The Coffin-Siris syndrome

Qutub H Qazi, Lynne S Heckman, Demetrios Markouizos, Ram S Verma

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 of the fifth terminal phalanges was described by Coffin and Siris¹ 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.

State University of New York Health Science Center at Brooklyn, New York, USA.
Q H Qazi, D Markouizos

Long Island College Hospital, Brooklyn, New York, USA.
L S Heckman, R S Verma

Correspondence to Dr Qazi, Department of Pediatrics, Box 49, 450 Clarkson Avenue, Brooklyn, NY 11203, USA.

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.

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.

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

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.^{1 2} 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,² duodenal ulcer,³ neonatal intussusception,¹ intestinal malrotation,⁴ and redundant gastric mucosa in the antrum of the stomach resulting in obstruction of the gastric outlet.⁵ 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.^{1 2 4 6 7} Cleft palate was described in three patients,^{1 4 7} and Dandy–Walker

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

malformation in two.¹⁻⁴ Abnormalities such as hypoplasia of the distal portions of the clavicles,⁸ microscopic hindbrain abnormalities,⁹ and abnormalities of internal genitalia¹⁰ 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.² The degree of developmental delay and mental retardation is variable. The coarse facial features of prominent lips, wide nasal tip, and hypertrichosis of the eyebrows may not be present at birth but develop after early infancy, and hypotrichosis of the scalp appears to improve with age.²

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,³⁻¹¹ patients reported as having Coffin-Siris syndrome were examples of other conditions, but those reported by Mattei *et al*¹² 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.¹³

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.¹⁴ 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^{2,12,15,16} and partial expression in one parent^{1,3,4,15} 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.

- 1 Coffin GS, Siris E. Mental retardation with absent fifth fingernails and terminal phalanx. *Am J Dis Child* 1970;119:433-9.
- 2 Carey JC, Hall BD. The Coffin-Siris syndrome. *Am J Dis Child* 1978;132:667-71.
- 3 Weiswasser WH, Hall BD, Delavan GW, Smith DW. Coffin-Siris syndrome. *Am J Dis Child* 1973;125:838-40.
- 4 Tunnessen WW, McMillan JA, Levin MB. The Coffin-Siris syndrome. *Am J Dis Child* 1978;132:393-5.
- 5 Bodurtha J, Kessel A, Berman W, Hartenberg M. Distinctive gastrointestinal anomaly associated with Coffin-Siris syndrome. *J Pediatr* 1986;109:1015-7.
- 6 Ueda K, Saito A, Nakano H, Linumo K. The Coffin-Siris syndrome: a case report. *Helv Paediatr Acta* 1980;35:385-90.
- 7 Lucaya J, Garcia-Conesa JA, Bosch-Banyeras JM, Pons-Peradejordi G. The Coffin-Siris syndrome: a report of four cases and review of the literature. *Pediatr Radiol* 1981;11:35-8.
- 8 Schinzel A. The Coffin-Siris syndrome. *Acta Paediatr Scand* 1979;68:449-52.
- 9 DeBassio WA, Kemper TL, Knoefel JE. Coffin-Siris syndrome: neuropathologic findings. *Arch Neurol* 1985;42:350-3.
- 10 Coffin GS, Siris E. The Coffin-Siris syndrome. *Am J Dis Child* 1985;139:12.
- 11 Barber N, Say B. Coffin-Siris syndrome. *Am J Dis Child* 1978;132:1044.
- 12 Mattei JF, Laframboise R, Rouault F, Giraud F. Brief clinical report. Coffin-Lowry syndrome in sibs. *Am J Med Genet* 1981;8:315-20.
- 13 Gorlin RJ. Letter to the Editor: Lapsus-caveat emptor: *Coffin-Lowry* syndrome vs *Coffin-Siris* syndrome—an example of confusion compounded. *Am J Med Genet* 1981;10:103-4.
- 14 Qazi QH, Nangia B. Abnormal distal phalanges and nails, deafness, mental retardation, and seizure disorder: a new familial syndrome. *J Pediatr* 1984;104:391-4.
- 15 Haspelagh M, Fryns JP, van den Berghe H. The Coffin-Siris syndrome: report of a family and further delineation. *Clin Genet* 1984;26:374-8.
- 16 Franceschini P, Cirillo Silengo M, Bianco R, Biagioli M, Guala A, Lopez Bell G. The Coffin-Siris syndrome in two siblings. *Pediatr Radiol* 1986;16:330-3.