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, anteverted, 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.

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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.
The Coffin-Siris syndrome

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 in four. Postnatal growth deficiency and mental retardation are regular features in older infants and children.

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
- Bushy 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

Figure 3  Radiographs of (a) hand and (b) foot at 5 weeks of age.
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 hypertrichosis of the scalp appears to improve with age.

The presence of an unusual combination of coarsened facial features, body hirsutism, scalp hypertrichosis, 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, pre- and 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 and partial expression in one parent lend 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.