

Do you know this syndrome?^{*}

Você conhece esta síndrome?^{}*

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CASE REPORT

A 36-year-old female patient sought medical assistance from a dermatologist for a case of scalp alopecia she had acquired as a child, which had worsened in recent years. The clinical and dermatological examination revealed diffuse alopecia, particularly androgenetic pattern alopecia, on the frontoparietal region (Figure 1). There was a retraction of the frontal capillary implantation line and superciliary and ciliary alopecia on the third lateral, bilaterally. Various features stood out, such as the patient's short stature (141 cm), presence of an Olympian forehead, alar hypoplasia, pear-shaped nose, long philtrum, thin lips (Figure 2), low set ears and long throat. Other features were associated, such as ogival palate, malposition of the teeth especially the upper, lower, central and lateral incisors, and microdontia of the upper, lower and lateral incisors. On the hands, we noted brachydactylia of the first fingers; swelling at the proximal interphalangeal joints, except the first ones, and radial deviation, particularly of the second and third

fingers of both hands (Figure 3). Intellectual development was normal. The patient denied having similar cases in her family or parents being related by consanguinity (Figure 4).

The patient was submitted to a biopsy of the scalp; wide-ranging biochemical and endocrinological laboratory investigations, chromosomal analysis and radiological study.

The latter identified cone-shaped alterations in the epiphyses of the proximal interphalangeal joints (Figure 5), asymmetry of size between the humerus (long), radio-ulnar articulation (short) of both upper limbs, and asymmetry between the femur (long), tibia and fibula (short) in the lower limbs. The biochemical and endocrinological study showed only discreet prolactin alterations (38 ng/ml, normal from 6-to-24 ng/ml). The metaphase chromosome analysis revealed 46 XX karyotypes (normal for females), with no chromosomal breaks. The patient was not investigated for the presence of specific genic mutations.



FIGURE 1:
Scalp with diffuse alopecia (Ludwig degree III)



FIGURE 2:
Superciliary distal alopecia, pear-shaped nose, long philtrum, thin and absent lips



FIGURE 3: Short first fingers, radial deviation of the second and third fingers

The histopathologic examination of the punch biopsy longitudinal cut of the scalp revealed rare hair follicles with infundibular dilatation, hyperkeratosis and mild mononuclear infiltrate of the fibrous sheath.

WHAT SYNDROME IS IT?

Trichorhinophalangeal Syndrome Type I

In 1966 Giedion¹ was the first author to establish a correlation between the main clinical and radiological alterations present in the syndrome and recognize its genetic character. He also proposed a name for it, which is still used today in the international literature either as "Trichorhinophalangeal Syndrome" or "Tricho-Rhino-Phalangeal Syndrome". There are currently three recognized variants, identified as follows: trichorhinophalangeal syndrome type 1 (TRPS1), characterized clinically by the association of slow-growing scalp hairs, a pear-shaped nose, long philtrum, fine upper lip and bone defects, especially cone-shaped epiphyses of the fingers. Other phenotypic alterations may be associated and found described in chart 1.² Trichorhinophalangeal syndrome type 2 (TRPS2) or Langer-Giedion syndrome,³ features microcephaly, mental retardation, multiple cartilaginous exostoses in the ribs and vertebrae, as well as other less severe osteoarticular manifestations (Chart 1).² Trichorhinophalangeal syndrome type 3 (TRPS3), or Sugio-Kajii syndrome, is a variant closer to type 1. It differs phenotypically by increased shortening of all fingers, metacarpals and metatarsals, and a short stature.⁴

TRPS1 occurs due to haploinsufficiency of the gene encoding the so-called "Zinc-Finger" transcription factor TRPS1, located on the long arm of chromosome 8 (8q24.12).⁵ This protein appears to be

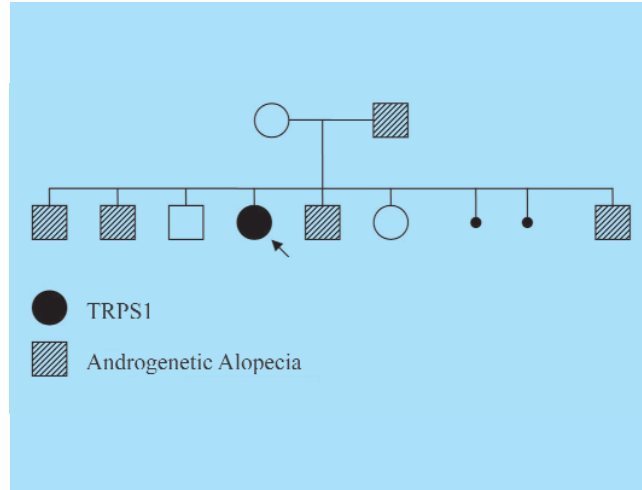


FIGURE 4: Heredogram

related to androgen regulation of the prostatic-specific antigen genic expression.⁶ The syndrome's segregation form is predominantly autosomal dominant, with high penetrance and a female predominance of 1.7:1 (IC 95%, 1.1 to 2.9) in family cases.⁷ In the descriptions of the syndrome's nine allelic variants, at least three were sporadically identified. The real prevalence of new mutations cannot be estimated at the present time. Additional mutations of TRPS1 provoke phenotypic alterations that are responsible for trichorhinophalangeal syndrome type 3. The deletion of TRPS1 associated to the Exostosine type 1 gene (EXT18q24.11) leads to trichorhinophalangeal syndrome type III.⁵

The case described above phenotypically fits the TRPS1 category, but must be corroborated by



FIGURE 5: X-ray of the hands shows cone-shaped epiphyses in the proximal interphalangeal joints of the second, third, and fourth fingers (arrows)

CHART 1: Phenotypic manifestations described in trichorhinophalangeal syndrome

Trichorhinophalangeal syndrome type I	Trichorhinophalangeal syndrome type II (Langer-Giedion)	Trichorhinophalangeal syndrome type III (Sugio-Kajii)
Sparse and fragile hair	Sparse hair	Same characteristics as type I
<i>Pili torti</i>	Prominent pear-shaped nose	Accentuation of short stature
Trichorrhexis nodosa	Phalangeal cone-shaped epiphyses (XR)	Accentuated shortening of the phalanges, metacarpals and metatarsals
Prominent pear-shaped nose	Multiple exostoses	
Broad and high nasal bridge	Prominent ears	
Phalangeal cone-shaped epiphyses (XR)	Microcephaly	
Curved fingers and toes	Short stature	
Brachydactylia	Hyperextensive joints	
Fine and fragile nails	Redundant skin in infancy	
Short stature	Increase in nevi	
Winged scapula	Mental retardation	
Deep voice		
Degenerative joint disease in youth		

genic molecular analysis.

Among the possible clinical alterations observed in TRPS1 and its intensity, alopecia might be more cumbersome for patients depending on the degree of gene expression. Giedion¹ described scalp hypotrichosis as an outcome of the presence of slow-growing fine scalp hairs. Since then there have been few trichological studies, and their diagnostic value is imprecise. In the occipital region trichogram, Lalevic-Vasic⁸ observed the presence of 52% of hairs in a dystrophic anagen state and 48% in a telogen state. The histopathologic examination of the same region shows rare hair follicles, described as minute and superficial anagen follicles. Under polarized light, monochromic hair was observed to have slight fissures on the verge of becoming breakages, described as "*en bout de doigt*". Trichorrhexis nodosa type breakages and trichoptilosis splits were less frequently observed. Other authors have observed trichograms with a compatible standard of androgenetic alopecia in combination with diffuse alopecia with 38% of hairs on the frontal region in a telogen state, 6% catagen and 56% anagen. For hairs on the occipital region, the hairs presented with a telogen state in 26%, a catagen state in 1% and 72% in the anagen state.⁹ In the same study, performed with the scanning electron microscope, the stalk of hair was found to have an elliptic form. In the histopathologic examination, a reduction in the number of follicles was observed in the longitudinal and transversal cuts. Most of bulbs were anchored in the subcutaneous tissue. There was also presence of anagen follicles in smaller diameters and an absence of inflammatory infiltrate.¹⁰ In addition to hypotrichosis

of the scalp, it is quite common for hairs to be increasingly rare on the third lateral of the superciliary region, but not as frequent on the ciliary, axillary and pubic regions.¹¹ By contrast, reports do exist on patients having normal hair growth.^{12,13}

Orofacial alterations in TRPS1 have been rarely described, but the presence of supernumerary teeth, report of "bad bite" microdontia and hypodontia have been observed.¹⁴ Presence of micrognathism and condylar dysplasia have all been linked to TRPS2.¹⁴

Among the osteoarticular alterations, in his assessment of the X-rays of 69 TRPS1 patients, Giedion¹ noted that beyond cone-shaped epiphyses in the middle phalanges, 52% of cases showed shortening of the metacarpals. Also observed were alterations of the proximal and distal phalanges, as well as shortening of the metatarsals.¹⁵ The alterations described may entail not only cosmetic damage, but also functional impairment over the long term, especially.

The differential diagnosis of TRPS1 is done mainly with other variants of the same syndrome and with other syndromes that include alopecia and structural abnormalities of the nose and osteoarticular abnormalities, with Larsen syndrome¹⁶ orofacial-digital syndrome, Coffin-Siris and McKusick type chondrodysplasia⁹ among those cited.

Although considered rare, we posit that trichorhinophalangeal syndrome is more frequent than what has been described until now. It is up to dermatologists to be aware of and alert for patients complaining of a premature onset of androgenetic pattern alopecia.⁹ □

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