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Syndrome of the month

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Coffin–Siris syndrome

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In 1970 Coffin and Siris described three unrelated female children with severe mental and developmental retardation, sparse scalp hair, and coarse appearing facies with bushy eyebrows, a wide mouth, and thick lips. There were, in addition, lax joints and brachydactyly of the fifth digits of both hands and feet with absence of the nails and terminal phalanges.[1]

To our knowledge, there have been 31 cases of this condition reported and these are reviewed in the present paper with the addition of two new cases.

Frequency of features.

	Total cases	Our cases	
Sex F:M	25:6	1:1	
Low birth weight	15/30	+	+
Growth deficiency	17/21	+	+
Postnatal	14/17	−	−
Developmental delay	29/29	+	+
Mental retardation	19/19	+	+
Retarded bone age	10/14	?	+
Microcephaly	20/29	−	+
Sparse scalp hair	21/26	+	+
Coarse face	25/29	+	+
Bushy eyebrows	22/29	−	+
Broad nose/nasal tip	22/27	+	+
Wide mouth	21/25	+	+
Thick/prominent lips	26/30	+	+
Hypoplastic/absent nails on 5th digits	31/31	+	+
Generalised hirsutism	23/28	+	+
Feeding problems	24/28	+	−
Recurrent respiratory infections	13/21	−	+
CNS defects	5	−	+ DW
Cardiac defects	9/20	−	−
Renal defects	3/10	−	−
Scoliosis	6/15	−	−

DW=Dandy–Walker malformation.

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Clinical features (table, figs 1 to 4)

The main features are growth and developmental retardation, sparse scalp hair, bushy eyebrows, wide mouth with prominent or thick lips especially the lower lip, and body hirsutism. Absent or hypoplastic nails of the fifth fingers and toes with absent or hypoplastic phalanges are also present.

CRANIOFACIAL

Microcephaly is present in 20/29 of the cases. The face is described as coarse with hypertrichosis, although there is sparse scalp hair. There are bushy eyebrows (22/29), a flat nasal bridge (19/23), a broad nasal tip (22/27), and a wide mouth (21/25) with prominent or thick lips (26/30).

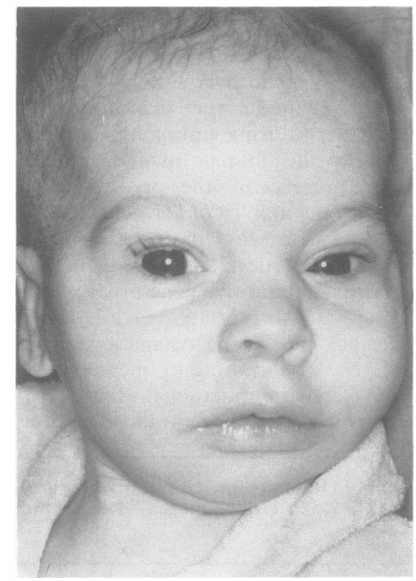

Figure 1 Case 1, face. Note facial hirsutism and sparse scalp hair.

Case 1 described by Carey and Hall[2] and that of Ueda *et al*[3] did not have bushy eyebrows, only long eyelashes. Furthermore they did not have coarse features and the case of Ueda *et al*[3] did not have sparse scalp hair or body hirsutism. It might be that the coarse facies need not be present in early infancy, and it is documented that the sparse hair can disappear with age, but as the two cases mentioned above also had cardiac lesions, they might represent different entities.

LIMBS

Absent or hypoplastic nails of the fifth digits are a constant feature (100%), and other digits are affected to a lesser degree (22/25). There are only three cases in which the thumb or big toe or both are involved.[2 4 5]

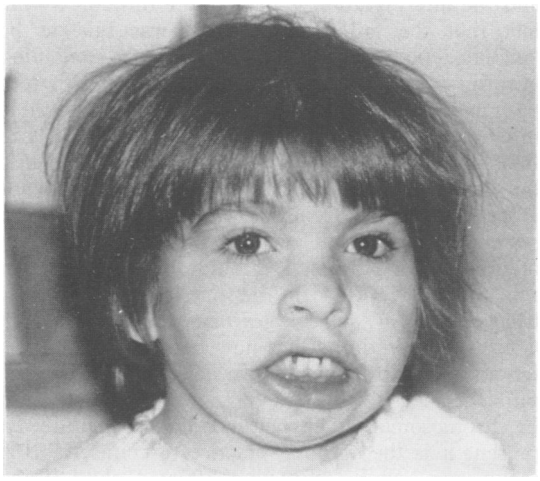

Figure 2 Case 1, face at 5 years.

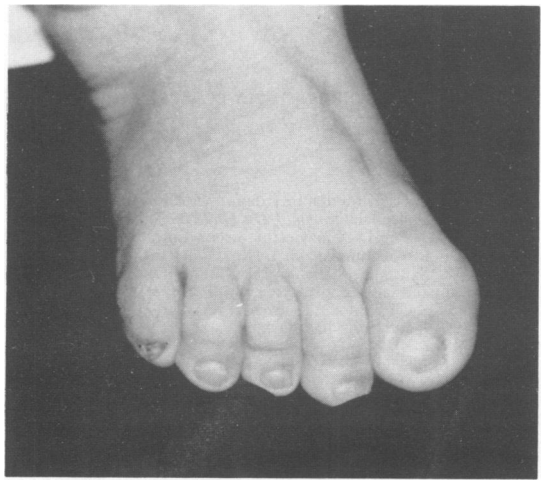

Figure 3 Case 1, foot at 5 years. Note hypoplastic nails.

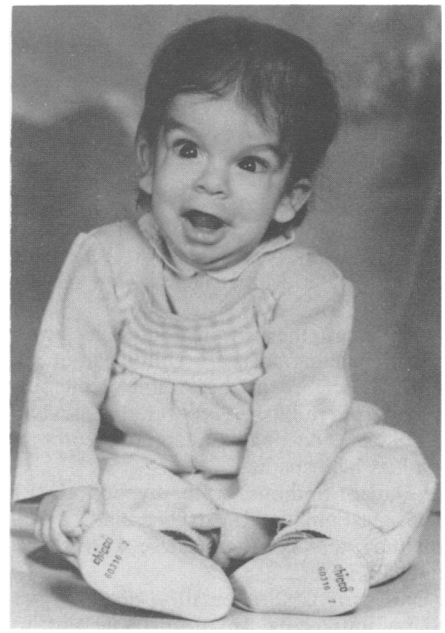

Figure 4 Case 2.

GROWTH AND MENTAL DEVELOPMENT

Some mothers (5/18) have noted a decrease in fetal activity during intrauterine life, and a low birth weight was reported in 15/30 cases.

In early infancy, feeding difficulties (24/28) and frequent respiratory infections (13/21) are common. The presence of growth retardation occurred in 17/21 cases and is essentially postnatal (14/17).

Developmental delay occurred in all cases and mental retardation in 19/19, where this was mentioned, although to a variable degree. The mental retardation was described as severe in 10/19 cases, but in the additional 12 cases there was no mention of mental retardation. Most of these patients were still very young and three had already died.

SKELETAL RADIOGRAPHS

Absence or hypoplasia of the distal and middle phalanges, especially those of the fifth digits of the hands and feet, is always present. Retarded bone maturation is common (10/14). There are occasional abnormalities such as radial head dislocation (4 cases), narrow intervertebral disc spaces (3), scoliosis (6), hypoplastic clavicles (2), mild coxa valga (6), hip dislocation (3), cone shaped epiphyses and pectus excavatum (2). Absent or hypoplastic patellae were present in eight cases.

OTHER FEATURES

Hypotonia or lax joints or both were present in 23/24 cases. Body hirsutism was present in 23/28 cases especially on the forehead and back.

OCCASIONAL ABNORMALITIES

There have also been several other features described: epicanthus (5 cases), palpebral ptosis (3), preauricular appendages (1), cutis marmorata (3), and a single palmar crease (4).

In two cases there were one and two small cutaneous haemangiomas.[1 4] Umbilical or inguinal hernia was described in three, and of the six males ascertained from published reports, three had bilateral cryptorchidism, one had unilateral cryptorchidism, and one had hypospadias.

The ocular findings were hypophoria, hypermetropia, astigmatism, strabismus, nystagmus, buphthalmos, and cataract. These were reported in only five children.[1 6-9]

Regarding the CNS anomalies, necropsy was performed on four cases. In the original Coffin–Siris[1] report, case 1 had a Dandy–Walker malformation. In the report of Tunnessen *et al*[10] a Dandy–Walker malformation was present, with agenesis of the corpus callosum and the anterior commissure. In the case described by DeBassio *et al*[11] there was hypoplasia of the corpus callosum, abnormal olives, abnormal arcuate nuclei, and ectopic cerebellar nuclei, and in the report of MacDonald *et al*[12] an atrophic cerebrum was present. Mastroiacovo *et al*[13] reported the only live child in whom CNS anomalies were detected, who had a large cisterna magna.

There were 10 cases (out of the total of 20) in which the patients had cardiac defects. Out of these we were able to review photographs of nine.[1-3 7 8 10-12 14] The lesions were: a patent foramen ovale (1), tetralogy of Fallot (1), atrial septal defect (4), patent ductus arteriosus (3), ventricular septal defect (2), pulmonary stenosis (1), and persistent left superior vena cava (1). Two of these cases are case 1 of Carey *et al*[2] and the one by Ueda *et al*,[3] but these patients do not have the usual facial features of the syndrome. It should be concluded that cardiac anomalies are unusual in Coffin–Siris syndrome and the other features have to be characteristic before making a positive diagnosis. There were four cases described with renal anomalies including hydronephrosis in two cases,[6 10] one case of congenital microureters with stenosis of the vesicoureteral junction,[6] and one of an ectopic kidney.[13]

In the gastrointestinal system there have been two cases of perforated ulcer, one gastric[15] and one duodenal,[2] one case of intestinal malrotation,[10] one of intussusception,[1] and one of necrotising enterocolitis and pyloric stenosis.[12]

The 17 karyotypes mentioned were normal.

Inheritance

The suggestion that Coffin–Siris syndrome is inherited as a autosomal recessive trait is based on four reported sibships. The cases described by Mattei *et al*[6] are not totally convincing. They were the offspring of seemingly unrelated parents from North Africa but the authors note that "consanguinity is difficult, sometimes impossible, to rule out reliably". The sibs reported by Carey and Hall[2] are difficult to evaluate in that only one survived (that case looks genuine whereas the other had a coarse facial appearance "similar to that seen in Hurler's syndrome" and it must remain uncertain whether that child had the same condition (the fifth fingers were short with absence of the nails)). The third reported sibship, that of Haspeslagh *et al*,[16] is also difficult to be sure about, and the interpretation is made more difficult by the fact that the father of the sibs was said to be 'analphabetic' and had thick, bushy, conjoining eyebrows and bilateral hypoplasia of the fifth toes with hypoplastic nails. The mother was of borderline intelligence in this non-consanguineous mating. The final sibship is that reported by Franceschini *et al*,[17] but pictures of the second sib are not convincing (nor is the single case of Gellis and Feingold[18]). The single patient reported by Uzielli *et al*[8] was the product of first cousin parents. It should also be noted that the patient reported in the Baraitser and Winter *Colour atlas of clinical genetics* (1983) as having Coffin–Siris syndrome has now been shown to have trisomy 9p, and it remains possible that some of the published single cases and even sibships will prove to be chromosomal rather than mendelian in nature. At present it is the authors' practice to counsel a 10% recurrence risk for a further affected child if the phenotype is correct and further evidence is needed to confirm whether the condition follows autosomal recessive inheritance.

Addendum

Recently, a convincing single case was reported by Qazi *et al*.[19]

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