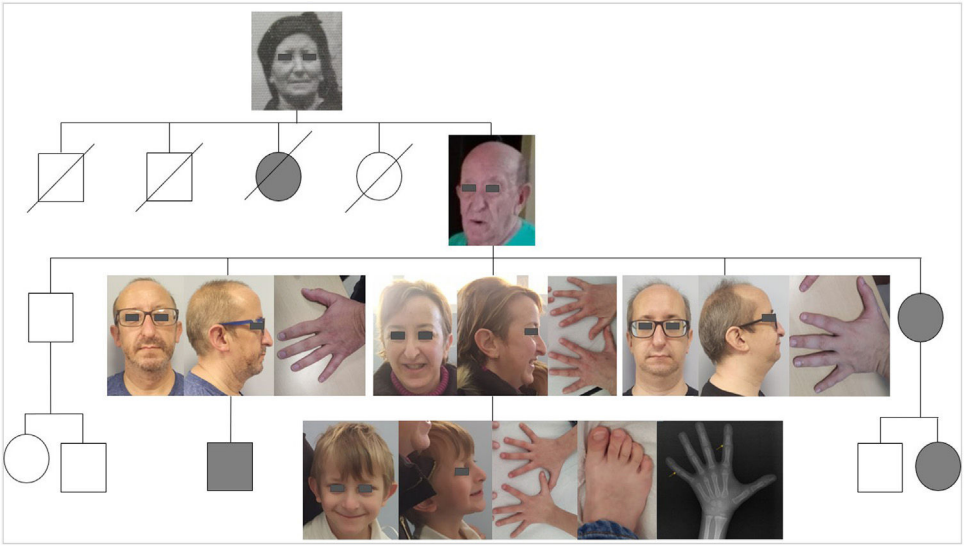

Figure 1 Pedigree of the family with TRPS. Plain radiograph of the hand and wrist in the index case showing the cone-shaped epiphyses of the phalanges (arrows).

Table 1 Personal history and findings of physical examination and genetic testing in members of the family with TRPS.

Personal history	Index case Mild global developmental delay; adenoid hypertrophy	Mother Moderate endometriosis; retinitis pigmentosa carrier	Uncle 1 Hiatal hernia; hypertension	Uncle 2 Operated right femur and tibia fractures	Uncle 3 Septoplasty for deviated septum
Educational attainment	Primary education	EGB[a]	EGB[a] and VE	EGB[a] and VE	EGB[a] and administrative training
Sparse hair and lashes	Yes	Yes	Yes	Yes	Yes
Thinning of brow tails	Yes	Yes	Yes	Yes	Yes
Brittle or pale nails	Yes	Yes	No	No	Yes
Triangular facies	Yes	Yes	Yes	Yes	Yes
Bulbous nose	Yes	Yes	No	Yes	Yes
Long and flat philtrum	Yes	Yes	No	Yes	Yes
Thin upper lip	Yes	Yes	No	Yes	Yes
Protruding ears	Yes	Yes	No	Yes	Yes
Bulging forehead	Yes	Yes	No	Yes	Yes
Micrognathia	No	No	No	Yes	Yes
Clinodactyly of fifth finger and toe	Yes	Yes	No	Yes	No
Short stature (height $z \leq -2$)	Yes (z −2.68)	Yes (z −2.83)	No (z −1.96)	Yes (z −3.23)	No (z −1.54)
Hyperlordosis or scoliosis	No	Yes	No	Yes	No
Hypotonia or hypermobility	Yes	No	No	Yes	No
Other			Syndactyly (2nd and 3rd toes)		Mild limb length discrepancy
Pathogenic *TRPS1* variant	Yes	Yes	No	Yes	Yes

VE, vocational education.
[a] EGB: *Educación General Básica*. First 8 years of education in past education system in Spain (corresponding to current 6 years of primary education + first 2 years of compulsory secondary education).

it tends to be mild, except in patients with TRPS type II, in whom it is more common.[1,2]

Funding

This research did not receive any external funding.

References

1. Maas S, Shaw A, Bikker H, Lüdecke HJ, van der Tuin K, Badura-Stronka M, et al. Phenotype and genotype in 103 patients with tricho-rhino-phalangeal síndrome. Eur J Med Genet. 2015;58:279–92.
2. Maas S, Shaw A, Bikker H, Hennekam RCM. Trichorhinophalangeal Syndrome. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. Gene Reviews. Seattle (WA): University of Washington; 2017. p. 1993–2022.
3. Vargas Lebrón C, Ruiz Montesinos MD, Moreira Navarrete V, Aróstegui Gorospe JI. Síndrome tricorinofalángico. Reumatol Clin. 2020;16:499–501.

María del Carmen Cortés Jiménez[a,*], Raquel M. Fernández García[b], Emilio García García[a]

[a] *Unidad de Pediatría, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[b] *Departamento de Medicina Maternofetal, Genética y Reproducción, Hospital Universitario Virgen del Rocío, Sevilla, Spain*

* Corresponding author.
E-mail address: mc.cortes95@gmail.com
(M.d.C. Cortés Jiménez).

https://doi.org/10.1016/j.anpede.2023.07.010