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Case Report

THE COSTELLO SYNDROME: ARE NASAL PAPILLOMATA ESSENTIAL?

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Summary Two patients with the Costello syndrome are presented. One was a 7-year-old girl with a history of infantile hypotonia and feeding difficulties. The other was a 3 5/12-year-old boy with a history of neonatal sepsis and respiratory problems. Both had relative macrocephaly at birth, curly hair, large ear lobes, epicanthic folds, a low nasal bridge, thick lips, a short and wide nose, a short neck, a barrel chest, redundant skin, tight Achilles tendons, and pes equinovarus. Nasal papillomata, as described in Costello's two patients, were absent in both patients. Borochowitz *et al.* (1992) described five patients with what we interpreted as the Costello syndrome but without nasal papillomata. In view of these findings, nasal papillomata are not likely to be essential in the diagnosis of the Costello syndrome.

Key Words Costello syndrome, nasal papillomata, tight Achilles tendons, redundant skin, facio-cutaneous-skeletal syndrome

INTRODUCTION

Costello (1977) reported two children with a characteristic facies, loose skin of the hands and feet, postnatal growth failure, mental retardation, and nasal papillomata: a combination now known as the Costello syndrome. Der Kaloustian

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et al. (1991) and Martin and Jones (1991) each reported a patient with the syndrome with nasal papillomata. More recently, Borochowitz *et al.* (1992) described five patients with "new multiple congenital anomalies." The clinical manifestations of the five patients were, except for the absence of nasal papillomata, essentially identical with those of the Costello syndrome. We here report two unrelated children with the Costello syndrome without nasal papillomata.

CASE REPORTS

Patient 1. This 7-year-old girl was the only child of unrelated healthy parents. The mother was 32 years old and the father 48 at her birth. Polyhydramnios was noted at 6 months of pregnancy. Vaginal delivery was induced at 37 weeks of gestation in view of possible impending fetal distress. Her birth weight was 3,584 g (+1.9 S.D.), length 49.5 cm (−0.9 S.D.), and OFC (head circumference) 37 cm (+2.4 S.D.). She showed respiratory distress, and neonatal hyperbilirubinemia of which the latter was relieved with phototherapy of 13 days' duration. She was hypotonic and sucked poorly during infancy. Normal tests at age 12 months included skull roentgenography, brain CT, EEG, serum and urine amino acids, and urinary mucopolysaccharide excretion. Her bone age was not retarded. Chromosomes of cultured skin fibroblasts were normal. She controlled her head at age 12 months, walked alone at 30 months, spoke several words at 3 years, and spoke short sentences at 4 years. At age 4 years, she developed talipes equinovarus with tight Achilles tendons.

At age 6 5/12 years, she weighed 18 kg (−0.7 S.D.), and height 104.5 cm (−2.2 S.D.). She was cheery and sociable. Her OFC was relatively large at 53.4 cm (+2.3 S.D. for the height age). She had curly hair, a bulging forehead, epicanthal folds, posteriorly rotated ear lobes, a broad nose with a low nasal bridge, thick lips, and micrognathia. Her neck was short, and her chest was barreled (Fig. 1). Her skin was dark and redundant, especially so on the hands and feet (Fig. 2). Acanthosis nigricans was noted on her neck and cubital fossae. Her fingers were hyperextensible, but her ankle joints were limited in dorsiflexion with tight Achilles tendons. Her voice was low-pitched and husky. Her DQ score was 51. Her serum insulin level was normal as was the oral glucose tolerance test.

Patient 2. This 3-year 5-month old boy was the only child of nonconsanguineous healthy parents. The mother was 31 years old and the father 32 at his birth. The pregnancy was uneventful. He was delivered vaginally at 36 weeks of gestation. Birth weight was 2,960 g (+0.7 S.D.), length 48 cm (+0.3 S.D.), and OFC 34 cm (+1.0 S.D.). He was transferred to an NICU in view of progressive tachypnea. Subsequently, he developed polycythemia, hypoglycemic seizures, and sepsis with *Klebsiella pneumoniae*. Heart murmurs were audible, but echocardiography revealed no abnormalities. His karyotype was normal. He sucked poorly but discharged at 50 days of age. He controlled his head at 11 months, and sat at

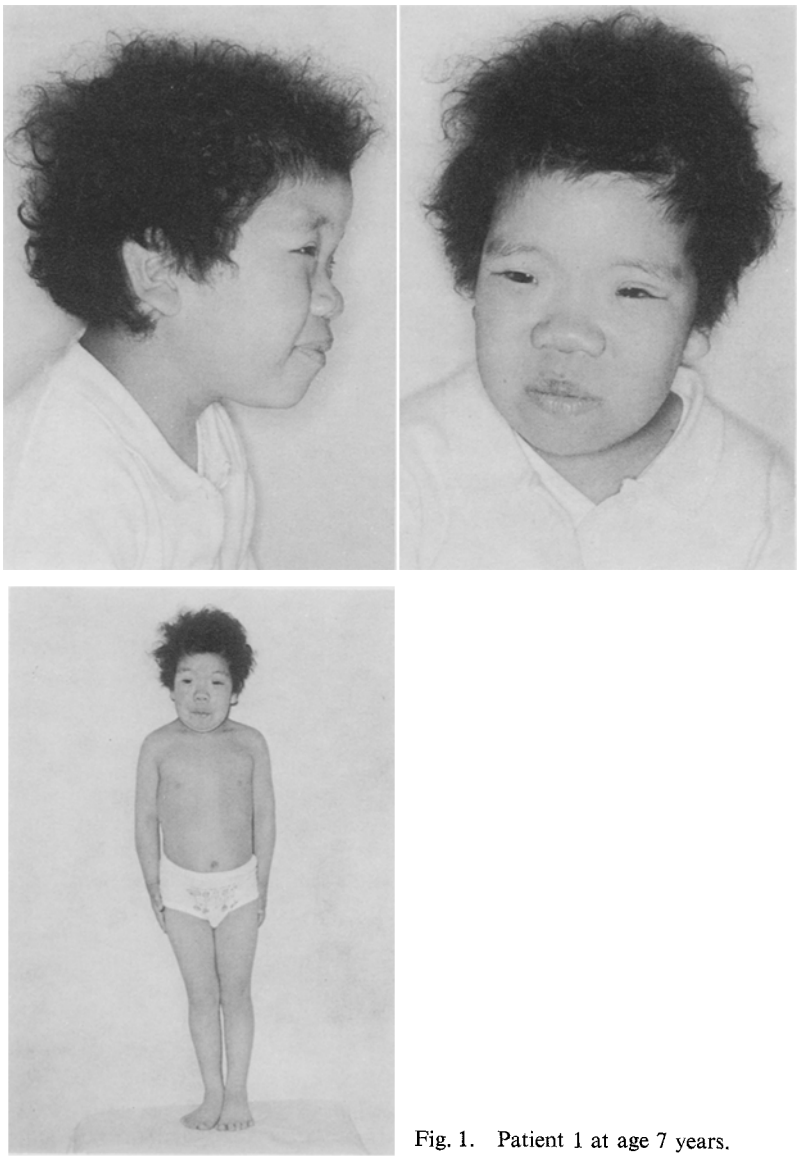

Fig. 1. Patient 1 at age 7 years.

21 months.

At age 3 5/12 years, he weighed 9.86 kg (−2.7 S.D.) and measured 78.5 cm (−4.7 S.D.). He was nervous. He rolled and crawled but did not walk. He had frontal bossing, curly hair, a low nasal bridge, epicanthal folds, full cheeks, micrognathia, a short neck, a barrel chest, redundant skin of the hands and feet, and hyperextensible fingers (Fig. 3). He showed generalized hypotonia, talipes

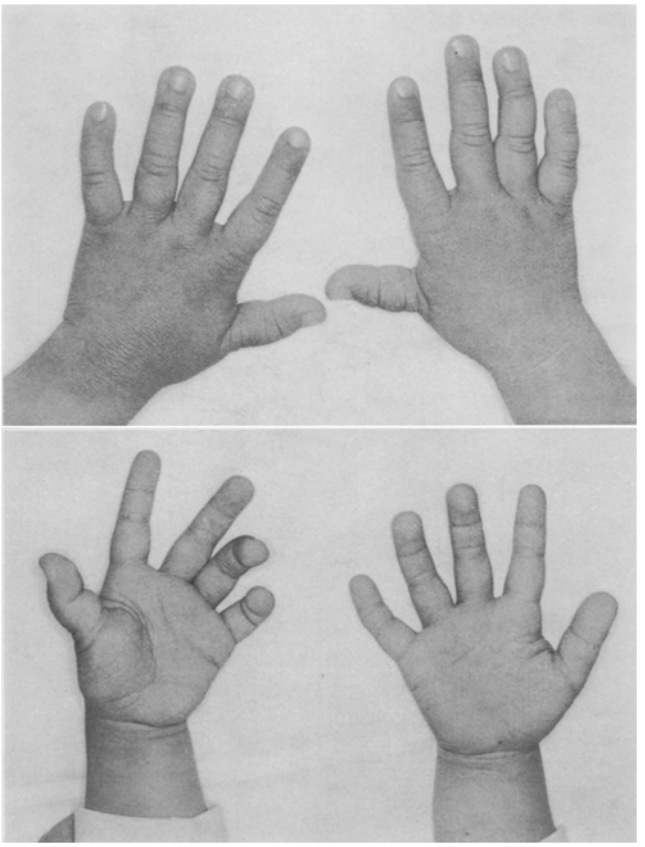

Fig. 2. The hands of Patient 1. Note the redundant, and loose skin.

equinovarus and tight Achilles tendons (Fig. 4). Nasal papillomata were not seen. He spoke no meaningful words and was tube fed.

DISCUSSION

The clinical findings in the two patients we described are presented in Table 1, together with those in nine patients in the literature with definite or probable Costello syndrome. Both of the two patients we described had relative macrocephaly at birth, curly hair, thick ear lobes, epicanthal folds, a short and wide nose with a low nasal bridge, thick lips, a short neck, a barrel chest, redundant skin on the hands and feet, hyperextensible fingers, thin nails, dark skin, tight Achilles tendons, and talipes equinovarus. All these features, except for the absence of nasal papillomata, are consistent with the description by Costello (1977). Borochowitz *et al.* (1992) reported five children, aged 2 to 7 years, with what they inter-

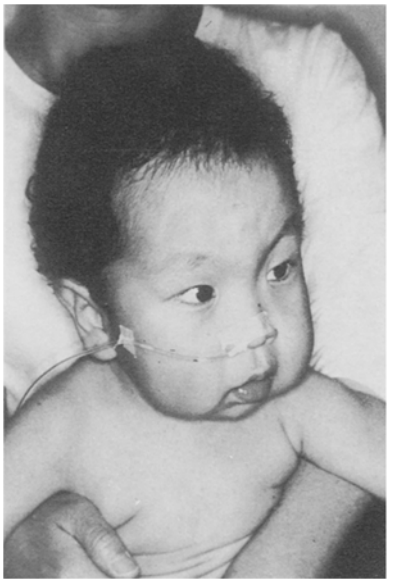

Fig. 3. Patient 2 at 3 5/12 years.

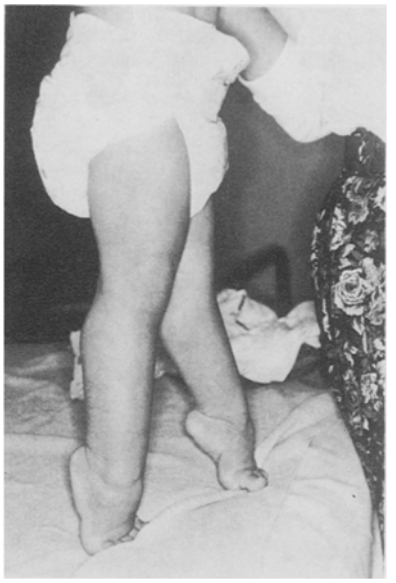

Fig. 4. Tight Achilles tendons of Patient 2.

preted as "new multiple congenital anomalies." However, their clinical manifestations are, except for the absence of nasal papillomata, essentially identical with the Costello syndrome (Table 1). In view of the similarities, it is likely that these five children represent a part of the spectrum of the Costello syndrome. In four patients with the Costello syndrome with nasal papillomata, the age at the onset of papillomata ranged from 2 years to 15 years (Costello, 1977; Der Kaloustian *et al.*, 1991; Martin and Jones, 1991). The two patients we described, were 7 years and 3 5/12 years, and thus the possibility cannot be ruled out that they later develop nasal papillomata. Nasal papillomata, however is not likely to be an essential criterion in the diagnosis of the Castello syndrome. The patients described by Costello (1977), der Kaloustian *et al.* (1991) and Martin and Jones (1991) all showed pes equinus abnormalities with tight Achilles tendons, as did the two patients we described, while all five patients reported by Borochowitz *et al.* (1992) had vertical talus (congenital rocker bottom feet). The reason for the difference is yet to be studied.

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Table 1. Clinical features of our patients, Costello syndrome, and new MCA/MR

			Costello syndrome			
Sex Age(yr)	Patient 1 F 7	Patient 2 M 3 5/12	Costello 1 M	Costello 2 F	Der Kaloustian M	Martin F
Parental consanguinity	−	−	−	−	−	−
Polyhydramnios	+	−	+	−	+	−
Gestation	37w3d	36w6d	38w	36w	40w	40w
Birth weight(g)	3,584	2,960	3,800	3,430	3,470	4,700
OFC at birth(cm)	37	34	38.1	34.9	NR	38.0
Growth and performance						
Poor postnatal growth	+	+	+	+	+	+
Feeding difficulty	+	+	+	+	+	+
Mental retardation	+ moderate	+ severe	+ mild	+ mild	+	+ moderate
Sociable, warm personality	+	−	NR	NR	+	+
Generalized hypotonia	+	+	NR	NR	NR	NR
Hoarse voice	+	+	NR	NR	NR	NR
Craniofacial						
Macrocephaly(relative or absolute)	+	+	+	+	+	+
Prominent forehead	+	+	(+)	(+)	(+)	(+)
Low set ears	+	+	+	+	+	+
Thick ear lobes	+	+	+	+	+	+
Epicanthic folds	+	+	+	+	+	+
Strabismus	+	−	+	+	NR	+
Downward slant of palpebral fissure	+	+	(+)	(+)	(+)	(+)
Short and wide nose	+	+	(+)	(+)	(+)	(+)
Depressed nasal bridge	+	+	+	+	+	+
Anteverted nostrils	+	+	(+)	(+)	+	+
Extended ala nasi	+	+	(+)	(+)	(+)	(+)
Full cheek	+	+	(+)	(+)	+	(+)
Thick lips	+	+	+	−	+	+
Enamel dysplasia	−	+	−	+	−	−
Short neck	+	+	+	+	+	+
Barrel chest	+	+	+	+	+	+
Extremities						
Hyperextensible fingers	+	+	+	+	+	+
Defect range of elbow motion	−	−	+	−	+	+
Tight Achilles tendon	+	+	+	+	+	+
Foot positional defect	+	+	+pes cavus	+	−	+
Rocker bottom feet	−	−	−	−	+	−
Skin/Hair/Nails						
Curly hair	+	+	+	+	+	+
Dark skin color	+	+	+	+	+	+
Hyperpigmentation	+	+	−	−	+	+
Cafe au lait spot	+	+	−	−	−	−
Hemangioma	+	−	−	−	−	−
Palmar nevi	+	−	−	−	−	+
Loose skin, esp. hands and feet	+	+	+	+	+	+
Deep plantar, palmar creases	+	+	NR	NR	NR	NR
Thin nails	+	+	+	+	+	+
nasal papillomata	−	−	+	+	+	+
Undescended testis	/	+	+	/	+	/
protruding nipple	+	+	NR	NR	NR	NR
Heart murmur	−	−	+	+	+	−
Congenital heart disease	−	−	−	−	−	+ mitral valve prolapse

NR:not reported; ( ):by photo;
OFC:occipito-frontal circumference; PS:pulmonary stenosis; PDA:patent ductus arteriosus

Borochowitz *et al.*, 1992).

new MCA/MR (Borochowitz et al, 1992)				
1	2	3	4	5
M	F	F	F	F
4	3mo	2.5	7	2 9/12
−	+	+	−	−
−	−	+	−	−
term	term	term	38w	term
4,100	4,200	3,650	3,440	3,980
33	35	37	34	35
+	+	−	+	+
+	+	−	NR	+
+	+	+	+	+
		mild	moderate	mild-moderate
+	NR	+	+	+
+	NR	−	NR	+
+	+	+	+	+
+	+	+	+	−
+	+	+	+	+
NR	NR	?	+	+
+	+	+	+	+
+	NR	+	+	+
NR	NR	NR	NR	NR
+	+	+	+	NR
+	+	+	+	+
+	+	+	+	+
+	+	+	+	−
+	+	+	+	+
+	+	+	+	−
+	+	+	+	+
NR	NR	NR	+	+
+	NR	+	+	+
NR	+	+	NR	NR
NR	NR	NR	NR	subluxation
+	+	+	NR	NR
NR	NR	NR	NR	NR
−	−	−	−	−
+	+	−	+	+
+	NR	NR	+	NR
+	NR	NR	+	NR
NR	NR	−	−	−
+	+	−	−	−
−	−	−	−	−
+	+	+	+	+
+	+	+	+	+
−	−	NR	−	+
−	−	−	−	−
−	N	N	N	N
NR	NR	NR	+	+
−	+	+	+	+
−	PS	PDA	PS	PS

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Note added in proof: Recently additional reports on Costello syndrome appeared in the Am J Med Genet **47**: Aug. 1993.