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The effect of growth hormone treatment in a child with tricho-rhino-phalangeal syndrome: A case report and review of the literature

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ABSTRACT

Tricho-rhino-phalangeal syndrome (TRPS) is characterized by craniofacial and skeletal malformations including short stature, cone-shaped phalangeal epiphyses and Perthes-like changes of the hip. We describe the response to growth hormone (GH) treatment in a boy with TRPS. The patient presented at age 3.5 years for evaluation of short stature (−3.2SD). On physical examination, the characteristic facial phenotype of TRPS was noted. Radiographs showed cone-shaped phalangeal epiphyses and bilateral small and fragmented femoral heads. The diagnosis was confirmed by Sanger sequencing of the *TRPS1* gene. Two GH stimulation tests revealed GH deficiency, and GH treatment was initiated. Subsequently, growth velocity improved, as did the radiographic appearance of the femoral epiphyses, as seen on sequential pelvis radiographs.

This observation suggests the possibility of a beneficial effect of GH treatment on both height and epiphyses status in TRPS patient with GH deficiency. Further studies are needed to support the observation.

1. Introduction

Trichorhinophalangeal syndrome (TRPS) is a rare autosomal dominant malformation syndrome characterized by distinctive craniofacial and skeletal abnormalities (Maas et al., 2015). Craniofacial features include slowly growing scalp hair, laterally sparse eyebrows, bulbous tip of the nose, long flat philtrum, thin upper vermilion border and protruding ears (Maas et al., 2015). Skeletal abnormalities include cone-shaped epiphyses at the phalanges, hip dysplasia and short stature (de Barros and Kakehasi, 2016). Radiological features of the hip of TRPS patients include joint dysplasia, small and fragmented femoral heads resembling but not identical to Legg-Calve-Perthes disease, and reduced joint space. Systemic manifestations may also be present, such as congenital heart defects and renal anomalies, including unilateral and underdeveloped kidneys, vesicoureteral reflux and stenosis of the ureter-bladder junction (Vaccaro et al., 2009).

Two subtypes of TRPS have been described (Maas et al., 2015). Type I is the classical form and is due to a mutation in the *TRPS1* gene that maps to 8q24. Type II is a contiguous gene deletion syndrome that involves *TRPS1* and *EXT1* genes, resulting in the additional finding of multiple cartilaginous exostoses and mild intellectual impairment. Some authors have proposed another subtype, TRPS type III, associated with more marked growth impairment and severe brachydactyly. However, the differences between TRPS type I and III are small and may represent a spectrum of severity (Maas et al., 2015).

TRPS1 is a transcription factor that regulates proliferation and apoptosis of chondrocyte through Stat3 signaling (Suemoto et al., 2007). TRPS1 deficiency has been postulated to impair chondrocyte differentiation in the growth plate and epithelial/mesenchymal cell interactions in developing hair follicles (Nishioka et al., 2008; Itoh et al., 2008). Moreover, patients with this syndrome may have growth hormone (GH) deficiency since this transcription factor has been found to be expressed in the pituitary and hypothalamus (Correa et al., 2018).

Linear growth is decreased in almost all TRPS patients, both prenatally and postnatally; adult height falls below −2 SD in about half the patients (Maas et al., 2015). Table 1 presents GH axis evaluation and the effect of GH treatment in children with TRPS who were described previously. Only children whose TRPS diagnosis was confirmed by DNA analysis were included in the table (Stagi et al., 2008; Sohn et al., 2012; Merjaneh et al., 2014; Marques et al., 2015; Riedl et al., 2004). GH deficiency (defined as low growth hormone concentrations in two stimulation tests) was found in some, but not all patients. The response to treatment was variable (Table 1).

We report a boy with TRPS type I and GH deficiency, and the effect

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Table 1
The effect of growth hormone treatment on linear growth in children with molecular diagnosis of TRPS.

Patient no.	TRPS subtype (gender)	Genetic diagnosis	GH axis evaluation	GH treatment initiation			Status at GH treatment cessation/end of study follow up		Citation
				Age	Bone age	Height SDS	Age	Height SDS	
1	TRPS1 (M)	c.2722 C > T	GH peak after clonidine 10.2 ng/ml, after insulin 5.4 ng/ml, low nocturnal GH (mean concentration of 2.38 ng/ml).	9y 9m	7y 8m	−2	15y 10m	−0.5	Stagi et al. (2008)
2	TRPS1 (F)	c.2520dupT	GH peak after insulin 3.17 ng/ml, after dopamine 5.08 ng/ml	4y	2.6y	−2.5	16y	−2.1 [a]	Sohn et al. (2012)
3	TRPS1 (M)	c.1630 C > T	GH peak after glucagon 9.86 ng/ml, after dopamine 9.7 ng/ml	14y	16y	−2.1	15y	−3.6 [b]	Sohn et al. (2012)
4	TRPS1 (M)	c.3368 G > A	GH peak after insulin 15.3 ng/ml, after arginine 8.2 ng/ml	8y 4m	4y	−2.4	10y 4m	−1.4	Merjaneh et al. (2014)
5	TRPS1 (F)	c.1198C > T c.2086 C > T (in heterozygosity)	GH peak after clonidine 6.22 ng/ml, after dopamine 1.7 ng/ml	10y	4y 6m	−2.03	Not reported	Not reported	Marques et al. (2015)
6	TRPS2 (F)	Deletion of 12–15 Mb	GH peak after arginine 3.1 ng/ml, after dopamine 6.8 ng/ml	10y 3m	6y 6m	−4.8	11.3	−3.7	Riedl et al. (2004)
7	TRPS1 (M)	c.3698G > A	GH peak after clonidine 3.3 ng/ml, after glucagon 1.7 ng/ml	4y	2y 9m	−3.6	9y	−1.7	Current report, 2019

[a] After final height was achieved, the patient underwent another GH stimulation test that confirmed adult GH deficiency. GH therapy was subsequently continued at a reduced dose.
[b] The patient's height increased by less than 1 cm during 6 months, probably since treatment was initiated at bone age of 16 years, i.e. near adult final height.

of GH therapy on his linear growth and on the radiographic appearance of the femoral epiphyses.

2. Case description

The patient presented at age 3.5 years for evaluation of short stature. He was born to non-consanguineous parents at term by vaginal delivery, with a birth weight of 3100 g. His history was significant for horseshoe kidney with left hydronephrosis due to stenosis of the ureter-bladder junction. At first evaluation, his height was 87 cm (−3.2 SD) and his weight was 12.4 kg (−2.0 SD). The mid-parental height was 164 cm, corresponding to −1.8 SD (the father's height was 165 cm and the mother's height 150 cm). On physical examination, the characteristic phenotype of TRPS was noted: sparse thin hair, laterally sparse eyebrows, a bulbous tip of the nose, a long philtrum and a thin upper lip (Fig. 1). Radiographs of the left hand at a chronological age of 4.8 years revealed bone age of 2.8 years, and cone-shaped epiphyses were identified (Fig. 2). Two growth hormone stimulation tests, with clonidine and glucagon, revealed severe GH deficiency (peak GH of 3.3 mcg/l and 1.7 mcg/l, respectively) with low insulin-like growth factor-1 (IGF1) (30.1 ng/ml, normal 35–217). Magnetic resonance imaging of the brain was unremarkable. These findings were compatible with GH deficiency, and GH treatment was initiated (0.03 mg/kg/day) at age 4 years. Linear growth improved significantly during GH treatment: 9 cm/year during the first year of treatment and 8 cm/year during the second year, compared to 3.6 cm/year before treatment (Fig. 1).

At age 6 years, the patient underwent surgery for correction of the ureter-bladder junction stenosis. Prior to the surgery a pelvic CT revealed bilateral irregularity of the proximal femoral epiphyses. Therefore, a pelvic radiograph was done that showed bilateral small and fragmented femoral epiphyses, resembling but not identical to Legg-Calve-Perthes disease. Since he did not have pain or a limp, GH treatment was continued. Subsequent radiographs of the pelvis done 8 and 19 months later showed improvement (Fig. 2). The boy continues to receive GH treatment. His current height at age 9 years is 123 cm (−1.7 SD) (Fig. 1). During the 5 years of treatment, his IGF1 level increased gradually from 30.1 ng/ml to 452 ng/ml.

Genetic analysis: Sanger sequencing of the TRPS1 gene identified a heterozygous sequence variant in exon 7 that results in an amino acid change (NM_014112.2: c.3698G > A; p.Cys1233Tyr). Two prediction programs (PolyPhen, SIFT) rate this mutation as disease causing. To the best of our knowledge, this mutation has not been described previously. Neither parent carries this mutation (the new variant was reported to ClinVar accession number SCV000925600).

3. Discussion

This report describes the linear growth of a boy with TRPS type I and GH deficiency treated with GH, and the radiographic appearance of his femoral epiphyses during treatment. Impaired growth is common in TRPS but is not universally expressed (Maas et al., 2015). The mean height SDS of 75 TRPS patients was −1.41 ± 1.15 (range −4.6 to +0.5) (Ludecke et al., 2001). GH treatment, initiated after appropriate evaluation of the GH axis, was reported in 11 patients (Stagi et al., 2008; Sohn et al., 2012; Merjaneh et al., 2014; Sarafoglou, Moassesfar, and Miller 2010; Naselli et al., 1998; Marques et al., 2015; Riedl et al., 2004). Table 1 presents seven patients whose TRPS diagnosis was confirmed by DNA analysis. GH deficiency was diagnosed in four of these patients, two additional ones were deemed growth hormone sufficiency and one patient had normal GH stimulation test result but low nocturnal GH, and was considered as partial GH deficient. The response to GH treatment was variable. In six patients, the height SDS increase was 0.4–1.9. One patient did not respond: a 14-year-old boy who did not show any growth velocity response after a 6-month GH trial, an outcome that could be expected due to his advanced bone age of 16 years (Sohn et al., 2012). The skeletal age in TRPS lags behind the

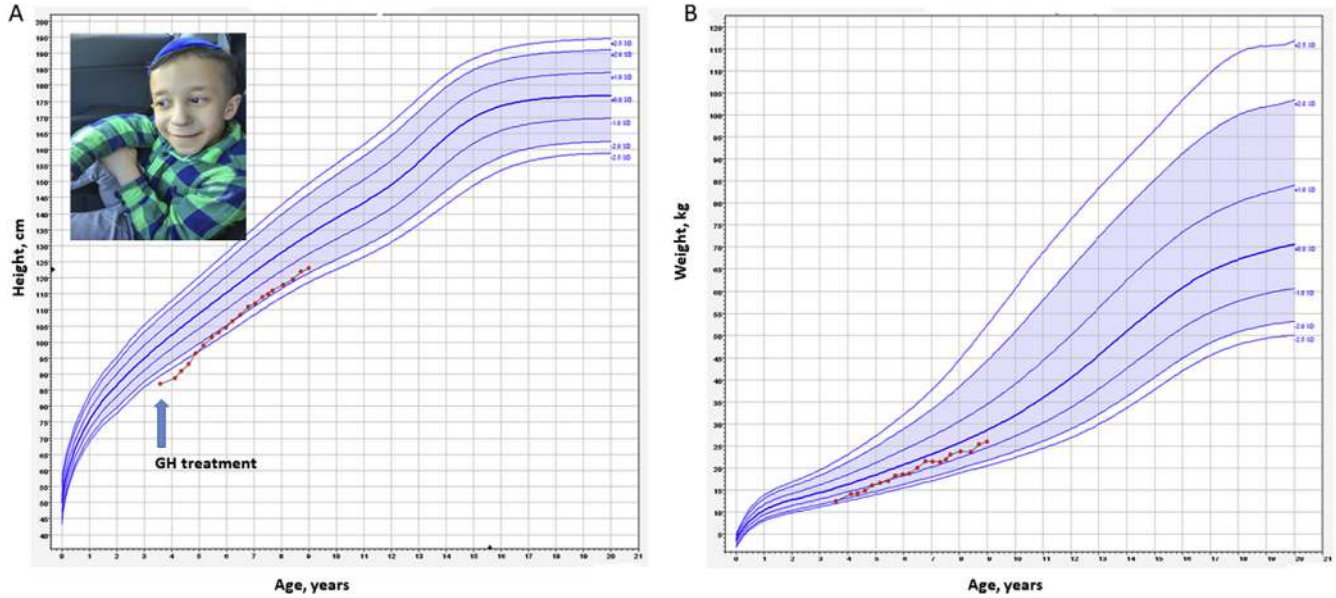

Fig. 1. Photo and growth charts of the patient. Note the typical features of sparse hair, laterally sparse eyebrows, bulbous nose, long philtrum and thin upper lip. (A) Weight (B) Height.

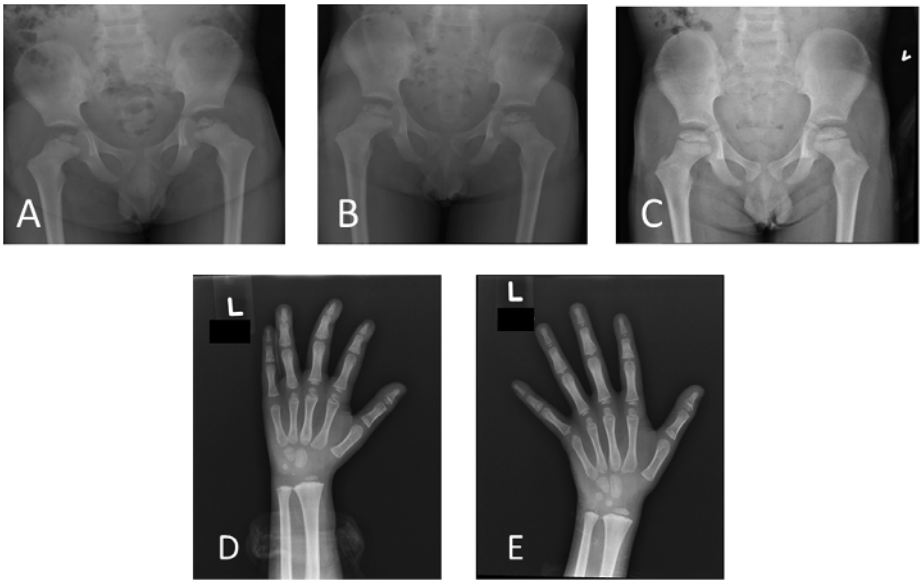

Fig. 2. (I) Sequential antero-posterior pelvic radiographs of the patient (A) at age 6 years, showing bilateral Perthes-like changes of the femoral head with fragmentation; (B) after 8 months; and (C) after 19 months, showing improvement. (II) Radiograph of the hands of the patient showing cone-shaped epiphyses and delayed bone age. (D) at age 5 years 11 months; and (E) at age 6 years 7 months.

chronological age until puberty, and then typically accelerates with irregular premature fusion of the epiphysis (Ludecke et al., 2001; Howell and Wynne-Davies, 1986). Therefore, in patients for whom GH treatment is considered, initiation before puberty is probably advisable, to achieve good response.

The mechanism by which GH treatment may improve growth velocity in children with TRPS has yet to be elucidated. In a cell culture model that mimics *TRPS1* mutations, IGF-1 expression by a chondrogenic cell line derived from a murine teratoma (ATDC5) was reduced by blockade of *TRPS1* expression with microRNA (Zhang et al., 2012). It is therefore possible that high systemic IGF-1 concentrations, resulting from growth hormone therapy, compensate for low local IGF-1 concentrations in the growth plates of individuals with *TRPS1* mutations. Indeed, the IGF1 concentrations of our patient had increased during GH treatment within the normal range.

Patients with TRPS frequently have hip deformities such as coxa vara, coxa plana, coxa magna and secondary joint degeneration, characterized by joint space narrowing and subchondral sclerosis (de Barros and Kakehasi, 2016). The long-term morbidity of TRPS is due to the early osteoarthritis-like changes with marked epiphyseal involvement which affect the large joints, especially the hips (Maas et al., 2015), and osteopenia (Stagi et al., 2008). We describe here, for the first time, improvement in the radiographic appearance of the femoral epiphysis following GH treatment. This observation may be coincidental. However, previous studies demonstrated that hip pathology in TRPS takes a rather progressive course, leading to pain and decreased mobility in adolescence or early adulthood (Dunbar, Sussman, and Aiona 1995; Morris et al., 1985). Not infrequently a hip prosthesis is implanted at as early an age as 30 years (Maas et al., 2015). For example, Hufeland et al. described a family with 4 cases of TRPS type 1 over 3 generations, who were not treated with GH (Hufeland, Rahner, and Krauspe 2015). The index case and also his mother, his aunt and his grandmother were diagnosed with Perthes-like changes of the hip during childhood. Pelvic radiographs of the adult patients revealed varying stages of sequelae compatible with those known in true Perthes disease. The grandmother had bilateral total hip replacement at age 52 years. We suggest that

high systemic IGF-1 concentrations, resulting from growth hormone therapy, may have a beneficial effect on the epiphyses of children with TRPS. Receptors for IGF1 are expressed on chondrocytes in the epiphyseal growth plate (Yakar and Isaksson, 2016) and also on all osteogenic cells including osteoblasts, osteocytes and osteoclasts (Yakar and Isaksson, 2016; Sheng et al., 2013). It is possible that low local IGF-1 concentrations of individuals with TRPS (Zhang et al., 2012) have a role in the pathogenesis of the Perthes-like changes of the hip, while high systemic IGF-1 concentrations, resulting from growth hormone therapy, compensate for it. Interestingly, Sarafoglou et al. described improved bone mineral density in response to GH therapy in two siblings with TRPS type 1 (Sarafoglou, Moassesfar, and Miller 2010).

In conclusion, our observations support the evaluation of the GH axis in children with TRPS and severe short stature. In children with abnormal GH stimulation tests, GH treatment may be considered. Children who initiate treatment with GH should be monitored carefully. Specifically, pelvic radiographs should be evaluated before and during GH therapy. We suggest that initiation of GH treatment may benefit both height and epiphyses status in some cases. Further studies are needed to support this observation.

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CRediT authorship contribution statement

Yael Levy-Shraga: Writing - original draft, Conceptualization. **Dalit Modan-Moses:** Writing - review & editing, Conceptualization. **Shlomo Wientroub:** Writing - review & editing, Supervision. **Dror Ovadia:** Writing - review & editing. **Leonid Zeitlin:** Writing - review & editing, Supervision.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2019.103830.

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