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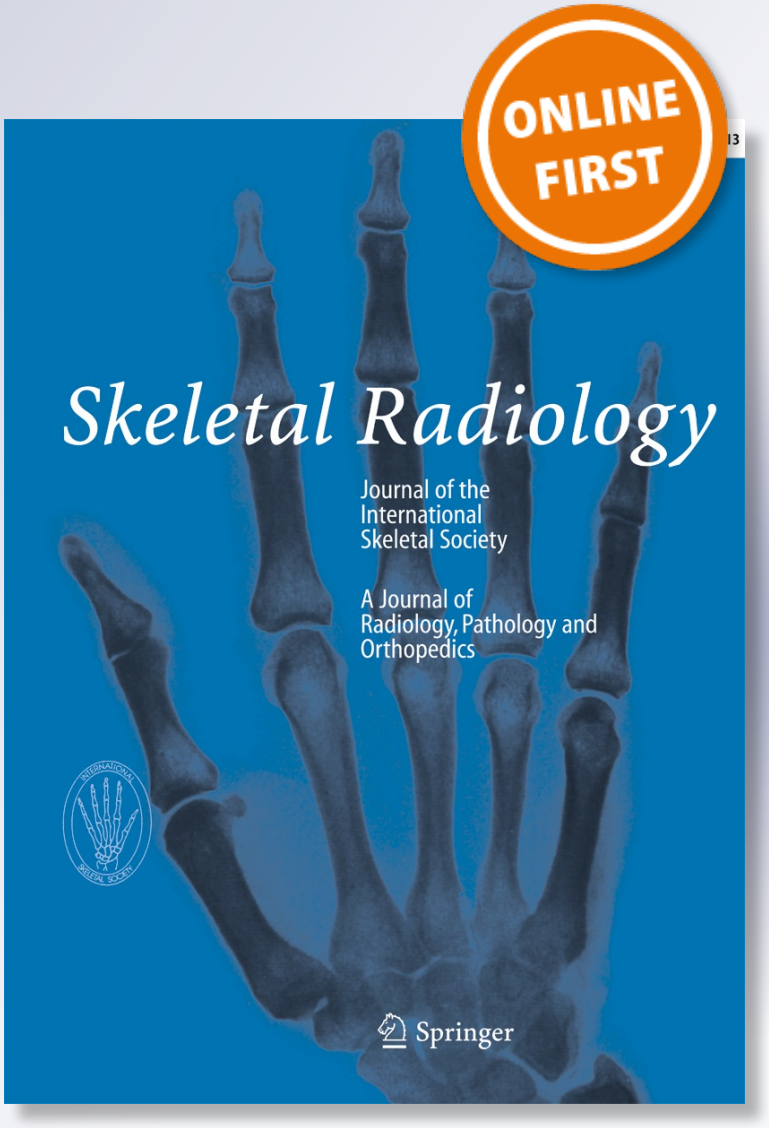
Skeletal Radiology
Journal of the International Skeletal Society A Journal of Radiology, Pathology and Orthopedics

ISSN 0364-2348

Skeletal Radiol
DOI 10.1007/s00256-013-1726-0



Springer

Skeletal Radiol
DOI 10.1007/s00256-013-1726-0

CASE REPORT

Langer–Giedion syndrome: the evolving imaging features in hands and beyond

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Received: 6 June 2013 / Revised: 17 August 2013 / Accepted: 26 August 2013

Abstract Trichorhinophalangeal syndrome (TRP) is a group of rare genetic disorders with characteristic clinical and radiological features. In this case report we discuss the evolution of imaging features in hands in a Chinese boy diagnosed with TRP II (Langer–Giedion syndrome, LGS). This article ramifies the diagnostic value of serial hand radiograph in clinically suspected cases of TRP.

Keywords Trichorhinophalangeal syndrome · Langer–Giedion syndrome · Cone-shaped epiphysis · Ivory epiphysis · Exostosis · Triphalangeal thumb · Brachydactyly

Introduction

Trichorhinophalangeal syndrome (TRP) is a rare genetic disorder characterized by abnormalities in hair (tricho), nose (rhino), and digits (phalangeal). It was first described by Andreas Giedion, a Swiss pediatric radiologist who had been the chief of the Department of Radiology, University of Zurich Children's Hospital. In 1966, he reported the association of slowly growing hair, long pear-shaped nose with bulbous tip, and finger deformities [1]. In 1969, Giedion and Leonard O. Langer Jr. independently described a patient with these features as well as multiple exostoses [2]. Langer was an American radiologist and the co-author of the classical atlas Bone Dysplasias. In 1974, the name LGS or TRP II was introduced subsequently by Hall et al. [3].

The diagnosis of TRP is mainly based on clinical and radiographic features. Here we report our experience with this disease in a 4-year-old mentally retarded Chinese boy who was referred to our Orthopaedic Department for management for his right thumb deformity and multiple exostoses.

Case report

A 4-year-old mentally retarded Chinese boy was referred to our Orthopaedic Department for management for his right thumb deformity and multiple bony hard bumps suspicious of exostoses. His family history was unremarkable. He underwent excision of bilateral duplicated thumbs at the age of three in China. Despite the surgery, his right thumb had persistent limited movement. On physical examination he was found to have developmental delay and microcephaly. He had dysmorphic facial features of fine and sparse hair, prominent eye brows, flat nasal bridge, bulbous nose, long philtrum, and bat-like ears (Fig. 1). Bilateral thumb clinodactyly and little finger brachydactyly were identified. Bony hard bumps suspicious of exostoses were present at bilateral wrists, ankles, and rib cage. The diagnosis of LGS was made clinically based on these characteristic features.

The radiographs taken in China before surgical excision of the duplicated thumbs could not be traced. Hand radiographs taken on presentation to us showed triphalangeal right thumb with extra phalange between the proximal and distal phalanges (Fig. 2). Clinodactyly were present at both thumbs. Cone-shaped epiphyses were noted at the proximal phalanges of right thumb and left ring finger. Ivory epiphyses were evident in all the distal phalanges with epiphyses ossified. Bilateral

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Published online: 27 September 2013

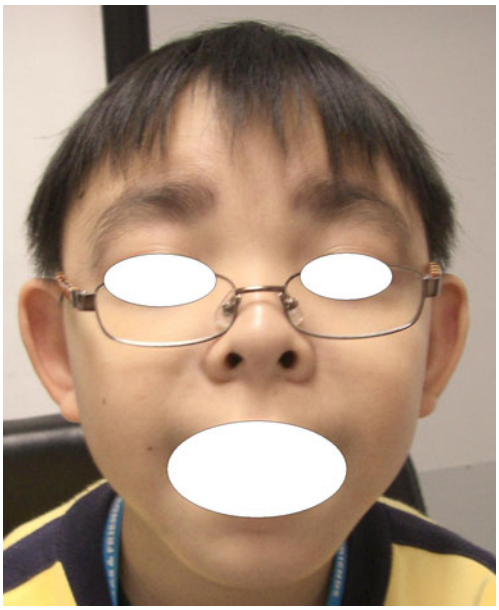

Fig. 1 Clinical photo of patient with dysmorphic facial features of fine and sparse hair, prominent eye brows, flat nasal bridge, bulbous nose, long philtrum, and bat-like ears—classic features of TRP

5th middle phalanges were hypoplastic. There were small exostoses at the right 1st metacarpal, right distal ulna, and left distal radius. These radiological findings confirmed the clinical suspicion of LGS. Genetic testing was inconclusive. The karyotype was 46XY and no deletion or duplication of the subtelomeric regions of chromosomes was detected. The detail on the technique utilized in the genetic test was not described in the report.

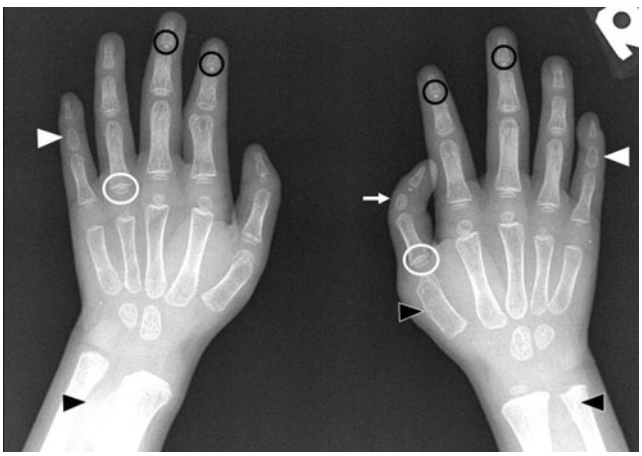

Fig. 2 Hand radiograph taken at the age of four, after excision of bilateral duplicated thumbs. The right thumb is triphalangeal with extra phalange between the proximal and distal phalanges (*white arrow*). There is mild clinodactyly at both thumbs. Cone-shaped epiphyses are present at the proximal phalanges of right thumb and left ring finger (*white circles*). Ivory epiphyses are evident in all distal phalanges with epiphyses ossified (*black circles*). Bilateral 5th middle phalanges are hypoplastic (*white arrowheads*). There are small exostoses at right 1st metacarpal, right distal ulna, and left distal radius (*black arrowheads*)

In order to improve the mobility and deformity of right thumb, the patient received wedge osteotomy of the extra phalange with fusion to the distal phalange. In the follow-up hand radiograph taken at the age of 10, the extra phalange had partially fused to the distal phalange (Fig. 3). The ivory epiphyses and cone-shaped epiphyses became more extensive. Ivory epiphyses were present in all the distal phalanges and cone-shaped epiphyses were evident in bilateral metacarpals, middle, and distal phalanges. There was mild shortening of bilateral fourth and fifth metacarpals. The exostoses had progressed in both the number and size. They were noted at the right thumb metacarpal, bilateral distal ulnae and radii, bilateral lower ribs, left iliac bone, right proximal femur, bilateral distal tibiae and left distal fibula (Fig. 4a–d).

Discussion

In 1984, Sugio et al. reported on nine patients in a family with an autosomal dominant anomaly characterized by typical features of TRP 1 as well as severe metacarpophalangeal shortness [4]. They reported the anomaly as Ruvalcaba syndrome, which Hunter disagreed as mental retardation and microcephaly, were lacking while typical features of TRP were present [5]. In 1986, Niikawa and Kamei reported a sporadic case with similar features and proposed that the condition should be recognized as TRP III [6].

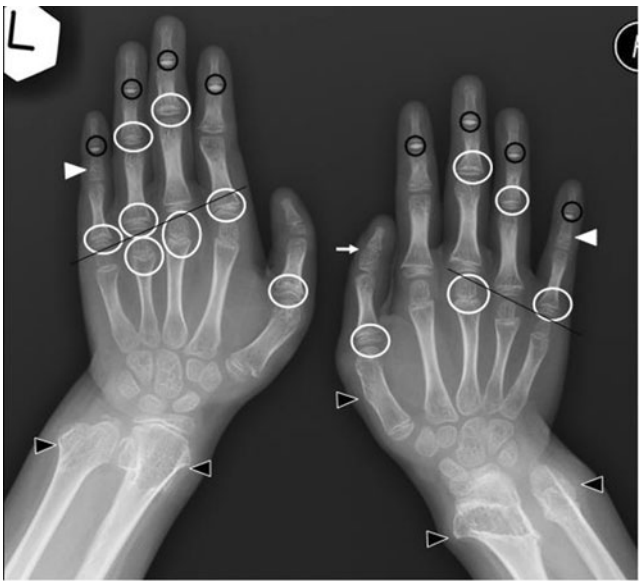

Fig. 3 Hand radiograph taken at the age of 10. The extra phalange of right thumb has partially fused with the distal phalange (*white arrow*). Ivory epiphyses are present in all distal phalanges (*black circles*). Cone-shaped epiphyses scatter among the metacarpals, middle and distal phalanges of both hands (*white circles*). Bilateral 4th and 5th middle phalanges are slightly short (*white arrowheads*). The exostoses have increase in both number and size. They are evident at the right 1st metacarpal, bilateral distal radii and ulnae (*black arrowheads*)

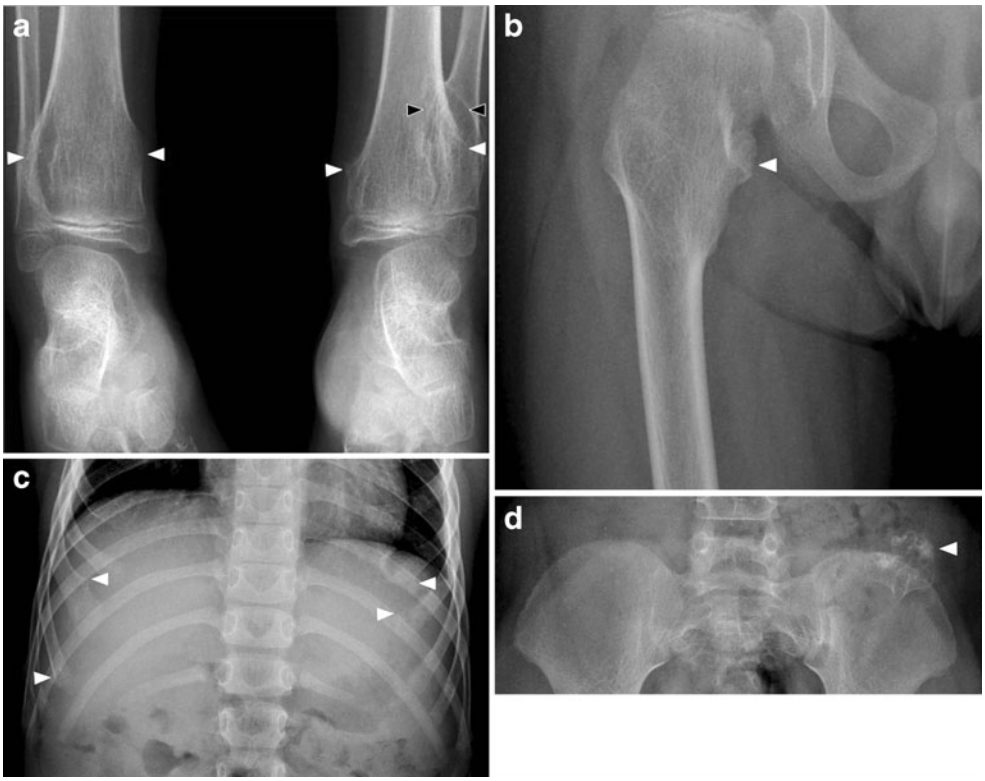

Fig. 4 Multiple sessile exostoses are noted at **a** bilateral distal tibiae (*white arrowheads*) and left distal fibula (*black arrowheads*); **b** proximal right femur (*white arrowhead*); **c** bilateral lower (*white arrowheads*) ribs and **d** left iliac bone (*white arrowhead*)

Although TRP III was initially distinguished from TRP I by severe short stature and marked brachydactyly, it represents the severe end of the same clinical spectrum caused by mutation of the same gene in the long arm of chromosome 8 (8q23.39) [7]. It is postulated that nonsense mutations happen in the TRP I phenotype, while missense mutations cause the TRP III phenotype [7]. The mode of inheritance in TRP I and III is autosomal dominant. In contrast, TRP II (LGS) are usually sporadic and caused by deletion of contiguous genes in the long arm of chromosome 8 (8q24.11-13), in which involves loss of functional copies of the TRP I and the multiple exostoses type I genes [8, 9]. Therefore TRP II combines the features of TRP I and multiple exostoses (diaphyseal aclasis) type I.

Clinically, patients with TRP have sparse, thin, slow-growing hairs. A high frontal hair line with bitemporal regression is common. In TRP I and III, the eyebrows may be thickened medially and thin or even absent laterally. In TRP II, the eyebrows can be normal. Sparse eyelashes and secondary sexual hairs may be evident. Long pear-shaped nose with bulbous tip and long philtrum are characteristic [1]. Deformities of the fingers and toes can result from cone-shaped epiphyses and irregular premature fusion, which could be mistaken as juvenile rheumatoid arthritis [10]. The middle phalanges are most commonly involved. Sometimes there is abnormal patellae with recurrent dislocation. Perthes-like change of the hip is common and can lead to severe secondary osteoarthritis in adult [11, 12]. In TRP II, patients have additional features of multiple exostoses since early childhood, microcephaly, skin and joint laxity [2, 3]. Mental impairment is common. Orthopaedic treatment would be required in those with musculoskeletal disorders, for example, digit deformities, exostoses with pressure symptoms or malignant transformation, Perthes-like disease, and degeneration of hip and knee [8, 9, 13–16]. The features of different types of TRP are summarized in Table 1 [4–6].

The diagnosis of TRP is mainly based on clinical and radiological findings. Confirmation with genetic analysis is helpful in case of nonclassical clinical presentation. Genetic analysis, however, may not be regarded as the diagnostic gold standard. There are reported cases of TRP II found to have an apparent normal karyotype [17–19]. It is likely related to different scale of chromosome deletion among different patients: while the deletion is visible in some cases, it could be too minute (might even down to DNA level) to be detected in others by techniques available [18].

Radiologically, the most consistent finding in TRP is cone-shaped epiphyses (cone) [8, 9, 13–16]. Mesophalangeal cones type 12 of Giedion is characteristic, in which the periphery towards the base thins [10]. It may appear as a tongue-like structure when the physis is still open. The surrounding metaphysis can present as a narrow wedge and appear as a second "tongue". These features increase steadily between 6 years of age and closure of the physis. The excavation sign is almost always present in type 12 cone, with progressive excavation of the cone's base. Its milder variant, type 12A cone, is occasionally seen in TRP I and III and almost in all TRP II [10].

Table 1 Features of TRP I, II, and III

Type	I	II	III
Chromosomal deletion	8q23.39	8q24.11-13	8q23.39
Mode of inheritance	Autosomal dominant	Sporadic	Autosomal dominant
Retarded growth	+	+	++
Mental retardation	−	common	−
Microcephaly	−	+	−
Eyebrows	Thickened medially and thin or even absent laterally	Can be normal	Thickened medially and thin or even absent laterally
Brachydactyly	Mild	Mild	Mild to severe
Bullous end metacarpals	−	−	+
Cone-shaped epiphyses	+	+	+++
	Mainly type 12 cones, occasionally type 12A cones	Almost always type 12A cones	Mainly type 12 cones, occasionally type 12A cones
Exostosis	−	+	−
Skin and joint laxity	−	+	−
Maculopapular nevi	−	+	−

Compared with type 12 cone, type 12A cone is more symmetrical, fuses at it apex with the metaphysis, with milder or absent thinning and infrequent excavation sign at its base. Type 12 or 12A cone can occasionally present at the proximal phalanges. Short metacarpals or metatarsals and phalanges can result from irregular epiphyseal closure. Sometimes the mesophalange can be normal. Both type 12 and 12A cones may occur together or rarely completely absent in TRP. Cone-shaped epiphysis is often not detectable before 2 years of age, although mild metaphyseal concavity, a manifestation of future cone-shaped epiphysis, can sometimes present during the first year of life [10].

Cone-shaped epiphysis can also be seen in normal and other pathological conditions (Table 2). In normal subjects, the distal phalange of the thumb and 5th middle phalange are commonly involved [16]. The involvement of proximal phalanges of third and fourth middle phalanges suggests pathology. Ivory epiphysis is another characteristic feature of TRP, which is known as uniformly sclerotic epiphysis lacking internal trabeculation. As cone-shaped epiphysis, ivory epiphysis can occur in both normal and pathological conditions (Table 3) [16]. Only the distal phalanges and the 5th middle phalanges are involved in normal variant. Ivory epiphysis at the proximal phalange strongly suggests generalized bone disease. The presence of both ivory and type 12 or 12A cone are suggestive of TRP. Other hand features in TRP include triphalangeal thumb which can be associated with polydactyly, shortening of the metacarpals (especially 4th and 5th metacarpals), and shortening of the phalanges [14].

Table 2 Differentials of cone-shaped epiphysis

Normal variant
Cono-renal syndrome
Trichorhinophalangeal syndrome
Acrodysostosis
Asphyxiating thoracic dysplasia
Chondroectodermal dysplasia
Metaphyseal chondrodysplasia
Chondrodysplasia punctata
Cleidocranial dysplasia
Peripheral dysostosis
Any type of metaphyseal-epiphyseal insult

Conclusions

Langer–Giedion syndrome is a rare disease with characteristic clinical and radiological features. A radiographic triad

Table 3 Differentials of ivory epiphysis

Normal variant
Condition associated with growth retardation
Trichorhinophalangeal syndrome
Cockayne syndrome
Down syndrome
Multiple epiphyseal dysplasia, spondylo-epiphyseal dysplasia
Diastrophic dysplasia
Hypopituitarism
Morquio syndrome

consisting of ivory epiphysis, type 12A coned epiphysis, and exostosis is suggestive of LGS, yet further research is needed to validate its diagnostic value. Since the radiological features in hands can evolve with time, serial hand radiographs is valuable in clinically suspected cases with negative or inconclusive radiological findings in initial imaging.

Declare The authors declare that they have no conflicts of interest.

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