

Syndrome of the month

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Rubinstein-Taybi syndrome

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In 1963 Rubinstein and Taybi¹ described seven children with mental handicap, broad thumbs and big toes, and very similar faces. They believed this to be a new and recognisable syndrome. The following year Coffin² confirmed this view, reporting six further cases, and it was he that proposed the eponymous title.

Epidemiology

This is a rare cause of mental handicap. Case finding studies in several English speaking countries have found about one case per 300 institutionalised subjects.^{3,4} Assuming that at that time about 1 per 1000 of the general population required institutionalisation the population frequency would be about 1 in 300 000. Sex ratio, parental ages, pregnancy history, and birth weights³ have been unremarkable in all studies. Cases have been reported from all racial groups.^{4,5}

Clinical features^{1,2,4,6,7}

Mental handicap or developmental delay is universally present with IQ estimations ranging from 20 to 80. The mean in those diagnosed young is probably around 50 though in two reported adult series, all institutionalised, the mean was 36 in one⁶ and 27 in the other.⁸

Stature is generally below the 25th centile, with the majority falling below the 3rd centile. Head circumference is also usually below the 3rd centile but may reach the 25th. In infancy the anterior fontanelle may be unusually large.

The following facial features are diagnostically important (figs 1 and 2).

EYES

Antimongoloid slant to palpebral fissures secondary to maxillary hypoplasia, long eyelashes, arched

eyebrows, and epicanthus. Ptosis, myopia, exotropia, coloboma, strabismus, and cataracts have also been reported.

NOSE

Classically the nose has a beaked or pinched appearance. The columella is long and protrudes beyond the alae nasi. The septum may be deviated. The bridge is often broad and flat.

MOUTH

The palate is usually high arched.

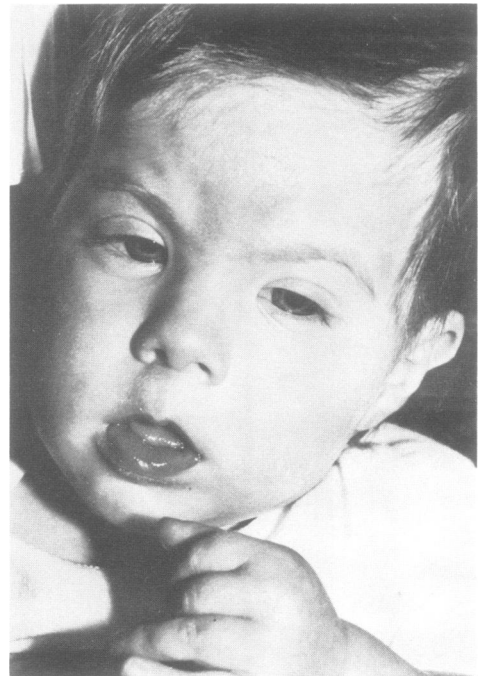


FIG 1 Facial features of child aged nine months.



FIG 2 Facial features of child aged 12 years.



EARS

The helices are frequently thickened or otherwise unusual and the ear may be low set or malrotated.

Abnormalities of the hands and feet are essential diagnostic features, in particular the shape of thumbs and big toes.

HANDS

The thumbs are disproportionately broad, especially the distal phalanx, which may be spatulate. The fingers, especially the distal phalanges may also be broad. Clinodactyly of the fifth finger and single palmar creases are less specific features. Syndactyly and polydactyly also occur (figs 3 and 4).

FEET

The big toe is usually large and broad. Adults frequently show hallux valgus and paronychia (fig 5).

OTHER SYSTEMS

Genitalia. Undescended testes are common in males and angulated penis is also reported.

Locomotor. Joint laxity is frequent and brisk reflexes have been observed in a number of cases. These features together with the skeletal anomalies described below are likely to account for the characteristic stiff, awkward gait, with flat feet, and slight hip and knee flexion.

ASSOCIATED FEATURES

Frequent respiratory infections in infancy,^{1 6} double rows of teeth,⁹ hirsutism,⁶ naevus flammeus,^{1 2 7} and keloid scar formation^{1 9} have been mentioned



FIG 3 Hand of nine month old child.

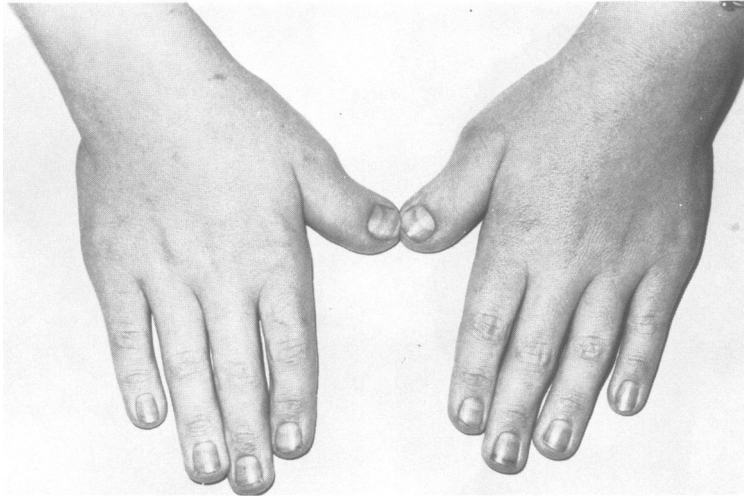


FIG 4 Hands of child of 12 years.

in several case reports and are probably significant associations. Two (possibly three) cases of acute lymphatic leukaemia have been described in affected children.¹⁰ Several series include children with mild renal anomalies⁷ and patent ductus arteriosus.⁷

X ray findings^{1 3 6 11}

A number of abnormalities have been consistently reported and are reviewed by Robson *et al.*¹¹ Generalised delay of skeletal maturation is frequently present. The foramen magnum is often large and

abnormalities of the cervical spine are common. In one case cervical spondylolisthesis led to tetraplegia.¹¹ Fusion of the first and second ribs and sternal abnormalities may be present.

X rays in the hands and feet show short, broad, often irregular terminal phalanges of the thumb and hallux, sometimes with angulation in the thumb (fig 6). Duplication of these terminal phalanges has also been described. Less common, but probably significant, are reports of dislocation of the radial head and patella.⁹



FIG 5 Feet of 12 year old child.

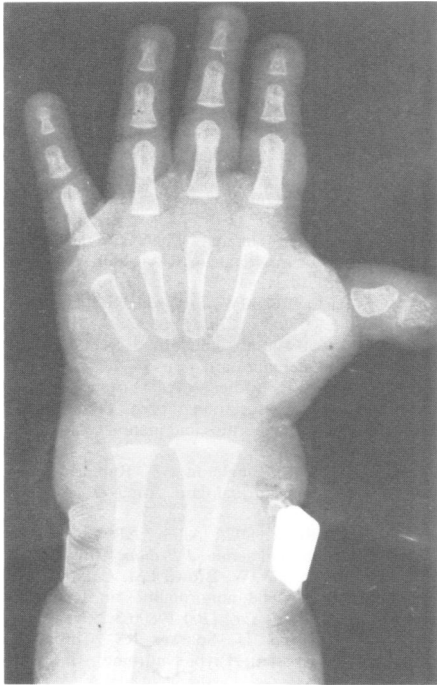


FIG 6 X ray of hand at 14 months (bone age nine months).

Differential diagnosis

As with other syndromes in which diagnosis depends entirely on the clinical features, this is not always easy. The facies is sometimes reminiscent of that seen in Treacher-Collins syndrome or occasionally Seckel or Hallermann-Streif syndromes. Broadening of the thumb and big toe may be judged subjectively when the facies are suggestive. Also, broad thumbs may occur independently in a mentally handicapped person, either as part of normal variation or as dominantly inherited brachydactyly type D. Both facial and acral features should be present for a secure diagnosis.

Aetiology and genetics

Chromosome studies have been essentially normal. One preliminary report¹² suggested that an interstitial deletion of chromosome 15, similar to that seen in Prader-Willi syndrome, might be present, but this was recognised to be an artefact and the suggestion withdrawn.¹³

Consanguinity (father-daughter incest) was present in one of the cases of Padfield *et al*⁶ and Der Kaloustian *et al*¹⁴ have described a first cousin marriage that gave rise to two affected children.

These children, however, did not have broad thumbs and toes, so their diagnosis must remain in doubt.

Other family studies have failed to confirm the suggestion of autosomal recessive inheritance. Simpson and Brissenden,³ studying 112 families, found two affected among 243 sibs. This is considerably higher than expected from the population frequency but quite incompatible with autosomal recessive inheritance.

Gillies and Roussounis¹⁵ described a pair of affected sibs and a second family in which they proposed the operation of a dominant gene with variable expression. In this family there were five sibs, one male being mentally handicapped. He had a sister with a similarly affected son and a brother with three children including a son, who showed developmental delay of varying degree. Facial features are said to be similar but not all had broad thumbs, so the authors suggested that insistence on this feature for diagnosis may result in under-reporting of multiplex families. However, the face of the proband is not entirely typical and the suggestion of dominant inheritance here seems far fetched.

More recently Cotsirilos *et al*¹⁶ have suggested autosomal dominant inheritance for a 'syndrome similar to Rubinstein-Taybi'. They described a family in which an apparently affected mother had two affected children and four affected sisters. The two children and the five adults all had broad thumbs and big toes but the illustrations of the mother's thumbs would be quite compatible with dominantly inherited stub thumbs or brachydactyly type D. She was of normal intelligence as were her four broad thumbed sisters. The older child had facial features compatible with Rubinstein-Taybi syndrome, delayed bone age, brisk reflexes, and mild mental handicap so the diagnosis seems appropriate for him. The younger sib was only eight weeks old and the facial features, though suggestive, were not classical. The mother's facial features similarly showed the appropriate nose shape but not the other characteristic features. The authors suggested that all seven broad thumbed family members were affected despite only one being mentally handicapped. They invoked variable expression of an autosomal dominant gene to explain this. A more likely explanation is that there was one truly affected subject in a family in which broad thumbs were segregating in an autosomal dominant manner.

The case for autosomal dominant inheritance seems as yet unproven. Since no subject showing all the classical hallmarks of the syndrome has reproduced, there remains the possibility of the full blown syndrome arising from a dominant mutation.

Twin studies are of great interest as six concordant and four discordant monozygotic pairs have been reported.^{5 16-18} Zygosity has been well established in the majority of these pairs. The figures preclude standard single gene aetiology and yet the frequency of concordance suggests that the causal factor was present at the time of conception or at least before the twinning event. An as yet sub-microscopic chromosome deletion could be the responsible factor, with twins being discordant where the event occurred at, or immediately after, the blastocyst splitting. By analogy with Prader-Willi syndrome very occasional families would carry balanced rearrangements and have more than one affected child.

An alternative suggestion made by Schinzel *et al*¹⁷ is that the syndrome could arise from an early defect in morphogenesis which might even be causally related to the twinning process.

This discussion has presupposed that the syndrome is a single homogeneous entity. It is possible that a proportion of cases arise from dominant mutations while the remainder are phenocopies arising after conception. The most attractive and unifying hypothesis is that of a chromosome micro-deletion. The twin and family data, as well as the variation in the severity of mental handicap and in the expression of physical features, are all entirely compatible with this mechanism. Time will tell whether or not it is the correct one.

Conclusion

Although at present the aetiology of this syndrome remains unknown, the family studies mentioned above³ show that the risk of recurrence in sibs is low. A figure of 1% seems appropriate for genetic counselling purposes.

Dr M Baraitser kindly supplied the photographs for figs 1 and 3.

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