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TRICHO-RHINO-PHALANGEAL SYNDROME TYPE II
THE LANGER-GIEDION SYNDROME

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Summary A case of tricho-rhino-phalangeal syndrome associated with short stature of postnatal onset, multiple exostosis and mental retardation (TRP syndrome Type II, or the Langer-Giedion syndrome) is reported. This case was the ninth such instances of this combination to be reported in the world literature. Like the other eight, it was sporadic. In addition, Perthes-disease-like bone changes, speech disturbance and pulmonary stenosis were observed.

The mean age of the father, but not the mother, at the birth of the reported cases, including the present one, is higher than that of the general population. The absence of affected siblings in TRP syndrome Type II may exclude recessive inheritance. Rather, the observed increase in paternal age and the low fitness of the patients may point to the possibility that the abnormality is due to a newly-mutated dominant gene, which is eliminated within each generation as soon as it has been produced.

INTRODUCTION

The term "tricho-rhino-phalangeal (TRP) syndrome" was first coined by Giedion in 1966. The characteristics of this syndrome are hypotrichosis of the scalp hair, a peculiar pear-shaped nose, a long philtrum, and cone-shaped epiphyses of the middle phalanges of both hands, resulting in deformity of the fingers.

The purpose of this paper is to report a sporadic case of TRP syndrome associated with short stature of postnatal onset, multiple exostosis, mental retardation (TRP syndrome Type II, or the Langer-Giedion syndrome), Perthes-disease-like bone changes, speech disturbance and pulmonary stenosis.

CASE REPORT

Y. H., a 10-year-old boy

Chief complaints. Short stature of postnatal onset, mental retardation, lumps around the knees and dull pain of the left hip and bilateral knee joints.

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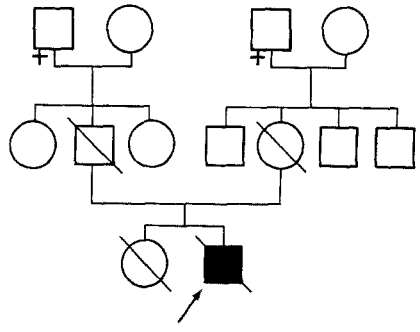

Fig. 1. Pedigree chart of the patient's family.

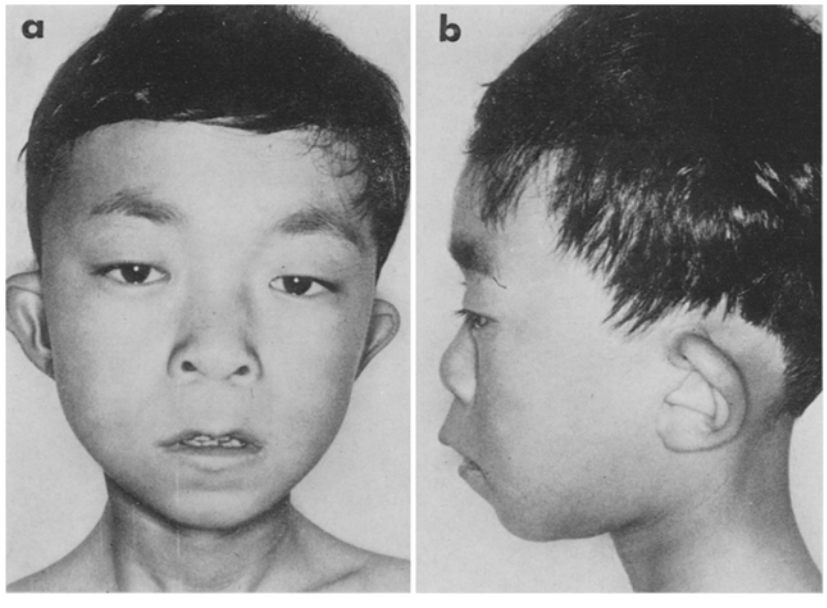

Fig. 2. External appearance of the head and face showing marked hypotrichosis of the scalp hair, a peculiar pear-shaped nose, a long philtrum and bat ears. a. Front view, b. Lateral view.

Past and family histories. The patient was born on Sept. 27, 1967, at the 42nd gestational week. He was the product of a normal pregnancy and delivery, with no history of maternal illness or exposure to teratogenic agents. The birth wright was 2,800 g. His father was 38-year-old and his mother 32-year-old at the time of the patient's birth. The mother had no history of previous abortion. Both parents and an elder sister were alive and well. There was no history of consanguinity or malformations in the family (Fig. 1). At the age of one year, pulmonary stenosis

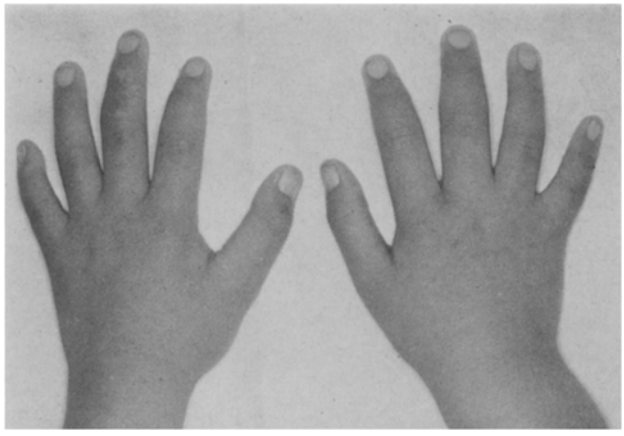

Fig. 3. External appearance of the hands showing marked shortening of the middle phalanges of the index through little fingers. The base of the middle phalanges of the fingers are broad.

was detected by a cardiologist. However, surgery was not indicated. There was no history of severe respiratory infection during infancy.

Present illness. Since early childhood, stunting, or postnatal growth deficiency, mental retardation, speech disturbance and markedly sparse scalp hair were noted. Starting at around the age of seven, lumps and dull pain around both knee joints, as well as dull pain around the left hip joint were also noted.

Clinical findings. The patient was a relatively well-nourished boy with a markedly short stature of 121.2 cm, low body weight of 20 kg and small head circumference of 48.5 cm (as compared with Japanese norms for his age of 130 cm, 27 kg and 53 cm, respectively).

The scalp hair was noticeably fine and sparse (hypotrichosis), and the facies was peculiar: the nose was wide, round and pear-shaped, the philtrum markedly long and the upper lip thin; the eyelids were somewhat ptotic and epicanthus was observed; the external ears were low set and markedly anteverted (bat ears); and the mandible was micrognatic (Figs. 2a and b).

At the proximal metaphyses of both humeri and at the lateral and medial condyles of both femora and tibiae, round bony lumps were also evident. The motility of the knee and ankle joints was limited bilaterally. There was swelling at the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints on the index to little fingers. The middle phalanges of these digits were short, and the fingers taper-shaped. Flexion of the PIP and DIP joints was lowered by 40 to 60 degrees (Fig. 3).

There was neither joint laxity nor redundant skin. Nevi of the skin were not observed.

The systolic murmur was heard by heart ausculation.

There was marked speech disturbance.

Examination of mental development revealed retardation. The DQ (Developmental Quotient) examination undertaken when the patient was seven and a half years of age showed moderate retardation: 73% in social affinity, 80% in motility and 80% in speech.

Chromosomal analysis showed normal male: 46XY.

Roentgenographic findings. In the hands, cone-shaped epiphyses with premature epiphyseal closure were observed in the middle phalanges of the right index through little fingers, of the left index, middle and little fingers, of the basal phalanx of the left thumb and of the distal phalanges of both thumbs (Type 12 cone-shaped epiphysis as defined by Giedion in 1969). Spur-like bony protrusions (exostoses) were seen in the metaphyses of the right second through fifth and the left fourth and fifth metacarpals, of the basal phalanges of the right middle and little fingers, of the left thumb, and of the middle phalanges of the right index, middle and ring fingers and of the left index and middle fingers. Bone shadow of the epiphyses of the terminal phalanges of both little fingers were markedly condensed. The right fourth and fifth metacarpals slightly shortened (Fig. 4).

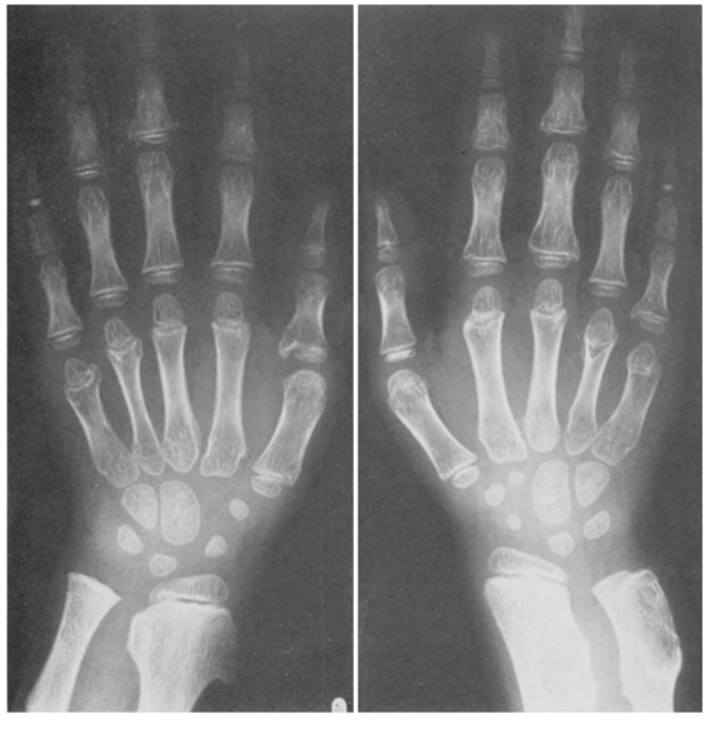

Fig. 4. Dorso-palmar roentgenogram of the hands showing Type 12 cone-shaped epiphyses and exostoses.

In the feet, cone-shaped epiphyses with premature epiphyseal closure were observed at the basal phalanges of the first through fifth toes. Spur-like bony protrusions (exostoses) were noted in the metaphyses of the right first through fifth metatarsals and of the left second, third and fourth metatarsals and in the meta-

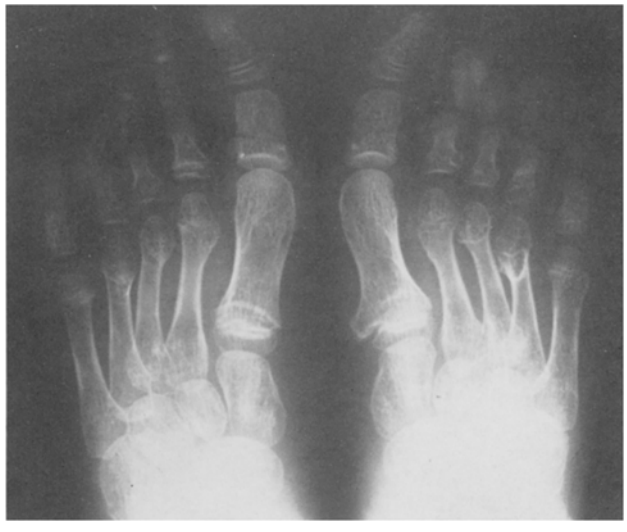

Fig. 5. Dorso-plantar roentgenogram of the feet showing Type 12 cone-shaped epiphyses and exostoses.

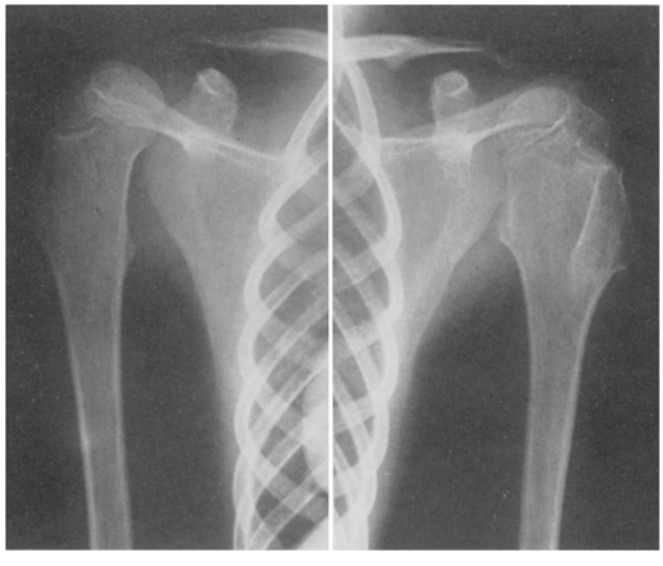

Fig. 6. Antero-posterior roentgenogram of the upper humeri showing exostoses at the metaphyses.

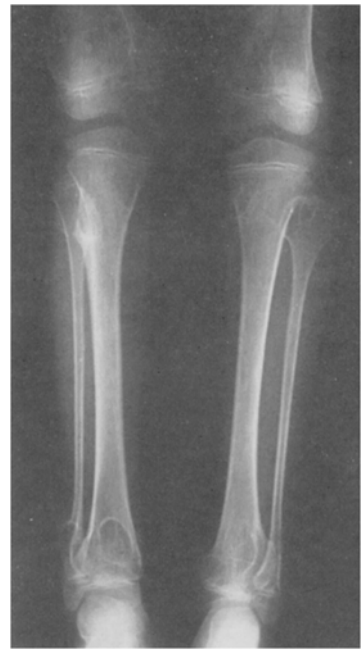

Fig. 7. Antero-posterior roentgenogram of the lower legs showing exostoses at the distal metaphyses of the femora, and the proximal and distal metaphyses of the tibiae and fibulae.

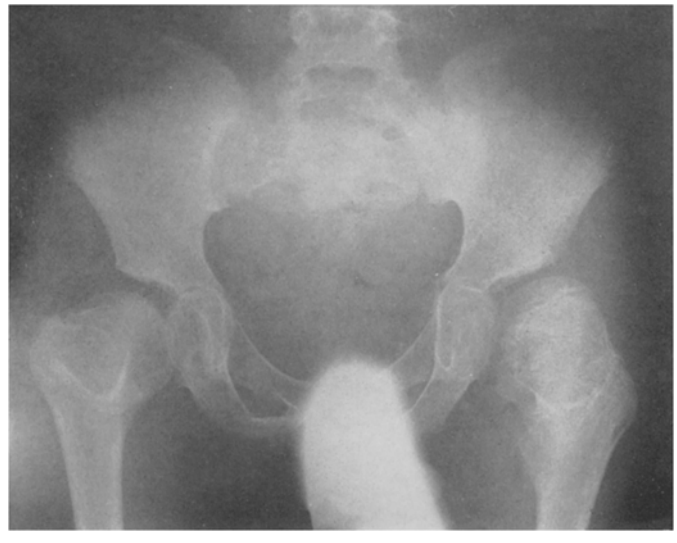

Fig. 8. Antero-posterior roentgenogram of the hip joints showing marked deformities of the heads and necks.

physes of the basal phalanges of the right second, third and fourth toes and the left first, third and fifth toes (Fig. 5).

Exostoses were seen in the proximal metaphyses of both humeri (Fig. 6), in the distal metaphyses of the radii and ulnae (Fig. 4), in the distal metaphyses of the femora, in the proximal and distal metaphyses of the tibiae and fibulae (Fig. 7), and at the costchondral junctions of the ribs.

At the right hip joint, the epiphysis of the femoral head was noticeably flat and the head markedly broadened. The neck was short and showed coxa vara deformity. These findings were considered to be Perthes-disease-like bone changes. At the left hip joint, the epiphysis of the femoral head was slightly flat, and marked coxa valga deformity was noted. At the medial parts of the femoral head and neck, there was a bony protrusion, irregular in contour. These findings were considered to be mixed Pethes-disease-like and exostosis-related changes (Fig. 8).

DISCUSSION

In 1969, Giedion published a classification of peripheral dysostoses and presented numerous patients with various phenotypes. Among his examples were five cases of Type 12 peripheral dysostosis and cartilaginous exostosis, one of which he felt might be an independent syndrome. This particular patient had hyperplastic skin, hypermobile joints, bat ears, a bulbous nose, a prominent philtrum, multiple exostoses, Type 12 cone-shaped epiphyses, postnatal growth deficiency and mental retardation.

Almost one year earlier, Langer briefly commented on a child with similar findings whom he felt represented an entity distinct from TRP syndrome. This patient, however, was reported in detail as an example of TRP syndrome by Gorlin *et al.* in 1969.

In 1974, Hall *et al.* reported five original cases of similar findings, which they termed the Langer-Giedion syndrome. During the same year, Spranger *et al.* classified TRP syndrome into Type I and Type II. They described hair, nose and hand changes very similar to those of TRP syndrome Type I were present in TRP syndrome Type II. Furthermore, in TRP syndrome Type II, short stature, mental retardation and multiple exostoses were seen as associated findings. They also called TRP syndrome Type II the Langer-Giedion syndrome.

In 1977, Stoltzfus *et al.* described an eighth patient with all the major features of the Langer-Giedion syndrome.

The pertinent features of the individual cases of TRP syndrome Type II, or the Langer-Giedion syndrome, are shown in Table 1. The case presented here showed almost all the characteristic findings of this syndrome.

Perthes-disease-like bone change were observed in three cases, including the present one. One of the authors, Sugiura, reported Perthes-disease-like bone changes and spondylolysthesis associated with TRP syndrome Type I in 1978.

Table 1. Pertinent features of the individual cases of tricho-rhino-phalangeal syndrome Type II.

Author(s)	Giedion	Gorlin *et al.*	Hall *et al.*					Stoltzfus *et al.*	Present case
	1	2	3	4	5	6	7	8	9
Craniofacies									
Typical facial appearance	+	+	+	+	+	+	+	+	+
Microcephaly (mild)	+	+	+	+	+	+	+	+	+
Sparse scalp hair	−*	+	+	+	+	+	+	+	+
Bat ears	+	+	+	+	+	+	+	+	+
Mental deficiency	+	+	+	+	+	+	+	+	+
Short stature of postnatal onset	+	+	+	+	+	+	+	+	+
Osseus									
Multiple exostoses	+	+	+	+	+	+	+	+	+
Cone-shaped epiphyses of the hands	+	+	+	+	+	+	+	+	+
Perthes-disease-like bone changes	−	+	−	+	−	−	?	?	+
Fractures	−	+	−	−	−	+	+	−	−
Skin									
Redundant, loose skin in early childhood	+	+	+	?	+	?	?	+	?
Nevi	−*	−*	+	−	+	+	+	+	−
Others									
Recurrent respiratory infections	+	+	+	−	−	?	?	+	−
Disproportionate delayed onset of speech	−	+	+	+	+	+	−	+	+

* Not noted in original evaluation but presence suggested in reviewing photographs.

The presence of redundant or loose skin during infancy and early childhood was noted in five patients. Hall *et al.* (1974) reported that this skin abnormality disappeared or regressed significantly between the ages of 6 and 14. The present case was a 10-year-old boy who showed no redundant skin.

Another skin finding presented in the above-mentioned five patients were small brown-to-black maculopapular nevi located about the upper trunk, neck, scalp and face. These lesions were not noted in the present case.

Condensation of bone shadow of the epiphyseal nuclei of the terminal phalanges of the little fingers noted in the present case was observed as associated bone changes in TRP syndrome Type I (Giedion, 1973).

Genetic hypothesis for TRP syndrome Type II (the Langer-Giedion syndrome)

According to Giedion *et al.* (1973), autosomal dominant transmission of TRP syndrome Type I was evident in 16 males and 30 females in 14 families. Sugiura

Table 2. Parental ages at birth of reported patients with tricho-rhino-phalangeal syndrome Type II.

Author(s)	Giedion	Gorlin *et al.*	Hall *et al.*					Stoltzfus *et al.*	Present case	Mean
	1	2	3	4	5	6	7	8	9	
Paternal age	?	34	26	36	27	?	?	38	38	33.3
Maternal age	?	22	22	27	22	?	?	28	32	25.5

et al. (1976) reported three Japanese families with TRP syndrome Type I indicating autosomal dominant inheritance through two or three generations.

No evidence for genetic factors in TRP syndrome Type II, however, has been presented. All nine reported cases were sporadic. And none was known to have married or to have had children, probably as a result of social handicap due to mental retardation.

As shown in Table 2, the mean age of the father, though not the mother, of the reported cases, is higher than that of the general population. A similar phenomenon has been established in sporadic cases due to new mutation in some dominant conditions such as achondroplasia, myositis ossificance progressiva and Apert's syndrome (Mørch, 1941; Penrose, 1955; Tünte and Lenz, 1967), whereas there is no increase of mean parental ages in familial cases transmitted from the affected parents. The increasing frequency of mutation with paternal age alone may be attributable to copying errors in gonial mitosis, which increase with paternal, but not maternal age.

The absence of affected siblings in TRP syndrome Type II may exclude recessive inheritance. Rather, the observed increase in paternal age and the low fitness of the patients may point to the possibility that the abnormality is due to a newly mutated dominant gene which is eliminated within each generation as soon as it has been produced.

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