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**Case Report**

# Trichorhinophalangeal syndrome

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## Abstract

Trichorhinophalangeal syndrome (TRPS) is the collective name of three rare congenital conditions characterised by craniofacial and skeletal abnormalities. The three known types of TRPS have different modalities of genetic transmission: namely, TRPS I and III are inherited as an autosomal dominant disease, while the cases of TRPS II are essentially sporadic. The diagnosis of the different types of TRPS is based on clinical and radiological findings, eventually integrated by genetic analysis, particularly useful in some cases with the non-classical clinical presentation. Alopecia and structural abnormalities of the nose and the hands should be considered as clinical hallmarks, whereas endocrine disorders, renal alterations, ureteral reflux, heart pathology and bone dysplasia have been documented, in the setting of a multisystem involvement.

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## Introduction

Trichorhinophalangeal syndrome (TRPS) is the collective name of three rare congenital conditions characterised by craniofacial and skeletal abnormalities. The three known types of TRPS have different modalities of genetic transmission: namely, TRPS I and III are inherited as an autosomal dominant disease, while the cases of TRPS II are essentially sporadic. The diagnosis of the different types of TRPS is based on clinical and radiological findings, eventually integrated by genetic analysis, particularly useful in some cases with the non-classical clinical presentation. Alopecia and structural abnormalities of the nose and the hands should be considered as clinical hallmarks, whereas endocrine disorders, renal alterations, ureteral reflux, heart pathology and bone dysplasia have been documented, in the setting of a multisystem involvement. Pigmentation disorders have never been

reported in TRPS patients.

Herein is described a case of skin discoloration occurring in a boy affected by TRPS: it was only a fortuitous association?

## Case report

A 16-year-old boy presented to our department with a complaint of an asymptomatic dirt-like hyperpigmentation of the upper chest and abdomen, which had been present for about six months (Fig. 1). The condition became progressively more evident after holidays at the seaside, despite the routine hygiene and the application of various emollients and oils.

The patient was apparently healthy, although his hairs were referred as slowly growing and being, in

fact, thin and sparse. General physical examination was notable for *pectus excavatum* (Fig. 1), short and stubby hands with lateral deviations and deformations of the interphalangeal joints (Fig. 2). About these, he presented the report of a previous x-ray examination, showing cone-shaped epiphyses of the second to the fifth middle phalanges of both hands and bilateral brachymetacarpalia of the metacarpal IV. The short stature had also been strictly checked by his paediatrician, as well as the flat feet, the arched palate and the hypoplastic mandible.

Biochemical and endocrinological investigations failed to demonstrate abnormal pituitary gland, related to the GH-IGF-1, hypothalamic-pituitary-thyroid, -adrenal and -gonadal axis, and prolactin secretion.



Figure 1: Physical examination showing skeletal abnormalities (*pectus excavatum* and left hand) and darkening of the skin of the lateral thorax

On mother repeated interviewing, it emerges that other two members of the family (the father and the sister of the patient) presented similar skull features, having both triangular face, bulbous pear-shaped nose, elongated philtrum, thin upper lip, horizontal groove on the chin and protruding ears. In particular, the sister, who was 20, was previously diagnosed with TRPS type I in 2008 through cytogenetic analysis. About the cutaneous concern, anamnesis was not significant for possible underlying diseases (diabetes, obesity or supplementations/medications assumption) and only

the sister manifested similar hyperpigmentation of the umbilicus and axillae. He also denied local trauma, eczema or excessive use of cosmetics before.



Figure 2: Particular of the hand: note the lateral deviations and deformations of the interphalangeal joints

On physical examination, abnormal brown to dark discoloration of the lateral part of the thorax was apparent (Fig. 3). Dermoscopy of the lesions showed large polygonal plate-like brown scales arranged together giving an irregular mosaic pattern (Fig. 4).



Figure 3: Brown to dark discoloration of the lateral part of the thorax.

Tentative rubbing with 70% isopropyl alcohol led to the partial removal of the hyperpigmented patch (Fig. 5), and the patient refused any further diagnostic procedure (e.g. punch biopsy).

## Discussion

Trichorhinophalangeal syndrome type I is a malformation syndrome characterised by craniofacial and skeletal abnormalities [1]. Inherited in an autosomal dominant manner with high penetrance and variable expressivity, TRPS have sparse and

slow-growing hair, pear-shaped nose, elongated philtrum, thin upper lip, protruding ears and bone deformities, including cone-shaped epiphyses of the phalanges, hip malformations and short stature as typical clinical features [2].

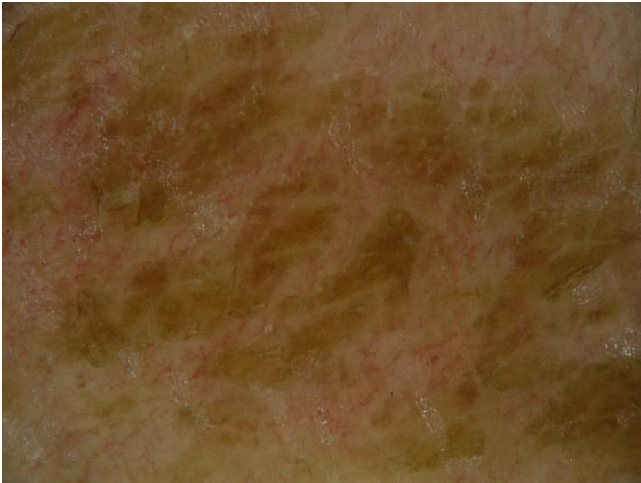


Figure 4: Dermoscopy of the affected area (original magnification x60)

Although there is a great variability in the clinical findings with considerable overlap, even among subjects of the same family, three subgroups of TRPS can be distinguished: TRPS I, associated with alterations of chromosome 8 band q24.1, TRPS II caused by a larger deletion, involving the TRPS 1 and EXT 1 (hereditary multiple exostoses) genes (8q24.11-q24.13), and TRPS III which results from missense mutations in exon 6 of TRPS1 [3].

Short stature is usual in TRPS type I [4]. Winged scapulae, multiple cartilaginous exostoses, redundant skin, and mental retardation are distinctive characteristics of TRPS type II, while severe brachydactyly, due to short metacarpals, and severe short stature are typical of TRPS type III [1, 5].

The diagnosis of the different types of TRPS is based on clinical and radiological findings, eventually integrated by genetic analysis, particularly useful in some cases with non-classical clinical presentation; other syndromes that include alopecia and structural abnormalities of the nose and the hands should be considered in differential diagnosis (Larsen's syndrome, oral-facial-digital syndrome, Coffin-Siris syndrome, alopecia-onycho-dysplasia-hypohidrosis-deafness syndrome, trichoonychodental dysplasia, Clouston's syndrome, Ellis-van Creveld syndrome) [1, 2, 6, 7].

TRPS may be associated with endocrine disorders, renal alterations, ureteral reflux, heart pathology and bone dysplasia: thus, a follow-up has to be set up in order to make an early diagnosis of a possible multisystemic involvement, a Perthes-like disease (dysplasia of the hip in >70% of the cases) [9], because of the frequent evolution in avascular necrosis of the femoral head (Legg-Perthes-Calvé disease) [9], or the appearance of exostoses because

of a possible, although rare, sarcomatous degeneration [2]. Radvanyi et al. also showed that the TRPS1 gene is overexpressed in more than 90% of breast cancers [10].

Apart from the above mentioned cutaneous involvement, no other skin abnormalities have been reported in TRPS. In particular, no pigmentation disorders have been noted, according to with the updated literature.

With regard to our case, dermatological findings should not strictly considered in the field of pigmentation disorders, since Terra Firma Forme Dermatitis (TFFD), or Duncan 'dirty' disease, implies Incomplete maturation of keratin squames, combined with retention of melanin and build-up and compaction of scales, sebum and dirt through inadequate cleansing [11]. In fact, TFFD is an idiopathic benign condition that may represent an exasperating skin defect, as it involves exposed areas in psychologically more fragile patient categories (mainly children and adolescents) with the features of 'dirt' and giving the picture of poor body hygiene [12]. Atopy seems to be a predisposing condition [13].



Figure 5: Partial removal of the pigmentation

By excluding other dirty-appearing disorders, and using some ancillary tools (e.g. dermoscopy), the diagnosis is easy [13], thus avoiding inappropriate exams and unnecessary treatments [11, 12].

The occurrence of some cases presenting 'topographic' disease (Unal E et al., unpublished data) and the anecdotal association with genetic diseases (Guarneri C et al., unpublished data) may suggest the possibility of a 'syndromic' phenotype, as in this case, and it is worthy of attention in future cases of these conditions.

However, in clinical practice, TFFD is more frequent than the only 44 cases reported in literature lead to expect [14].

In conclusion, TRPS is a group of rare congenital conditions characterised by craniofacial

and skeletal abnormalities, Type I and III being more frequent and inherited as an autosomal dominant character. As the diagnosis is based on clinical and radiological findings, eventually integrated with genetic analysis, the role of a dermatologist is pivotal, through recognising the typical hallmarks and managing the further in-depth analyses.

Specialist's should also be aware of unexpected clinical signs, thus eventually expanding the phenotype of the disease and/or characterising new variants.

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