□ Case Report □

Costello syndrome: three sporadic cases

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Costello syndrome (CS) is a rare multiple congenital abnormality syndrome characterized by a typical coarse face, developmental delay, psychomotor and growth retardation, neurologic abnormalities, cardiac and cutaneous anomalies, severe feeding difficulties with postnatal growth failure, and increased risk of tumors. Since Costello first described it in 1971 and again in 1977, over 100 cases have been reported worldwide. It was recently shown that CS is a congenital condition caused by heterozygous de novo missense mutations affecting the codon for glycine 12 or 13 of the HRAS gene. We experienced three unrelated cases with coarse faces, developmental delays, short statures, macrocephaly, and redundant skin with deep palmar and plantar creases, hypertrophic cardiomyopathy and atrial tachycardia, which are characteristic of CS. **(Korean J Pediatr 2007;50:1024-1029)**

Key Words : Costello syndrome, Maxillofacial abnormality, Developmental disabilities, Hypertrophic cardiomyopathy

Introduction

In 1971 and 1977, Costello described two children with psychomotor retardation, postnatal growth failure, macrocephaly, a coarse face, short neck, sparse curly hair, dark skin, and nasal papillomas[1, 2]. Subsequently, over 100 cases have been reported worldwide[3, 4].

Costello syndrome (CS) has emerged as a distinct entity that should be considered when evaluating patients with a coarse face and developmental delay. When the characteristic findings are present, including papillomas, ulnar deviation of the wrists and fingers, deep palmar and plantar creases, hypertrophic cardiomyopathy or atrial tachycardia, and malignant tumors, the clinical diagnosis is unambiguous.

Recently, heterozygous de novo missense mutations affecting the codon for glycine 12 or 13 of the HRAS gene were identified for the molecular confirmation of CS[5-7]. We experienced three unrelated Korean patients with similar findings and review the manifestations of CS.

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Case Report

Case 1

A baby boy was born at 37 gestational weeks to a 35-year-old mother and a 37-year-old father at a local hospital by vaginal delivery. Polyhydramnios was detected by ultrasonography from the third trimester of pregnancy. After birth, the baby was transferred to our hospital because of dyspnea, tachypnea, and chest retraction. Endotracheal intubation and mechanical ventilation were required to treat respiratory distress for 5 days. The family history was noncontributory, and two elder sisters were healthy. His birth weight was 3,440 g (>90th percentile), length was 54.5 cm (>90th percentile), and head circumference was 38.0 cm (>90th percentile). The physical features at birth included telecanthus, a depressed nasal bridge, a large mouth with macroglossia, abnormally shaped helices, multiple café-au-lait spots on the thigh and axilla, and bilateral cryptorchidism. His hair was short, soft, and curly (Fig. 1A). He had short hands with a deep palmar crease and redundant skin, and hyperextensible joints (Fig. 1B).

At 1 month of age, he developed intermittent multifocal atrial tachycardia, but the echocardiogram was structurally

normal. During the first 6 months of life, he was admitted several times because of feeding problems and atrial tachycardia (Fig. 1C). Medications such as digoxin and propranolol were started. At 6 months of life, his coarse facial features were more evident, leading to a clinical diagnosis of CS. Gastrostomy was required for enteral feeding because of failure to thrive. At 10 months, concentric hypertrophic cardiomyopathy was noted on echocardiography.

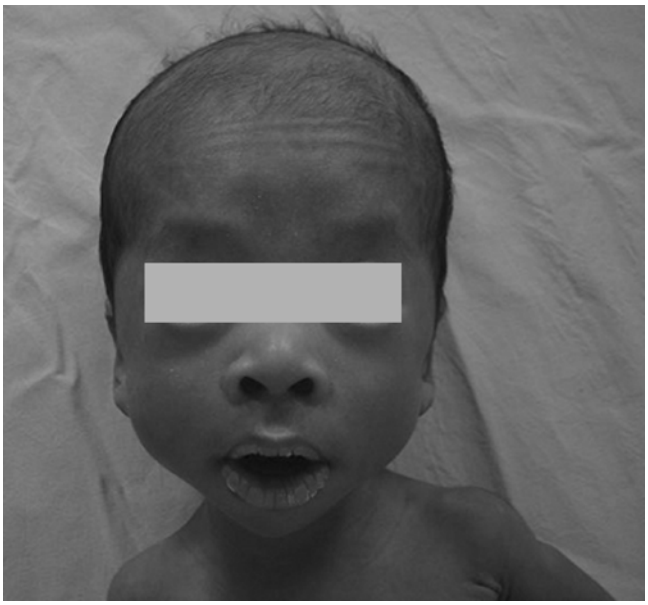

Fig. 1A. Patient 1 at age 6 months. Note the typical 'coarse' face, depressed nasal bridge, bulbous nose, low-set ears, and large lips.

Fig. 1B. This picture showed the remarkably hyperextensible distal interphalangeal joint.

The growth profile at birth was above the 90th percentile, but subsequently, he failed to thrive despite feeding via a gastrostomy tube since 6 months of life. At 1 year of age, growth status, including weight and length, was below the 3rd percentile and his development was delayed. Neurological investigations showed normal reflexes and sensory system, except for decreased muscle tone. The chromosome analysis was normal. The electroencephalogram showed diffuse low-amplitude activity without asymmetry or epileptiform discharge. Brain magnetic resonance imaging (MRI) was normal, except for generalized poor myelination. Cardiac compromise followed and he died at 1 year and 10 months of age due to hypertrophic cardiomyopathy (Fig. 1D).

Case 2

A baby girl was born at 31 weeks of gestation to a 33-year-old woman who had two previous pregnancies with her

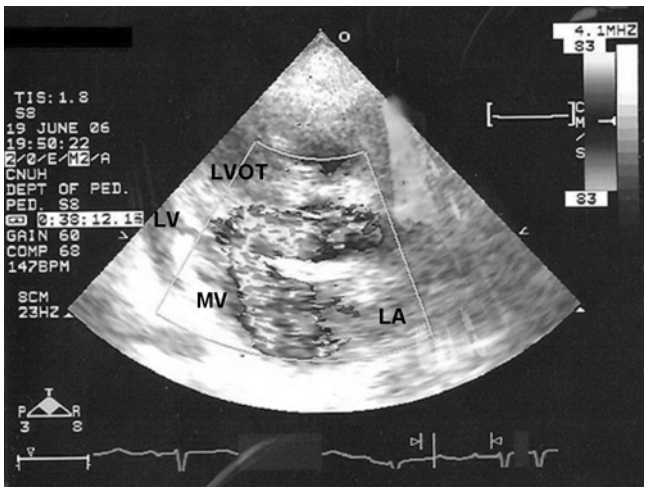

Fig. 1D. The echocardiogram showed severe subaortic septal hypertrophy causing left ventricular outflow tract obstruction and severe mitral regurgitation with left atrial enlargement. Abbreviations : LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve.

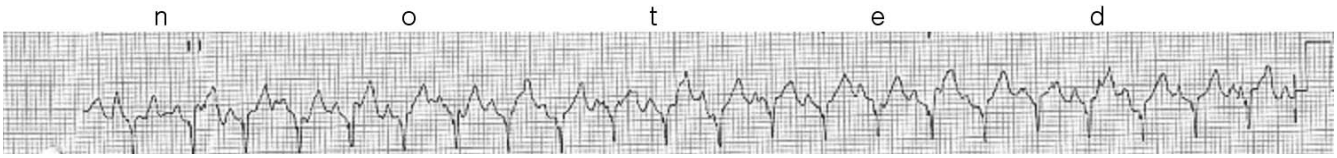

Fig. 1C. Electrocardiogram at age 1 month. Multiple episodes of atrial tachycardia were.

39-year-old partner. Pregnancy was complicated by polyhydramnios detected on ultrasonography from the third trimester, and she was delivered by cesarean section. Her birth weight was 2,200 g (>90th percentile), length was 42.0 cm (50-75th percentile), and head circumference was 32.5 cm (>90th percentile). The Apgar scores were 6 at 1 min and 7 at 5 min, respectively. Endotracheal intubation, surfactant therapy, and mechanical ventilation were required for respiratory distress syndrome.

The physical features at birth included a short bulbous nose, thick eyebrows, low-set ears, curly hair, deep creases on the soles of the feet, and loose skin (Fig. 2A). The liver was palpated two fingerbreadths below the costal margin; the anus was located close to the external genitalia and a 2 ×2 cm anal papilloma was noted (Fig. 2B). The neurologic examination revealed opisthotonos. Brain MRI indicated an unmyelinated neonatal brain. The chromosome analysis was normal.

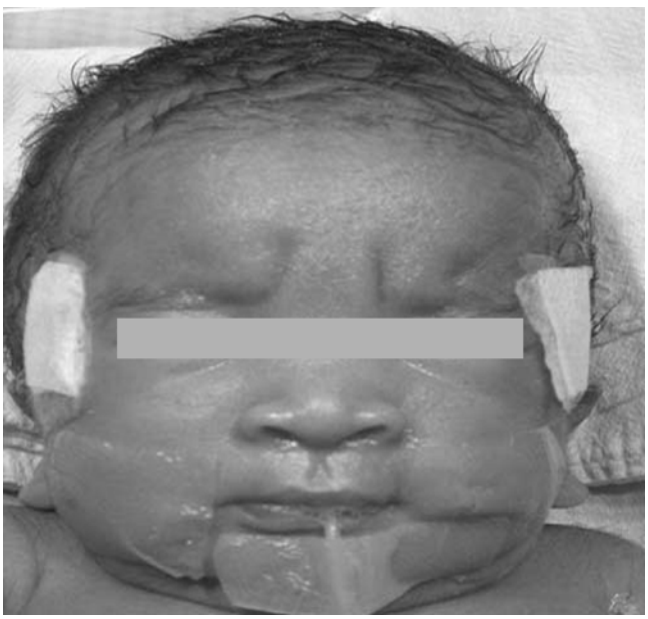

Fig. 2A. Patient 2 at age 1 month. Note the similar facial characteristics.

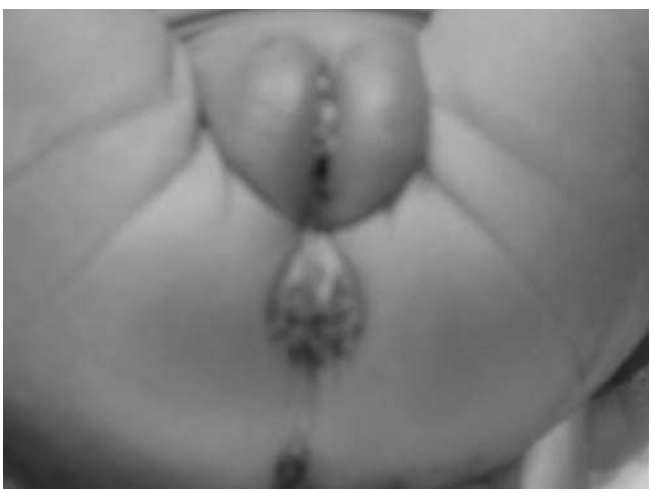

Fig. 2B. The anal papilloma was observed. The anus was located close to the external genitalia.

Echocardiography at 5 days of age showed hypertrophic cardiomyopathy including a thickened left ventricular wall, small left ventricular chamber, and asymmetric septal hypertrophy. In addition, the ductus arteriosus was patent. The 24 hours Holter electrocardiogram revealed occasional premature ventricular complexes, but was otherwise normal. Coarse facial features were evident prompting a clinical diagnosis of CS. At 40 days of age, apnea and bradycardia developed suddenly and she died.

Case 3

A baby boy was born following a 37-week gestational period to a 30-year-old woman and 35-year-old man; the baby had one previous normal sibling. Polyhydramnios was not detected on antenatal sonography. The pregnancy was

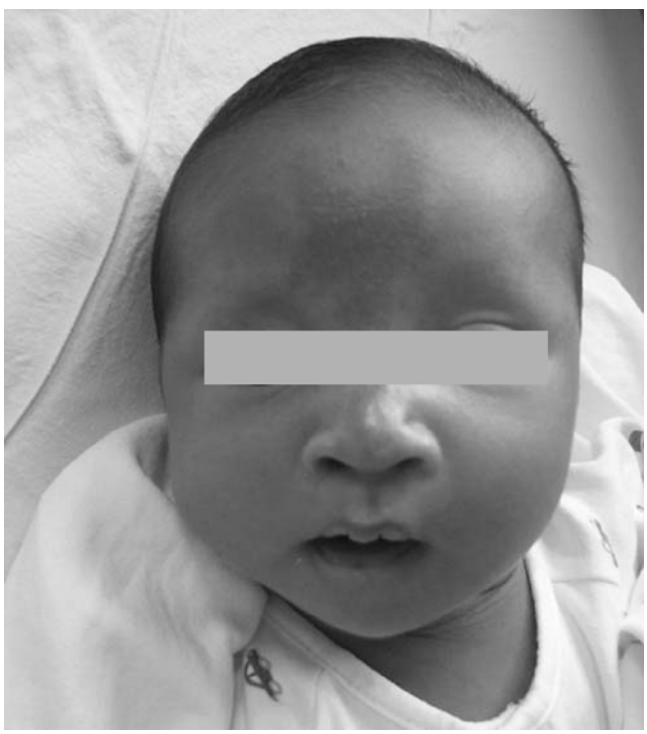

Fig. 3A. Patient 3 at age 1 month. In addition, he had salmon patches on the glabella and nose tip.

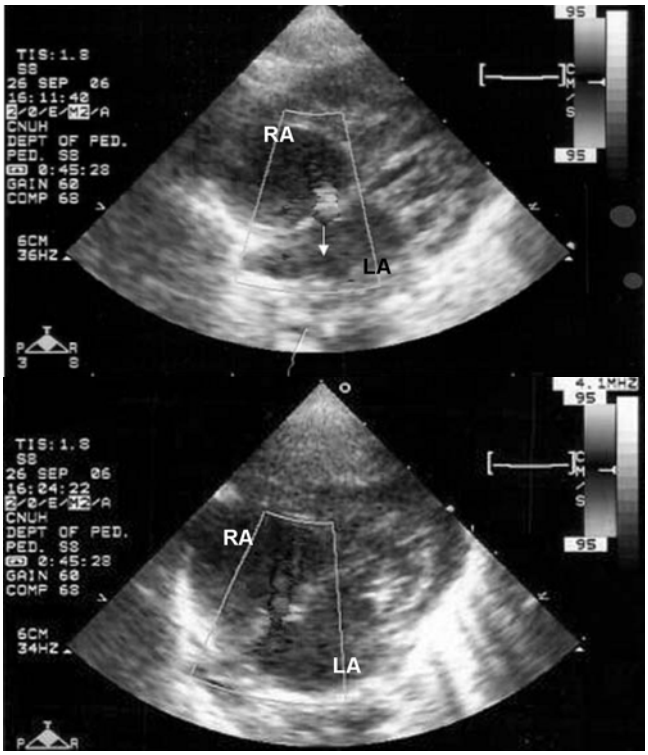

Fig. 3B. Echocardiogram at age 1 month. Multiple atrial septal defects were noted (white Arrows). Abbreviations : RA, right atrium; LA, left atrium.

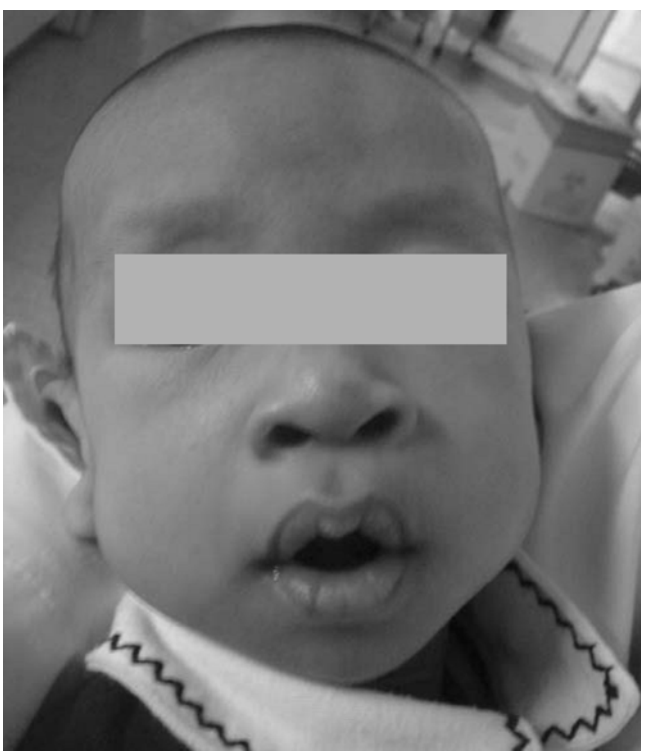

Fig. 3C. Patient 3 at 6 months. He had more typical coarse face than when he was 1 month of age.

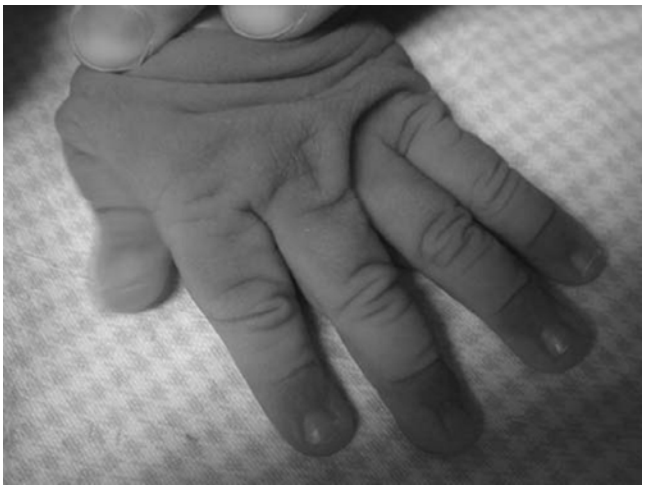

Fig. 3D. This is Patient 3 s hand. Note the redundant skin.

not complicated and he was delivered vaginally at a local hospital. The birth weight was 4,400 g (>90th percentile), length 56.5 cm (>90th percentile), and head circumference 38.0 cm (>90th percentile). At 2 days of age, he developed sinus tachycardia and was referred to our hospital. He had the coarse facial findings characteristics of CS, including thick lips and loose skin, deep plantar creases, and capillary hemangiomas over the glabella and nose (Fig. 3A). No papillomas or intracranial abnormalities were observed. The echocardiogram showed small multiple atrial septal defects (Fig. 3B) and cardiac function was good. He is now 7 months of age with retarded growth and development, showing typical morphology of CS (Fig. 3C, 3D) .

Discussion

CS is a rare disorder comprised of mental retardation, a distinctive facial appearance, cardiovascular abnormalities, tumor predisposition, and skin and musculoskeletal abnormalities[3, 4, 7, 8]. In most cases, the pregnancy is complicated by polyhydramnios[3]. Poor sucking is noted universally, and the polyhydramnios may be explained by prenatal swallowing difficulties. Two of our patients had a history of maternal polyhydramnios. All three of our patients were large for their gestational ages and their parents were older (the mothers were over 30 and the fathers over 35 years).

At birth, most children with CS have a normal or relatively high weight, normal length, and large head circumference, but severe early postnatal growth retardation is common. Our three patients were all large for gestational age at birth, but

later developed poor feeding and growth failure. The major facial signs give the Costello face a characteristic "coarse" impression, including curly and often sparse hair, low-set ears with large earlobes, thick eyebrows, epicanthal folds, down-slanting palpebral fissures, strabismus, a depressed nasal bridge, a bulbous nose with anteverted nostrils, full cheeks, a large mouth, and thick lips[1-4, 8].

In our three cases, patient 1 was diagnosed at 6 months of age when the facial characteristics became more typical, while the other two patients (patients 2 and 3) were diagnosed soon after birth because we were aware of this syndrome after experiencing patient 1. The hands and feet have been described as short and broad[9-11]. The fingers are generally hyperextensible and sometimes show hypoplasia of the distal phalanges. All of our patients exhibited these characteristics. Genital abnormalities are observed, such as undescended testes, a small penis, a hypoplastic scrotum, and large external genitalia[1, 2, 4]. Patients 1 and 3 had a hypoplastic scrotum and undescended testes. The most striking cutaneous sign of CS is the redundant, loose skin of the hands and feet, which is present at birth. The skin is thickened, and feels soft and velvety. All three of our patients showed typical cutaneous features. Another major sign presents as papillomas, which have been reported localized on the nose, mouth, anus, axillae, elbows, knees, vocal cords, and abdomen in CS[3]. They are not usually present in the newborn, although patient 2 had an anal papilloma at birth; patients 1 and 3 did not develop any papillomas before their deaths. Many brain anomalies have been found, ranging from mild brain atrophy to diffuse cerebral anomalies[3, 11]. In patient 1, the brain MRI at 7 days of age was nonspecific, except poor myelination. Congenital heart defects are common in CS. Hypertrophic cardiomyopathy, tachycardia, or structural anomalies are seen in about two thirds of patients, while one-third lack cardiac anomalies[12]. All of our patients had atrial tachycardia and patients 1 and 2 died from heart failure. A previous study showed that cultured fibroblasts from individuals with CS accumulate excessive chondroitin sulfate-bearing proteoglycans, associated with both impaired formation of elastic fibers and an unusually high rate of cellular proliferation[13]. According to Hinek et al. [14], the imbalance in sulfation of chondroitin sulf molecules and subsequent accumulation in cardiomyocytes is thought to contribute to the development of the hypertrophic cardiomyopathy of CS.

Psychomotor retardation is consistent. Most patients with CS are described as having a warm, sociable personality. Patient 1 did not walk or stand alone until he died at 22 months of age, and patient 3 also showed developmental retardation. Those with CS tend to develop benign tumors of ectodermal origin, especially papillomas. Ganglioneuroma, bladder carcinoma, acoustic neuroma, epithelioma, neuroblastoma, and especially embryonal rhabdomyosarcoma (10 times higher than general population) have also been found[8]. In patients 1 and 2, no tumors were found before the patients died, and none have been yet detected in patient 3. Gripp et al.[8] suggested a tumor-screening protocol consisting of abdominal and pelvic ultrasound examinations every 3-6 months from birth until 8 to 10 years, urinary catecholamine excretion measurements every 6-12 months until 5 years, and annual screening for hematuria until 10 years of age.

The recent identification of HRAS mutations in CS allows molecular confirmation of the diagnosis if such a mutation is identified[5-7]. We diagnosed CS based on the clinical characteristics alone. After we experienced the first case, we were aware of this disease and the next two cases were diagnosed earlier.

In conclusion, CS is a distinct multiple congenital malformation syndrome characterized by postnatal growth retardation, a distinct face, loose skin, and developmental delay.

한 글 요 약

Costello 증후군 3례

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Costello 증후군은 특징적 얼굴 형태(coarse face), 발달 장애, 지능 저하, 성장 지연, 신경학적 이상, 심근증, 피부 병변, 수유 장애, 상대적 대두증, 소관절의 과신전, 고형종 발생 증가 등을 특징으로 하는 드문 증후군으로 1977년 Costello에 의해 처음으로 보고되었으며, 이후 전세계적으로 약 100례 이상이 보고되었다. 최근 Costello 증후군은 HRAS 유전자 내의 glycine 12 또는 13 codon을 침범하는 *de novo* mutation에 의해 발생하는 것으로 알려져 있다.

저자들은 특징적인 얼굴 형태와 지능 저하, 대두증, 손과 발의 과도한 주름, 비후성 심근증과 심방성 빈맥으로 특징지어지는 Costello 증후군으로 진단된 환아 3례를 경험하였기에 이를 보고하는 바이다

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