Case Report

**THE COSTELLO SYNDROME:
A BOY WITH THICK MITRAL
VALVES AND ARRHYTHMIAS**

Yoshinori IZUMIKAWA,* Kenji NARITOMI, Takaya TOHMA,
Noboru SHIROMA, and Kiyotake HIRAYAMA

*Department of Pediatrics, University of the Ryukyus School of Medicine,
Uehara, Nishihara, Okinawa 903-01, Japan*

Summary A 3-year-old boy with Costello syndrome is reported. He had typical clinical features of the syndrome including severe postnatal growth retardation, poor sucking, mild developmental delay, a coarse characteristic facies, thick and loose skin of the hands and feet, sparse and curly hair, dark skin, and relative macrocephaly but lacked nasal papillomas. In addition, he had cardiac anomalies with extrasystoles and thick mitral valve tips. Mitral valve defects may be a clinical feature of the syndrome.

Key Words malformation syndrome, Costello syndrome, arrhythmia, mitral valve defects

INTRODUCTION

Since the report of two patients by Costello (1977), only two additional patients with the Costello syndrome have been published, which served to delineate the Costello syndrome (Der Kaloustian *et al.*, 1991; Martin and Jones, 1991). We report a 5-month-old boy presenting with the syndrome with arrhythmias and thickening of the mitral valve tips and interventricular septum.

CASE REPORT

A Japanese boy was born to nonconsanguineous parents: a G2P1, 32-year-old mother, and 38-year-old father. The pregnancy was uneventful except for genital spottings occurring thrice during the first trimester. The infant was delivered at

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*To whom correspondence should be addressed.

35 weeks of gestation by cesarean section because of premature rupture of the placental membranes. Polyhydramnios and cloudy amniotic fluid were noted. His Apgar score was 8, birth weight was 3,142 g (+2.0 S.D.), length 45 cm (−0.4 S.D.), and occipitofrontal circumference 34 cm (+1.1 S.D.). At age 2 days, he developed fever, tachypnea and jitteriness, and was transferred to a neonatal intensive care unit. No positive laboratory data were obtained to confirm intrauterine infections. Transient heart murmurs were noted, but echocardiography was normal. He sucked poorly and was tube-fed. He was discharged at age 3 months.

At age 5 months, the same patient was referred to us with failure to thrive, poor feeding and a peculiar facies. He measured 52.1 cm (−5.7 S.D.), weighted 4,460 g (−4.4 S.D.), and OFC 38.0 cm (−4.4 S.D.). He had a coarse facies with prominent scalp veins and sparse hair, a high, bossing, and hirs forehead, hypertelorism, epicanthal folds, a broad and short nose with a depressed nasal bridge, low-set and posteriorly angulated ears with thick lobules, thick lips, chubby cheeks, a small and pointed chin, a bifid uvula (Fig. 1). His neck was short. Other abnormalities noted included wide-set nipples, pectus excavatum, umbilical hernia, a narrow pelvis, limited extension of the elbows joints, limited abduction of the hip joints, loose, thick and hyperkeratotic skin of the hands and feet with deep flexion creases, hyperextensive fingers, protuberant fingertips, and protruding heels. His skin was dark, especially on the dorsal surface of the hands and feet (Fig. 2). He was hypertonic exaggerated deep tendon reflexes and an opisthotonus-like posture induced on physical examination. His feces had a foul smell, but its amylase and trypsin levels were normal.

Fig. 1. The facies of the patient at 7 months of age.

Fig. 2. The loose and thick hyperpigmented skin of the hands with deep creases.

Fig. 3. The facies of the patient at age 3 years.

While no heart murmur was audible, an echocardiogram revealed thickening of the mitral valve tips and interventricular septum. A brain CT scan revealed dilatation of the third ventricles and the lateral inferior horns of the fourth ventricle. Plain X-ray pictures showed sagittal cleft of the vertebrae. No carpal and tarsal bones appeared at 7 months. Other routine hematological and biochemical data as well as urinary mucopolysaccharides were normal. His karyotype was normal at the 550 G-banded level.

He started to walk at age 3 1/12 years. When last seen by us at 3 4/12 years, relative macrocephaly was apparent with an OFC of -0.7 S.D., while his height was -5.5 S.D. (Fig. 3). His hair was curly and grew slowly. He was sociable and pleasant. His DQ was estimated at 66.

DISCUSSION

As mentioned earlier, only 4 patients with Costello syndrome have been reported (Costello, 1977; Der Kaloustian *et al.*, 1991; Martin and Jones, 1991). The clinical features of the 4 patients are listed in Table 1 together with those in

Table 1. Comparison of the clinical findings of the Costello syndrome.

Clinical Manifestations	Costello		Der Kaloustian	Martin & Jones	Present patient	Total
	Case 1	Case 2				
Sex	M	F	M	F	M	
Gestation (wks)	38	36	40	40	35	
Hydramnios	+	—	+	+	+	4/5
Large-for-date	+	+	+	+	+	5/5
Postnatal growth retardation	+	+	+	+	+	5/5
Poor sucking	+	+	+	+	+	5/5
Mental deficiency	mild	mild	+	moderate	moderate	5/5
Sociable warm personality	?	?	+	+	+	3/3
Relative macrocephaly	+	+	+	+	+	5/5
Coarse facies	+	+	+	+	+	5/5
Low-set ears with thick lobes	+	+	+	+	+	5/5
Epicanthal folds	+	+	+	+	+	5/5
Strabismus	+	+	+	+	—	4/5
Thick lips	+	—	+	+	+	4/5
Depressed nasal bridge	+	+	+	—	+	4/5
High-arched palate	+	+	+	—	+	4/5
Thin deep-set nails	+	+	+	+	+	5/5
Loose skin (hands/feet)	+	+	+	+	+	5/5
Dark skin complexion	+	olive	+	+	+	5/5
Curly hairs	+	+	sparse → +	+	sparse → +	5/5
Deep palmoplantar creases	?	?	+p	+	+	3/3
Hyperkeratosis (palm/sole)	?	?	+	+	+	3/3
Short neck	+	+	+	+	+	5/5
Tight Achilles tendon	+	+	+	+	—	4/5
Foot defects	pes cavus	calcaneovalgus clawfeet	rocker-bottom feet	talipes equinovarus	prominent heel	5/5
Hyperextensible fingers	+	+	+	+	+	5/5
Pectus carinatum/ barrel chest	+	+	+	+	excavatum	4/5
Elbow limitation	+	—	+	+	+	4/5
Nasal papilloma (age of onset)	6	2	3	+	—	4/5
Heart murmur	+transient	+	+	—	+transient	4/5
Mitral valve defect	?	?	normal UCG	normal → MVP	+	
Delayed bone age	+	+	+	?	+	4/4
Full cheeks		+	+		+	3/5

our patient. They include polyhydramnios, postnatal growth retardation, poor sucking beginning shortly after birth, relative macrocephaly, coarse facies with high bossed forehead, epicanthal folds, strabismus, depressed nasal bridge, low-set ears with thick lobules, thick lips, high-arched palate, loose and thick skin of the hands and feet, hypoplastic deep-set nails, dark skin pigmentation, curly hair, short neck, tight Achilles tendon, foot deformities, elbow limitation, delayed bone age and nasal papillomata, the latter developing as early as 2 years of age. Our patient showed most of these clinical manifestations, which he had no papillomata at age 3 years.

Our patient had cardiac anomalies including nodal extrasystoles, and thick mitral valvular tips and interventricular septum. Mitral valve prolapse has been reported in a 15-year-old girl with the syndrome (Martin and Jones, 1991). An echocardiogram in her infancy was reportedly normal. Heart murmurs were noted in 3 other patients (Costello, 1977; Der Kaloustian *et al.*, 1991). The murmurs were transient in patient 1 of Costello (1977) as was the case in our patient. In the patient reported by Der Kaloustian, the echocardiogram was normal, while an attack of paroxysmal atrial tachycardia occurred. Cardiac abnormalities, especially those involving the mitral valves are likely to be a component of the Costello syndrome. Mitral valve abnormalities, loose and thick skin and umbilical or inguinal hernias are frequent in connective tissue disorders (McKusick, 1972). The Costello syndrome thus may be a connective tissue disorder.

All the patients with the syndrome reported so far are sporadic and without consanguinity. In view of these, autosomal dominant inheritance with a fresh mutation seems plausible. McKusick's catalog (McKusick, 1992) lists the syndrome as an autosomal recessive disorder (MIM218040).

ADDENDUM

Another 3 Japanese patients with the Costello syndrome were reported at the Annual Meeting of the Japan Society of Human Genetics in 1992 (2 cases by Yoshida *et al.*, a case by Kondo *et al.*). Yet another case was reported at the 1992 Annual Meeting of the American Society of Human Genetics (Gucsavas *et al.*, 1992). The patient, a 27-month-old boy, suffered from congestive heart failure due to atrial fibrillation developed at age 3 months. Echocardiography revealed a small atrial septal defect. It seems that the Costello syndrome is more common than so far realized.

The EBV-transformed lymphoblastoid cell line of the patient is available (#90-12). Kindly contact Dr. K. Naritomi.

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