Trichorhinophalangeal syndrome Type 1 with growth hormone deficiency.

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Abstract

A 10 year old boy, brought for the evaluation of short stature, was found to have facial dysmorphism in the form of a bulbous nose, long philtrum and a thin upper lip. He had lateral thinning of eye brows though his scalp hair was normal. Skeletal abnormalities included broad hands and feet, brachyclinodactyly, brachytarsia with broad thumbs and toes. Since he manifested the classic triad of craniofacial, skeletal and hair abnormalities, he was diagnosed to have Trichorhinophalangeal syndrome (TRPS) type 1. Radiological evidence of cone shaped epiphysis in some of the proximal phalanges was diagnostic. In addition, the boy had evidence of growth hormone deficiency and has been started on growth hormone therapy. TRPS type 1 with growth hormone deficiency is being reported for the first time from the Indian sub continent.

Keywords: Trichorhinophalangeal syndrome, Long philtrum, Cone shaped epiphysis, Hypotrichosis, Growth hormone deficiency

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Introduction

Trichorhinophalangeal syndrome (TRPS) is a rare genetic disorder characterised by a triad of hypotrichosis, craniofacial and skeletal abnormalities [1] including short stature. TRPS 1 gene is located on chromosome 8 (8q24.1) and is responsible for encoding a transcriptional repressor essential for hair growth and chondrocyte modulation [2]. We report a case of TRPS 1 with growth hormone (GH) deficiency in an adolescent boy.

Case report

A 10 year old male child presented to our institute for the evaluation of short stature. On examination, he had a bulbous pear shaped nose, with its tip overhanging the columella, a long philtrum, prominent ears, a thin upper lip, mentolabial groove and retrognathia [Fig 1]. There was thinning of the lateral aspect of both eyebrows (Herthoge sign) though scalp hair appeared to be normal. Interestingly, the mother informed us that the child had very sparse scalp hair during infancy and the rate of hair growth was very slow. He had short broad hands, clinodactyly of little fingers, radial deviation of the 4th finger, and pes planus. A striking feature was the rather broad thumbs and big toes. The testicular size corresponded to that of a 4 year old and SMR was prepubertal. The child had proportionate short stature (US: LS: 0.87) with a height age of 7 years (117 cm) and a weight age of 6 years (20 kg). He was of normal intelligence.

Routine blood biochemistry including renal function was normal. Fasting blood sugar, thyroid function and serum cortisol were also within normal limits. Growth hormone level, both basal (0.979ng/ml) and after clonidine stimulation (maximal levels at 60 minutes – 4.635ng/ml),
was subnormal. Low IGF 1 levels, of 74.6ng/ml (normal 88 – 252ng/ml), and delayed bone age confirmed growth hormone deficiency.

X ray of the wrist revealed only 5 carpal bones suggesting a bone age of 4 – 6 years. Skeletal x rays showed cone shaped epiphyses of the proximal phalanges of both the thumbs, little fingers, big toes and second toes [Fig 2] but x ray of the pelvis did not reveal any abnormality. MRI of the sella, echocardiogram, and ultrasound of the abdomen were normal. Karyotype was normal.

Figure 2. X rays of hands and feet showing cone shaped epiphyses

Trichorhinophalangeal syndrome type 1 with GH deficiency was diagnosed, though genetic confirmation could not be obtained. GH therapy at a dose of 0.3 mg/ kg/ week was started. Serial growth monitoring and IGF 1 levels will be done to assess the effect of growth hormone therapy.

Discussion

TRPS is a rare disorder, with autosomal dominant inheritance, involving the hair, nose and digits. It cannot be regarded as a mere cosmetic abnormality. Although it is compatible with longevity, there are cases with diabetes mellitus, hypothyroidism [3], growth hormone deficiency, renal disease and heart disease which may contribute to morbidity and mortality. TRPS gene is said to regulate apoptosis in the embryonic period by either down regulating pro survival factors like SOX9 and PTHrP or by suppressing signalling pathways such as Wnt and JAK-STAT, which are essential for the normal development of hair follicles and chondrocytes [4].

The phenotype has sparse, slowly growing hair [5], laterally thin eyebrows, bulbous tip of nose, long philtrum and thin upper lip. There are three distinct subtypes, all of whom have similar facial features and sparse hair. Type I is the most common. Type II has, in addition, multiple exostoses and mental retardation while type III has severe brachydactyly and severe growth retardation. There is a deletion of 8q24.12 in TRPS 1 but as this is a very narrow and dark band, karyotyping is often reported as normal.

The characteristic radiological features are cone shaped epiphyses of the phalanges, resulting in their shortening. This occurs due to the central projection of epiphysis causing a concavity in the adjacent metaphysis resulting in premature fusion of growth plate leading to brachydactyly and brachytarsaly as seen in the case reported. Osteoarthritis of the hip may be progressive in these patients and can be confused with Perthes disease.

Almost all cases of TRPS have varying degrees of short stature though GH deficiency has not been documented in most of them. Naselli et al [6] have reported two monozygotic twin girls with TRPS 1 who had no improvement in growth velocity following GH therapy although there was some evidence of GH deficiency. Stagi et al [7] have described two cases, with partial growth hormone deficiencies, that were responsive to GH therapy. Two cases reported by Sarafoglou et al [8] also responded to GH therapy, though they had normal GH levels and low IGF1. Sohn et al [9] reported two Korean children with TRPS among whom only the one with documented GH deficiency and normal IGF 1 benefitted with treatment. In world literature, though 9 cases have been given growth hormone therapy most of them did not satisfy all the criteria for GH deficiency unlike ours wherein GH deficiency was established conclusively.

Conversely, Merjaneh et al [10] have reported increased growth velocity and final height in a child with TRPS 1 with a normal function of the GH – IGF1 axis. This can be explained by the fact that the local IGF 1 levels may be low in the growth plates despite a normal serum level as is seen in cell culture models [11]. Therefore, a trial of GH administration is recommended in TRPS patients with short stature despite the presence/ absence of GH deficiency.

We conclude that in a country like ours where genetic confirmation is still not feasible, history and clinical examination remains the best tool to suspect TRPS. Our patient has complete growth hormone deficiency that has not been reported in patients with TRPS 1 so far.

References


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