

The Coffin-Lowry syndrome

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The Coffin-Lowry syndrome is a well defined clinical entity in which affected males manifest severe mental retardation in association with characteristic dysmorphic features, whereas the phenotypic spectrum in females ranges from normality through minor dysmorphism to the full blown syndrome as seen in the male. The eponymous title is derived from publications in 1966 and 1971 by Coffin *et al*¹ and Lowry *et al*² respectively. Initially the disorder was referred to as 'the syndrome of Coffin, Siris and Wegenkia'³ and 'Coffin's syndrome',⁴ with the term 'Coffin-Lowry syndrome' first being used by Temtamy *et al*⁵ in 1975.

This condition is not particularly rare. Over 50 cases have been reported in families of European,¹⁻¹¹ Asian,¹² and African¹³ origin. Two unrelated sibships, each containing multiple affected members, have been encountered in Leicestershire which has a population of approximately 850 000.

Clinical features

These are summarised in the table which is based on review of 58 published cases.¹⁻¹³

MALES

Growth parameters are generally normal at birth. Short stature becomes apparent during early childhood and has been noted as early as five months.⁸ Final adult height is usually well below the 3rd centile and may be further diminished by spinal involvement resulting in a low upper:lower segment ratio. Microcephaly occurs in a small number of cases. Ventricular dilatation with or without hydrocephalus has been documented,^{1 2 5 9 10} although it is not absolutely clear whether this is usually a consequence of raised intracranial pressure or of cerebral atrophy.

Craniofacial features are consistent and characteristic (fig 1). The forehead and supraorbital ridges are

prominent, with orbital hypertelorism and downward slanting, narrow palpebral fissures. The nose has a broad base, anteverted nares, thickened, flared alae, and a thick septum. There is mild midface hypoplasia in contrast to mandibular prognathism. The mouth is wide with thick, pouting lips. Orofacial findings include a high, narrow palate, malocclusion, hypodontia, peg shaped incisors, and midline lingual furrow.¹⁴ The ears appear to be large. This typical facies is usually apparent by the second year of life⁸ and shows progressive coarsening thereafter.

Truncal anomalies tend to be limited to pectus excavatum or pectus carinatum. Minor cardiac anomalies (murmurs, ventricular heave, and mitral incompetence)^{1 4 5 9} and inguinal herniae^{2 5 11 13} have been noted in only a few patients.

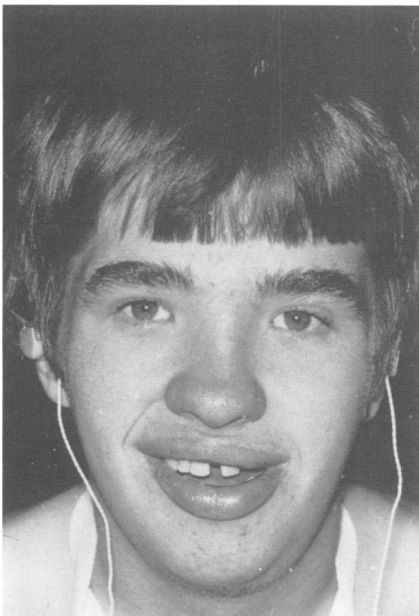
Limb abnormalities are relatively minor but very

TABLE Clinical features of the Coffin-Lowry syndrome (based on patients reported in references 1 to 13).

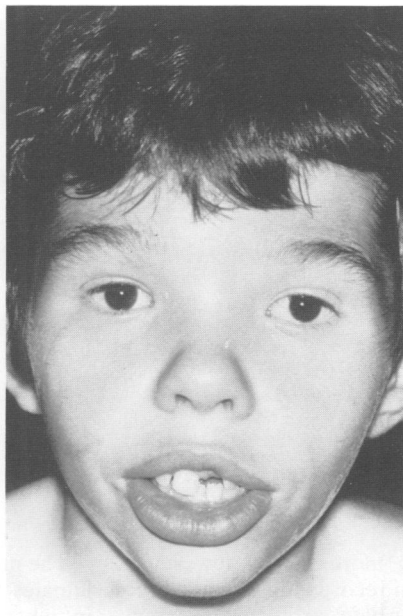
Clinical features	Males	Females
<i>Growth and CNS</i>		
Stature <3rd centile	29/30	10/21
<10th centile	1/30	3/21
Convulsions	8/17	—
Severe retardation	30/30	5/28
Mild retardation	—	18/28
Normal IQ	—	5/28
<i>Dysmorphism</i>		
Prominent brow/coarse facies	27/27	22/23
Hypertelorism/telecanthus	29/29	11/18
Antimongoloid slant	23/27	7/14
Broad nose/thick septum	25/25	19/20
Pouting, everted lips	27/28	16/20
Hypodontia	16/19	3/13
Pectus excavatum/carinatum	20/25	5/17
Kyphosis/scoliosis	21/28	5/19
Broad hands/tapering fingers	30/30	26/27
Hypothenar crease	16/17	13/15
<i>Radiology</i>		
Skull hyperostosis	14/22	8/15
Spinal changes	21/26	3/15
Distal phalangeal tufting	24/25	17/18
Delayed bone age	15/19	4/4



FIG 1 Facial views of four boys with the Coffin-Lowry syndrome. The boys in fig 1a are sibs, as are the boys shown in fig 1b and c.



(b)

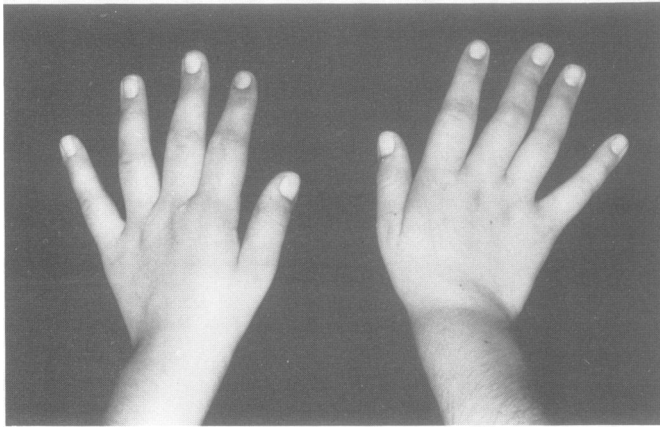


(c)

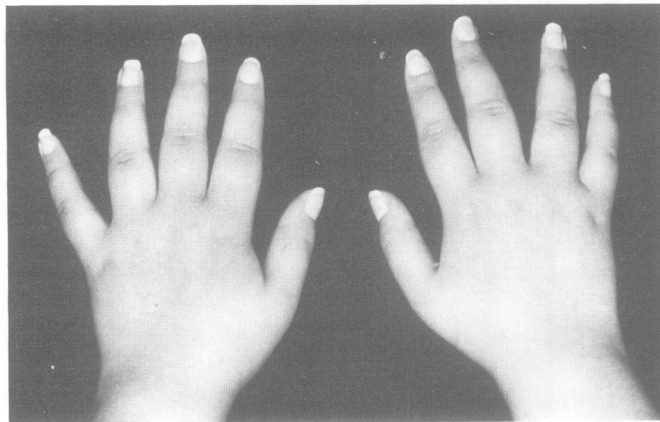
characteristic. The hands are broad and soft with puffy, tapering fingers and short, hyperconvex nails (fig 2). Many patients have a short horizontal crease in the hypothenar region. It has been suggested that the presence of increased subcutaneous fat in the forearms may serve as an early aid to diagnosis.¹⁵ *Skeletal involvement* may be minimal or potentially life threatening. The author knows of one adolescent male who died shortly after attempted surgical correction of a very severe kyphoscoliosis. His brother was similarly affected (fig 3). Radiological

findings may include calvarial hyperostosis, anterior wedging of the vertebral bodies, narrow intervertebral spaces, short metacarpals and phalanges, 'drumstick' terminal phalanges with 'tufting', and delayed bone age. These changes may show progressive deterioration as noted by Coffin *et al*¹ in their original paper entitled 'Mental retardation with osteocartilaginous anomalies.'

Mental retardation in affected males is invariably severe with IQ values as low as 16 having been recorded.⁹ Speech is particularly affected with many



(a)



(b)

FIG 2 The hands of a boy (a) and girl (b) with the Coffin-Lowry syndrome.

patients never mastering more than a few single words. Deafness has been recorded in at least three patients and may exacerbate problems of communication.^{8 9 11} Several patients have a history of recurrent generalised convulsions presenting as early as the first year of life.⁷

FEMALES

The clinical features are much more variable and usually much less severe than in the male. It should be remembered that the incidence figures given in the table are likely to be biased, since mildly affected or unaffected females will tend not to be ascertained. There do not appear to be any well documented published reports of an obligatory female 'carrier' who was found to be entirely normal on careful examination, although abnormalities may be limited to the hands.⁷

The most useful features in distinguishing 'carrier' females in whom the diagnosis has been made have a prominent, broad forehead with slightly coarse facies, broad nose, and full, everted lips (fig 4). The changes in the hands are strikingly similar to those seen in the male (fig 2), with radiological tufting of the distal phalanges. Over 50% of affected females have short stature and approximately 80% are mentally retarded, usually to a mild degree only. Psychiatric illness (psychotic behaviour and schizophrenia) has been described in two affected females.^{10 11}

Natural history

Problems are usually not suspected until early childhood. Thereafter the condition is relatively

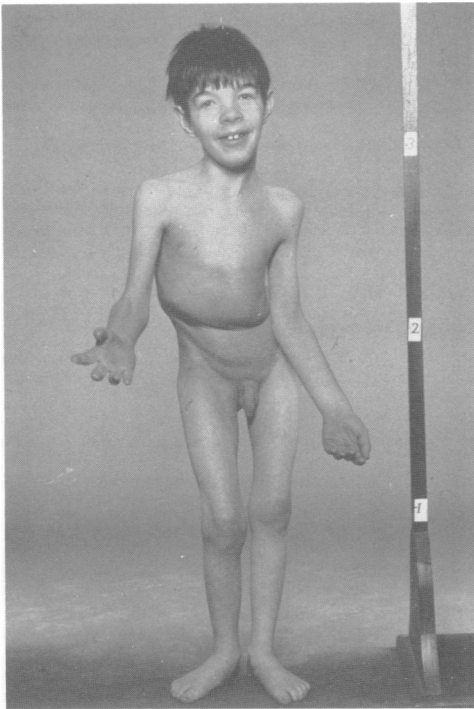


FIG 3 Whole body view of one of the sibs shown in fig 1a. Note the severe kyphoscoliosis.

static in many patients whereas others have been reported to show progressive deterioration in terms of mental retardation,^{4,5} muscle wasting,⁷ and integrity of connective tissue.⁵ Temtamy *et al*⁵ produced persuasive evidence for an underlying connective tissue diathesis, citing inguinal herniae, rectal and uterine prolapse, varicose veins, and mitral regurgitation in support of skin biopsy findings of reduced elastin¹ and abnormal vacuolation.⁵ Subsequent unconfirmed studies have suggested that abnormal storage also occurs in cartilage cells¹⁶ and that proteodermatan sulphate metabolism is abnormal in cultured fibroblasts.¹⁷

Recent reviews have favoured a non-progressive course, although there is general agreement that facial coarsening and skeletal involvement become more pronounced with age.^{9,10,13} It is possible that institutionalisation, poorly controlled convulsions, and raised intracranial pressure may account for apparent deterioration in mental skills.

Differential diagnosis

The long face, large, protruding ears, prognathism, mild connective tissue diathesis, and probable sex linked mode of inheritance are suggestive of the fragile X syndrome, so that careful cytogenetic studies are mandatory. Sotos syndrome, in which there may be a prominent forehead with downward slanting palpebral fissures, and Williams syndrome



FIG 4 Facial views of sisters with the Coffin-Lowry syndrome.

also feature in the differential diagnosis. Acromegaly has sometimes been suspected in older patients because of their coarse facies and broad, fleshy hands.

Inheritance

Everything points to the disorder showing sex linked semi-dominant inheritance. Males are consistently more severely affected than females and in all published families in which more than one generation is affected transmission is through the female. Since no affected male has ever reproduced, sex influenced autosomal dominant inheritance cannot be excluded. However, preliminary results using multipoint linkage analysis indicate that the gene causing the Coffin-Lowry syndrome is located on the short arm of the X chromosome.¹⁸

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References

- ¹ Coffin GS, Siris E, Wegienka LC. Mental retardation with osteocartilaginous anomalies. *Am J Dis Child* 1966;**112**:205-13.
- ² Lowry B, Miller JR, Fraser FC. A new dominant gene mental retardation syndrome. Association with small stature, tapering fingers, characteristic facies, and possible hydrocephalus. *Am J Dis Child* 1971;**121**:496-500.
- ³ Martinelli B, Campailla E. Contributo alla conoscenza della sindrome di Coffin Siris Wegienka: report of a case. *G Psichiatr Neuropatol* 1969;**97**:449-58.
- ⁴ Procopis PG, Turner B. Mental retardation, abnormal fingers, and skeletal anomalies; Coffin's syndrome. *Am J Dis Child* 1972;**124**:258-61.
- ⁵ Temtamy SA, Miller JD, Hussels-Maumenee I. The Coffin-Lowry syndrome; an inherited facioidigital mental retardation syndrome. *J Pediatr* 1975;**86**:724-31.
- ⁶ Sylvester PE, Rundle AT, Richards BW. The syndrome of Coffin, Siris and Wegienka; report of a case. *J Ment Defic Res* 1976;**20**:35-54.
- ⁷ Fryns JP, Vinken L, van den Berghe H. The Coffin syndrome. *Hum Genet* 1977;**36**:271-6.
- ⁸ Wilson WG, Kelly TE. Early recognition of the Coffin-Lowry syndrome. *Am J Med Genet* 1981;**8**:215-20.
- ⁹ Hunter AGW, Partington MW, Evans JA. The Coffin-Lowry syndrome. Experience from four centres. *Clin Genet* 1982;**21**:321-35.
- ¹⁰ Haspelslagh M, Fryns JP, Beusen L, et al. The Coffin-Lowry syndrome. A study of two new index patients and their families. *Eur J Pediatr* 1984;**143**:82-6.
- ¹¹ Collacott RA, Warrington JS, Young ID. Coffin-Lowry syndrome and schizophrenia; a family report. *J Ment Defic Res* 1987;**31**:199-207.
- ¹² Mechant RH. The Coffin-Lowry syndrome; a facio-digital mental retardation syndrome; a case report. *Indian J Pediatr* 1976;**13**:247-51.
- ¹³ Kousseff BG. Coffin-Lowry syndrome in an Afro-American family. *Am J Med Genet* 1982;**11**:373-5.
- ¹⁴ Salinas CF. Orofacial findings and genetic disorders. *Birth Defects* 1982;**18**(1):79-120.
- ¹⁵ Hersh JA, Weisskopf B, DeCoster C. Forearm fullness in Coffin-Lowry syndrome: a misleading yet possible early diagnostic clue. *Am J Med Genet* 1984;**18**:195-9.
- ¹⁶ Gorlin RJ, Brown D, Sauk J. Coffin-Lowry syndrome—a storage disorder? *Birth Defects* 1978;**14**(6B):175.
- ¹⁷ Beck M, Glössl J, Rüter R, Kresse H. Abnormal proteodermatan sulfate in three patients with Coffin-Lowry syndrome. *Pediatr Res* 1983;**17**:926-9.
- ¹⁸ Hanauer A, Alembik Y, Gilgenkrantz S, et al. Probable localisation of the Coffin-Lowry locus in Xp 22.2-22.1 by multipoint linkage analysis. *Am J Med Genet* (in press).

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