Triplets with growth failure, microcephaly, mental retardation, nail hypoplasia and corpus callosum agenesis: is it a variant of Coffin-Siris or a new syndrome?

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SUMMARY: Kırel B, Kural N, Yakut A. Adapınar B. Triplets with growth failure, microcephaly, mental retardation, nail hypoplasia and corpus callosum agenesis: is it a variant of Coffin-Siris or a new syndrome? Turk J Pediatr 2000; 42: 171-176.

We report eight-year-old triplet girls whose clinical features included microcephaly, severe mental retardation, hypoplasia of distal phalanges of both fifth and second fingers and nail hypoplasia on second fingers, dysmorphic facial features, and partial corpus callosum agenesis. During infancy, a Pavlik harness was used for congenital hip dislocation, and they had difficulty in feeding. One had been operated for patent ductus arteriosus. To our knowledge, this rare combination has not been previously reported in triplets whose clinical features closely resemble those of Coffin-Siris syndrome. The other diagnostic possibilities are also reviewed.

Key words: Coffin-Siris syndrome, growth failure, microcephaly, mental retardation, nail hypoplasia.

We describe eight-year-old triplet girls with microcephaly, severe mental retardation, hypoplasia of distal phalanges of both fifth and second fingers and nail hypoplasia on second fingers, dysmorphic facial features and partial corpus callosum agenesis. These reatures closely resemble the abnormalities seen in Coffin-Siris syndrome. Coffin and Siris[1] first described three unrelated girls with severe mental and developmental retardation, absence of nails and distal phalanges of their fifth fingers and toes, and lax joints. They had coarse facial features with bushy eyebrows, wide mouth, and thick lips. New additional cases were reported later[2]. Our triplets had some differences regarding the facial and skeletal characteristics in previously reported cases of Coffin-Siris syndrome and these are discussed below.

Case Reports

The triplet girls were first admitted to our hospital at six years of age when one of them (Case 1) presented with generalized edema due to nephrotic syndrome. The girls had similar growth and developmental history and physical dysmorphic characteristics (Table I). They were products of an uncomplicated 37 week pregnancy and of an uneventful normal delivery. At birth, weight and length were both below the 10th percentile for all three, and head circumferences were below the -2 standard deviation. They had a history of feeding difficulty during infancy, of using Pavlik harness for congenital hip dislocation and of delayed neuromotor development. Case 2 had been operated for patent ductus arteriosus at 18 months of age. Their parents were nonconsanguineous. They had one older healthy brother and one older healthy sister. Physical examinations of the parents and two older siblings were normal. There was no family history of similar characteristics. On admission, weight and height were both below the 5th percentile and their head circumference were below the -2 standard deviation. Physical examination revealed mental retardation, hypoplastic distal phalanges and nails of second fingers, slightly hypoplastic distal phalanges of fifth fingers (Fig. 1), microcephaly and dysmorphic features such as bushy eyebrows, short, broad nose, hypertelorism, micrognathia,

Table I: Clinical Features of The Triplets

	Case 1	Case 2	Case 3
Low birth weight	+	+	+
Body weight (kg)	15	15	16
Height (cm)	102	105	107
Head circumference (cm)	44	45	45
IQ score	46	44	42
Microcephaly	+	+	+
Dysmorphic facial features	+	+	+
Partial corpus callosum agenesis	+	+	+
Feeding difficulty	+	+	+
Congenital hip dislocation	+	+	+
Severe myopia	+	+	+
Second nail hypoplasia	+	+	+
Fifth finger hypoplasia	+	+	+
Distal phalanges hypoplasia of 2nd and 5th fingers and all toes*	+		
Pseudoepiphysis of distal phalanges of hallux*	+		
Retarded bone age*	+		
Patent ductus arteriosus		+	
Nephrotic syndrome	+		

* Radiographs were only available in Case 1.

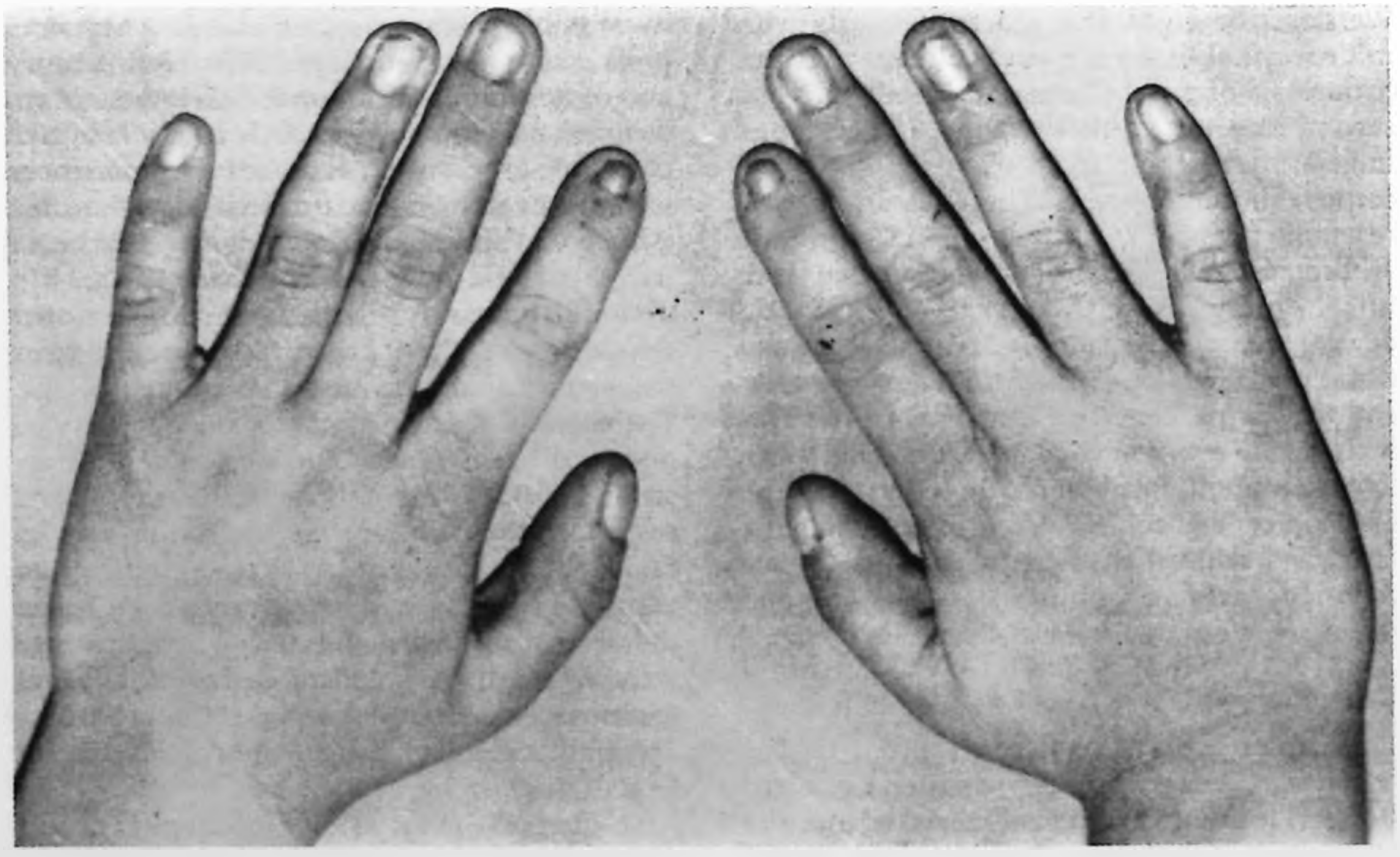

Fig. 1. Hypoplastic nails on the 2nd fingers and hypoplastic distal phalanges of 2nd and 5th fingers.

fish mouth, low anterior hairline and left preauricular skin tag and normal scalp hair (Figs. 2-4). Other systems and neurologic examination were normal. Magnetic resonance imaging of brain demonstrated partial corpus callosum agenesis in all triplets (Fig. 5). Other laboratory investigations of Case 1 were as follows: urine and blood biochemical analysis, immunologic study and abdominal ultrasonography were compatible with nephrotic syndrome. Radiographs that were available at eight years of age showed hypoplasia as well as widened epiphysial distances and thick epiphysis on the distal phalanges of the second fingers (Fig. 6). Both fifth fingers demonstrated similar epiphysial findings on distal phalanges but no conspicuous hypoplasia (Fig. 7). There were hypoplasia of distal phalanges of all toes and radiolucencies on the middle part of distal phalanges of the first toe, which is compatible with pseudoepiphysis (Fig. 8). Bone age was compatible with 6.5 years of age. Only bilateral acetabular hypoplasia was demonstrated on the pelvic radiography. Chromosomal analysis of blood showed normal

Fig. 2.

Fig. 3.

Fig. 4.

Figs. 2, 3, 4. Facial characteristics of the cases.

Fig. 5. Partial corpus callosum agenesis on MR imaging.

Fig. 6. Hypoplastic distal phalanges with epiphysial abnormality of 2nd fingers.

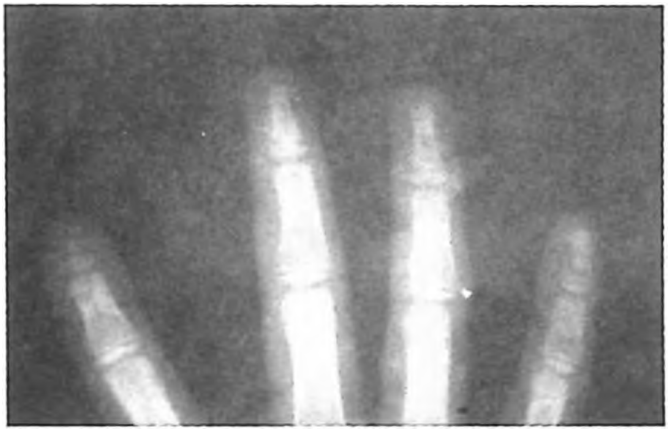

Fig. 7. Slightly hypoplastic distal phalanges with epiphysial abnormality of 5th finger on right hand.

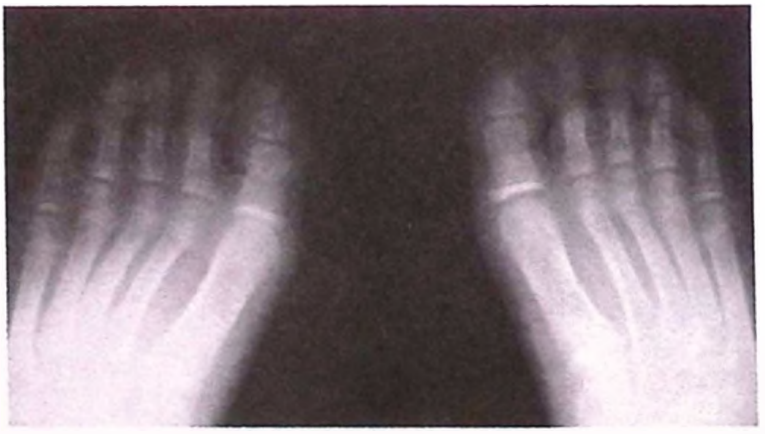

Fig. 8. Hypoplasia of distal phalanges of toes and pseudoepiphysis of distal phalanges of 1st toes.

karyotype. Nail-patella syndrome was ruled out because of presence of bilateral normal platellae and the pelvic findings on radiography. The nephrotic syndrome was steroid sensitive and still in remission after three years.

Discussion

In addition to microcephaly, mental retardation and growth failure, our triplets had dysmorphic facial characteristics and hypoplastic second nails and distal phalanges, which are more

impressive characteristics for the diagnosis. Hypoplastic nails are reported as a feature of several syndromes which are listed in Smith's Recognizable Patterns of Human Malformation[3]. Review of these syndromes showed that they had other quite different clinical characteristics and laboratory findings from our triplets.

Shortened distal phalanges and hypoplastic or aplastic nails of fingers have also been reported in anticonvulsant embryopathy. The triplets had dysmorphic facial features including short, broad, more or less turned-up nose, broad, low nasal bridge and hypertelorism[4-6]. Our triplets' facial features were very similar to the patients of anticonvulsant embryopathy seen in an atlas of characteristic syndromes[5]. But, our cases had no history of epilepsy, nor did the mother receive anticonvulsant therapy during gestation.

The features of the triplets also closely resembled Coffin-Siris syndrome, the main features of which are growth and developmental retardation, hypoplasia or absence of nail and distal phalanges with predominantly fifth digit involvement, hypotonia, infancy feeding problems, retarded bone age and craniofacial abnormalities. These features were present in variable frequency (Table II)[7-12]. The absent or hypoplastic nails and terminal phalanges of the fifth fingers and toes are constant features[7-12]. The other digits are also affected in Coffin-Siris syndrome[6-9]. Recently, this syndrome has also been defined as fifth digit syndrome by McKusick[2]. Our triplets' fifth digits were less involved than the other digits in contrast to the syndrome's definition.

Table II. Comparison of the Features of Our Cases with the Features of Coffin-Siris Syndrome

	Total cases*	Our cases
Sex: F/M	26/7	3/3
Low birth weight	17/32	+
Delayed growth postnatal	19/23	+
Developmental delay	31/31	+
Mental retardation	21/21	+
Retarded bone age	11/16	+
Microcephaly	21/31	+
Sparse scalp hair	23/28	–
Coarse face	27/31	–
Bushy eyebrows	23/31	–
Broad nose/nasal tip	24/29	–
Wide mouth	23/27	–
Thick/prominent lips	28/32	–
Hypoplastic/absent nails on 5th digits	33/33	–
Generalized hirsutism	25/30	–
Feeding problems	25/30	+
Recurrent respiratory infections	15/23	–
CNS defects	6	+
Cardiac defects	9/22	+
Renal defects	3/12	–
Scoliosis	6/15	–

* These frequencies adapted from Levy and Baraitser[7].

Body hirsutism is one of the most frequent features of Coffin-Siris syndrome. But, the second case reported by Weiswasser et al.[12], the third case of Coffin and Siris[1] and the case of Balcı, et al.[10] did not reflect body hirsutism, as was the case with our triplets.

Craniofacial abnormalities of Coffin-Siris syndrome include microcephaly, sparse scalp hair, coarse face, flat nasal bridge, bushy eyebrows, wide mouth, prominent lips. However, there are some cases without coarse face and bushy eyebrows reported[7]. Our triplets also had dysmorphic face, but it was not similar to previously described cases in this syndrome.

Central nervous system malformations associated with Coffin-Siris syndrome are Dandy-Walker malformation, partial corpus callosum agenesis, abnormal olive and arcuate nuclei and cerebellar heterotopias[1,13,14]. On the other hand, cardiac and renal defects and lax joints have also been described[1,6-10]. Our sibs had partial corpus callosum agenesis and congenital hip dislocation, and the second case had patent ductus arteriosus.

Although our triplets had some main and occasional features of Coffin-Siris syndrome, they had some skeletal and facial findings different from those seen in this syndrome, and they had no body hirsutism. Since the differential diagnosis did not lead us to another convincing diagnosis, we considered the triplets as having a variant of Coffin-Siris syndrome or a new syndrome.

Chromosomal analysis was available in only one of the triplets, and showed normal karyotype. The parents were nonconsanguineous, and there was no one resembling the triplets in the family, so we could not make any interpretation about the inheritance of these multiple and similar developmental abnormalities in the triplets.

In conclusion, to our knowledge, this is the first report of this combination in triplets. It might be a variant of Cofin-Siris syndrome or a new syndrome.

REFERENCES

1. Coffin GS, Siris E. Mental retardation with absent fifth fingernail and terminal phalanx. Am J Dis Child 1970; 119: 4332.
2. McKusick VA. Mendelian Inheritance in Man. Baltimore and London: The Johns Hopkins University Press; 1992: 396.
3. Jones KL. Smith's Recognizable Patterns of Human Malformation. Philadelphia: WB Saunders Co.; 1997: 818-819.

4. Hanson JW, Smith DW. The fetal hydantoin syndrome. J Pediatr 1975; 87: 285-288.
5. Widemann K, Grosse KR, Dibbern H. An Atlas of Characteristic Syndromes. A Usual Aid to Diagnosis. London: Wolfe Med Publications Ltd; 1985: 344.
6. Jones KL. Smith's Recognizable Patterns of Human Malformation. Philadelphia: WB Saunders Co; 1997: 582-583.
7. Levy P, Baraitser M. Coffin-Siris syndrome. J Med Genet 1991; 28: 338-341.
8. 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: 35-38.
9. Schinzel A. The Coffin-Siris syndrome. Acta Paediatr Scand 1979; 68: 449-452.
10. Balcı S, Erçal MD, Tokgözoğlu N, et al. Coffin-Siris Syndrome. Çocuk Sağlığı ve Hastalıkları Dergisi 1990; 33: 59-66.
11. Carey JC, Hall BD. The Coffin-Siris syndrome: five new cases including two siblings. Am J Dis Child 1978; 132: 667-671.
12. Weiswasser WH, Hall BD, Delavan GW, Smith DW. Coffin-Siris syndrome: two new cases. Am J Dis Child 1973; 125: 838-840.
13. DeJong G, Nelson MM. Choanal atresia in two unrelated patients with the Coffin-Siris syndrome. Clin Genet 1992; 42: 320-322.
14. DeBassio WA, Kemper TL, Knoefel JE. Coffin-Siris syndrome: neuropathologic findings. Arch Neurol 1985; 42: 350-353.