

CASE REPORT

Trichorhinophalangeal syndrome II, expanding the clinical spectrum



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Abstract We report a 4.5 year old Egyptian male child, fourth in the order of birth of healthy remote consanguineous parents. He has typical facial as well as skeletal features of Trichorhinophalangeal syndrome (TRPS) II. The facial features included bilateral downward slanting palpebral fissures, bulbous nose, long filtrum, retromicrognathia, sparse hair in the scalp and thick eyebrows. The skeletal features included retarded bone age, cone shaped epiphyses of the phalanges and multiple exostoses. The patient has also growth retardation, moderate mental retardation and hyperlaxity of the right knee joint. However our patient has some features not reported in TRPS II patients. These included bilateral partial ptosis, long eye lashes, preauricular skin tag, short 2nd right finger, short metacarpals of both thumbs. So we have to expand the clinical spectrum. Karyotype demonstrated 46,XY,del 8(q23.3-q24.1).

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1. Introduction

Trichorhinophalangeal syndrome (TRPS) is a rare genetic disorder characterized by abnormalities in hair (tricho), nose (rhino), and digits (phalangeal). Its diagnosis is mainly based on clinical and radiographic features [1].

In 1969, Giedion and Langer independently described a patient with features of TRF as well as multiple exostoses [2]. Then Hall et al., in 1974, introduced the name Langer–Giedion Syndrome (LGS) or TRPS II [3].

Three subtypes of TRPS have been described. TRPS I is caused by mutations in TRPS1 gene on chromosome 8, and is characterized by slow growing scalp hair, pear shaped nose, long filtrum and cone shaped epiphysis of fingers. TRPS II (OMIM 150230) is a contiguous gene syndrome which has in addition cartilaginous exostosis in ribs and vertebrae in addition to redundant skin and hypermobile joints. It is caused by loss of functional copies of TRPS1 and EXT1 genes secondary to 8q microdeletion [4,5]. Also while TRPS I is inherited in an autosomal dominant fashion, most cases of TRPS II are sporadic [1]. TRPS III, is a form of brachydactyly due to short metacarpals and severe short stature without exostosis. TRPS III is the severe end of TRPS spectrum and it is most often caused by a specific class of mutations in TRPS1 gene [4].

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We report a male patient with TRPS II with some unusual features after taking consent of the parents.

2. Case report

Our patient is an Egyptian male child, 4.5 years old, fourth in the order of birth of healthy remote consanguineous parents. The mother's age is 25 years, and the father's age is 35 years, and both are healthy. The patient presented to the Genetics Clinic complaining of dysmorphic features detected at birth, with poor weight gain. Pregnancy and delivery were uneventful, but the birth weight was 1.5 kg (< 5th centile). There is a family history of three first trimester abortions.

On examination the skull circumference is 46 cm (at 50th centile), anterior fontanel is 2 × 2 cm, length is 93 cm (< 5th centile), and weight is 11.6 kg (< 5th centile). The child has moderate mental retardation. The eyes show bilateral partial ptosis, long eye lashes, and bilateral downward slanting palpebral fissures, broad nasal bridge with bulbous pear shaped nose with tented nares, long wide prominent filtrum, thin upper and lower lips with hemangioma at and above the upper lip, and below the lower lip, as well as retromicrognathia. The ears are large and low set, with a preauricular skin tag at the right side. The hair is fine and scarce in some areas of the scalp. Eyebrows although thick, the hair is sparse (Figs. 1 and 2).

The upper limbs show bilateral clinodactyly of the 5th fingers and the right index finger is short with absent nail (Fig. 3). The lower limbs show hyperextension of the right knee joint (Fig. 4), bilateral overriding of the 2nd toe over the 3rd toe, partial syndactyly between 4th and 5th toes, and medial deviation of the 1st, 2nd and 3rd toes of the right foot (Fig. 5).

The chest wall is not symmetrical with the right side more prominent, with multiple firm swellings all over the body,

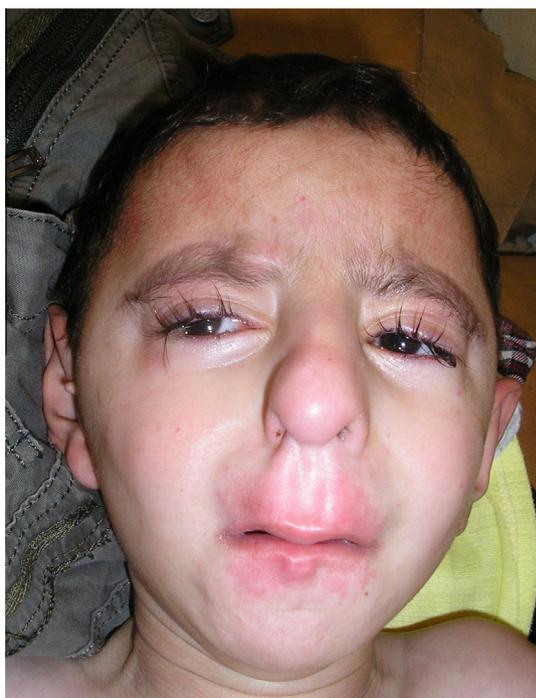


Figure 1 Facial features of the patient.



Figure 2 Large low set ear with a preauricular skin tag, and retromicrognathia.

related to bones not attached to the skin with different sizes ranging from 1 to 3 cm (Fig. 6).

Cardiac, abdominal, neurological and external genitalia examinations are normal.

Hand radiographs reveal hypoplastic middle phalanges of both fifth fingers. Cone shaped epiphyses are more appreciated at the proximal end of proximal phalanges of the second, third and fourth fingers. The first metacarpal bone is short and broad on both sides, and the fifth metacarpal bone has similar yet less pronounced appearance (Fig. 7). Metaphyseal expansion of the distal radius is associated with sessile exostoses on both sides (Fig. 8). Plain X-ray of both knee joints and legs reveals osseous excrescences projecting from lateral aspect of distal tibial diaphysis on the right side. Secondary scalloping of the opposing border of distal fibula is noted. Similar osseous projections are evident in the proximal tibia and fibula and distal femur on both sides. Metaphyseal expansion is also noted in the proximal tibia and distal femur on the right side



Figure 3 Bilateral clinodactyly of the 5th fingers, the right index finger is short with absent nail.



Figure 4 Hyperextension of the right knee joint.



Figure 6 Multiple firm swelling on ribs.



Figure 5 Bilateral overriding of the 2nd toe over the 3rd toe, and syndactyly between 4th and 5th toes, medial deviation of the 1st, 2nd and 3rd of the right foot, bilateral dysplastic nails of 3rd toes.

and proximal fibula on the left side. Sessile exostoses are noted at the proximal shaft of the right femur (Figs. 9 and 10). Chest radiograph revealed sessile cartilaginous exostoses projecting from the lateral scapular border of both sides (Fig. 11).

ECHO cardiography, pelviabdominal ultrasonography, and MRI brain were normal. karyotype revealed 46,XY,del 8 (q23.3q24.1).

3. Discussion

Our patient had the typical facial features of TRPS II including bulbous pear shaped nose, with tented nares, wide prominent filtrum, and thin upper and lower lips with hemangiomata



Figure 7 Plain X-ray of both hands reveals retarded bone age. The middle phalanx of both fifth fingers is hypoplastic (white arrows). Cone shaped epiphysis is more appreciated at the proximal end of proximal phalanges of the second, third and fourth fingers (black arrows). The metacarpal bone of the thumb is short and broad on both sides (black asterisk), the fifth metacarpal bone has similar yet less pronounced appearance (white asterisk).

above and below both lips, as well as thick eyebrows with sparse hair. However he had some facial features not reported before like bilateral partial ptosis, a preauricular skin tag, short 2nd finger and short metacarpals of both thumbs.

Our patient had also moderate mental retardation, sparse scalp hair, and subluxation of the right knee joint. He had also the typical skeletal findings including cone shaped epiphyses at the phalanges, retarded bone age, multiple cartilaginous exostoses and short stature as reported previously [6]. Some



Figure 8 Plain X-ray of both forearms show metaphyseal expansion of the distal radius on both sides associated with a sessile exostosis on the right side (arrow).

other skeletal abnormalities like tibial hemimelia (hypoplasia of the tibia) were described in some reported cases of LGS and an 8q23.1-q24.12 interstitial deletion [5] which was not found in our patient.

Our patient had also short stature. Pronounced short stature (-4.8 SD) was reported in a patient with LGS, who had growth hormone (GH) deficiency with diminished response in three stimulation tests [7]. Hearing was normal in our patient although hearing loss was reported previously [8].

ECHO cardiography, pelviabdominal ultrasonography, and MRI brain were normal in our patient. However, Frynes et al., [9] and Partington et al., [10] described hydrometrocolpos and hematometra as complications of this syndrome. Kozłowski et al. [11], and Partington et al., [10] described uretral reflux in LGS patients which required reimplantation of the ureters into the bladder. Also Ramos et al., [12] found persistent cloaca and the prune belly sequence, and Morioka, et al., [13] described a patient with submucous cleft palate.

There is remote consanguinity between the parents of our patient although consanguineous marriage rate is high in Egypt [14]. The parents had also 3 first trimestric abortions as well as one unaffected female child, and our patient is the only affected patient in his family which goes with the sporadic inheritance of LGS. Although few familial cases have been reported, Min et al., [15] reported TRPS II in a family with 2 affected and 2 unaffected sibs. The mother carried an interstitial translocation (46,XX, ins (13;8)(q23q24) which resulted in recurrence of TRPS II in this family.

Follow up of patients with TRPS II indicates that their practical skills are better than their intellectual capability, and, for this reason, they are often underestimated. Some patients develop seizures at variable ages. Osteomas on processes of cervical vertebrae may cause pressure on cervical



Figure 9 Plain X-ray of both knee joints and legs. Osseous excrescence is seen projecting from lateral aspect of distal tibial diaphysis (black arrow). Secondary scalloping of the opposing border of distal fibula is noted. Similar osseous projections are seen in the proximal tibia on the left side and distal femur on the right (white arrows). Metaphyseal expansion is also noted in the proximal tibia and distal femur on the right side and proximal fibula on the left side (asterisk).

nerves or dissection of cerebral arteries. Joint stiffness is observed during childhood, changes later to cause joint laxity causing. Almost all males become bald at or soon after puberty, and some develop gynecomastia. Growth hormone



Figure 10 Plain X-ray of the pelvis. Sessile exostosis is seen arising from the lateral border of the proximal right femur (arrow).



Figure 11 Plain X-ray of the chest. Metaphyseal expansion of the proximal end of both humeri (asterisk). Sessile exostoses are seen projecting from the lateral scapular border on both sides (arrows).

deficiency was found in few patients, TSH deficiency was reported only in one patient. Puberty and fertility are diminished, and no instance of transmission of the deletion from a non-mosaic parent to a child has been observed so far. Several affected females had vaginal atresia [16].

The tricho-rhino-phalangeal syndromes type I (TRPS I) and type II (TRPS II) result from the deletion of overlapping sets of genes within the Langer–Giedion syndrome chromosomal region (LGCR) on chromosome 8. Most TRPS II patients have cytogenetically visible deletions and are often mentally retarded [17]. There is no agreement as to the deleted band(s) on chromosome 8. Our patient had deletion in 8q23.3–8q24.1. LGS patients have a hemizygous deletion on chromosome 8q23.3–24.11 which spans at least the 2.8 Mb-region from TRPS1 through EXT1. Only patients with Langer deletions that extend more than this interval tend to have mental retardation. Also LGS was reported in a patient with molecularly proven mosaic interstitial deletion in 8q22.3–q24.13 which spans 19.79 Mb and 50 genes or loci including TRPS1 and EXT1 [6]. McBrien et al., [18] reported a boy with small microdeletion involving EXT1 alone but with some features of Langer–Giedion syndrome suggesting a functional disturbance of TRPS1. This boy, in addition to a mild Langer–Giedion like phenotype, also had some unusual features including prominent toe pads and fat pads on the soles of his feet similar to those described in Pierpont syndrome. There have been previous reports of patients with LGS phenotype and 8q24 deletions leaving the TRPS1 gene intact. One of those patients had normal height, mild developmental delay, dyslalia premature adrenarche, and premature pubarche [19].

Complex chromosomal rearrangement was also reported in a case of LGS with some atypical features. The karyotype included a 8q23.3–q24.1 deletion, as well as a 21q22.1 deletion and a balanced reciprocal translocation t(2;11)(p24;p15) de novo, confirmed by FISH analysis [20].

Prenatal diagnosis was molecularly proven at 32 weeks of gestation in a female fetus [21].

To conclude: From the above discussion early diagnosis of TRPS II is essential to provide genetic counseling to affected families and to assure orthopedic follow up and management

of growth, hearing and speech problems. Although the syndrome is considered rare, dermatologist must be aware of the patients complaining of a premature onset of androgenic pattern alopecia [22]. Also some additional features not reported previously were detected in our patient, thus, expanding the clinical spectrum.

Conflict of interest

The authors declare no conflict of interests.

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