The Coffin–Siris syndrome

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Abstract
We report a white female infant with typical features of Coffin–Siris syndrome including thick eyebrows, flat nasal bridge, antverted, wide nose tip, generalised hypertrichosis, scalp hypotrichosis, absence of the fifth fingernails and toenails, absence of the distal phalanges of the fifth fingers and of the second to fifth toes, small patellae, inguinal hernia, and sucking and feeding difficulties. There was decreased fetal activity and intrauterine growth retardation.

A syndrome of severe retardation of postnatal growth, mental retardation, lax joints, generalised hypertrichosis, hypotrichosis of the scalp, absence of the fifth fingernails and toenails, and absence the fifth terminal phalanges was described by Coffin and Siris in three unrelated female children. A good deal of phenotypic variability has been reported subsequently. We describe a female infant who presented the full clinical expression of the Coffin–Siris syndrome, and discuss the importance of various clinical features in ascertainment of the cases.

Case report (figs 1 to 3)
The proband, a white female infant, was delivered at 42 weeks of gestation by caesarean section because of fetal distress, with Apgar scores of 8 and 9 at one and five minutes. The mother was a gravida 3, para 2, 32 year old woman, and the father was 36 years old at the time of birth. The family history was unremarkable and the Caucasian parents were healthy and unrelated. The first four pregnancies of the mother were electively terminated. A 3 year old son is normal and healthy.

After the birth of her son the mother had used barrier contraceptives. She used a vaginal cream containing triple sulfa drugs to heal cervical inflammation from the fifth to the twelfth day of the menstrual cycle during which she conceived. She had a severe attack of influenza during the fourth month of pregnancy, but did not recall high fever, skin rash, or use of medications during the illness. There was no other known exposure to drugs or radiation. Fetal activity was described as very feeble.

The infant's birth weight was 2180 g, length 42 cm, (both below the 10th centile), and head circumference 32 cm. At birth her appearance was described as abnormal. Her neonatal course was marked by difficulty in sucking and swallowing, requiring intermittent tube feeding, and failure to thrive.

Examination at 5 weeks of age found the infant very jittery on handling. Moro and grasp reflexes were abnormal. There was slight asymmetry of the head; the left frontotemporal area appeared flatter than the right (fig 1a). The cranial hair was very sparse (fig 1b). The fontanelles were normal. Both ears were low set and the left was posteriorly rotated and had a deficient antihelix. The facial features included normal eyes with clear corneas and pupils, coarse facies, thick eyebrows and long eyelashes, hirsutism of the forehead, low, flat nasal bridge, wide, upturned nose tip, and long philtrum. The palate was highly arched and the distal frenulum of the tongue was short. Other abnormal findings included bilateral inguinal hernia, small patellae, contractures at the first interphalangeal joints of the fourth finger of the right hand, small fifth fingers without nails (fig 2a), overlapping second over first and fourth over fifth toes, absence of the fifth toenails (fig 2b), moderate hypotonia, and persistent cutis marmorata. External genitalia, heart sounds, and the remainder of the examination were normal.

Radiographical evaluation of the hands and feet showed bilateral absence of the terminal phalanges of the fifth fingers (fig 3a) and middle and distal phalanges of the third to fifth toes (fig 3b). Chest radiograph, electrocardiogram, echocardiogram, and sonograms of the kidneys and head were normal. Chromosome analysis performed on peripheral blood lymphocytes after G and R banding showed a normal 46,XX karyotype. The results of blood chemistry and screens for amino acids and thyroid function were normal.

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Received for publication 13 March 1989.
Revised version accepted for publication 31 October 1989.
Figure 1  The patient aged 3 months: (a) face and (b) scalp hair.

Figure 2  The patient's hand (a) and foot (b) at 3 months of age.
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Discussion

The infant described in this report has the typical features of the Coffin-Siris syndrome including thick eyebrows, flat nasal bridge, anteverted, wide nose tip, generalised hirsutism, sparse scalp hair, small patellae, absence of the fifth fingernails and toenails, absence of the distal phalanges of the fifth fingers and of the second to fifth toes, inguinal hernia, and sucking and feeding difficulties. There was decreased fetal activity and intrauterine growth retardation. Together, these findings are unique and allow ready recognition of the Coffin-Siris syndrome. A number of other features associated with the syndrome (table) are microcephaly, short philtrum, prominent lips, scoliosis, lax joints, short sternum, and dislocation of the radial head. Postnatal growth retardation and moderate developmental retardation are regular features in older infants and children.

Feeding difficulties and recurrent upper and lower respiratory tract infections are frequent during early life in patients with the Coffin-Siris syndrome. In a few cases feeding difficulties have been associated with a variety of gastrointestinal abnormalities, including perforated gastric ulcer, duodenal ulcer, neonatal intussusception, intestinal malrotation, and redundant gastric mucosa in the antrum of the stomach resulting in obstruction of the gastric outlet. Congenital heart disease is present in 30% of reported patients, and includes patent ductus arteriosus, septal defects, tetralogy of Fallot, patent foramen ovale, and other unspecified defects. Cleft palate was described in three patients, and Dandy-Walker syndrome and Dandy-Walker syndrome are present. The latter is characterised by a large, rounded fourth ventricle, and the occurrence of a number of other skull and facial anomalies, including coloboma of the upper part of the eyelid, dermoids, and epidermoids of the skin of the scalp and face. The association of this anomaly with the Coffin-Siris syndrome is not definitive, but it is a useful feature to look for.

Figure 3 Radiographs of (a) hand and (b) foot at 5 weeks of age.

Features of the Coffin-Siris syndrome.

Prenatal
Decreased fetal activity
Intrauterine growth retardation

Postnatal
Feeding difficulties
Postnatal growth deficiency
Respiratory infections
Developmental delay
Mental retardation
Body hirsutism
Hypotonia

Craniofacial
Microcephaly
Scalp hypotrichosis
Soup bowl eyebrows
Long eyelashes
Low, flat nasal bridge
Wide, upturned nose tip
Prominent lips
Wide mouth
Short philtrum
Cleft palate

Skeletal
Hypoplastic nails of fifth fingers and toes
Hypoplastic nails of other fingers and toes
Short fifth fingers
Absent distal phalanx of fifth fingers
Lax joints
Retarded bone age
Scoliosis
Small patella
Dislocated radial head

Other
Congenital heart defect
Cryptorchidism
Dandy-Walker syndrome
Gastrointestinal abnormalities
Inguinal hernia

1 2 4 6 7
malformation in two. Abnormalities such as hypoplasia of the distal portions of the clavicles, microscopic hindbrain abnormalities, and abnormalities of internal genitalia have been described in occasional patients.

Postnatal growth deficiency in weight and length is characteristic of the syndrome in older children, whereas prenatal growth deficiency is observed in only 30% of the patients. The degree of developmental delay and mental retardation is variable. The coarse facial features of prominent lips, wide nasal tip, and hypertelorism of the eyebrows may not be present at birth but develop after early infancy, and hypotrichosis of the scalp appears to improve with age.

The presence of an unusual combination of coarsened facial features, body hirsutism, scalp hypotrichosis, and bilateral absence of the fifth fingernails and toenails should strongly suggest Coffin–Siris syndrome. In the earlier publications, patients reported as having Coffin–Siris syndrome were examples of other conditions, but those reported by Mattei et al as having Coffin–Lowry syndrome clearly had the Coffin–Siris phenotype. The confusion in the latter instance arose out of the common name of Coffin associated with the two syndromes.

The differential diagnosis of Coffin–Siris syndrome includes Cornelia de Lange syndrome because of growth failure, hirsutism, mental retardation, and dislocation of the radial head; fetal hydantoin syndrome because of nail and phalangeal hypoplasia, prenatal postnatal growth retardation, cleft palate, and congenital heart disease; and nail-patella syndrome because of poor nail development, hypoplastic or absent patella, and dislocation of the radial head. Hypoplasia of the nails and distal phalanges and mental retardation are also features of the DOOR syndrome. However, coarsened facial features, body hypertrichosis, scalp hypotrichosis, and sensorineural deafness are distinctive features of the Coffin–Siris syndrome. There are no laboratory tests to confirm the clinical impression; careful examination including detailed radiographical examination is necessary in all suspected patients.

The aetiology of the Coffin–Siris syndrome is not known. Although most cases are sporadic, its occurrence in sibs lends support to an autosomal recessive mode of inheritance. An excess of females among patients (3:1 female-male ratio) may suggest early lethality for most affected male embryos. At present, prenatal diagnosis may be possible by detecting prenatal growth retardation and other abnormalities by ultrasound.