Tetralogy of Fallot and hypertrophic cardiomyopathy in a case of cardiofaciocutaneous syndrome

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Cardiofaciocutaneous (CFC) syndrome is a rare disorder characterized by psychomotor and growth retardation, a typical facial dysmorphism, congenital heart defects, and ectodermal abnormalities. Pulmonic stenosis, atrial and ventricular septal defects, patent ductus arteriosus, and hypertrophic cardiomyopathy are cardiac findings identified in patients with this syndrome; however, tetralogy of Fallot has never been associated with CFC syndrome. CFC should be considered in patients with skin abnormalities in addition to phenotypic features and a congenital heart defect, including tetralogy of Fallot.

Key words: cardiofaciocutaneous syndrome, tetralogy of Fallot, cardiomyopathy.

Cardiofaciocutaneous (CFC) syndrome (OMIM#115150) is a rare disorder that was first described by Reynolds and colleagues in 1986[1]. Psychomotor and growth retardation, a typical facial dysmorphism, congenital heart defects, and ectodermal abnormalities are the major abnormalities associated with this syndrome. Important differentials in the diagnosis of CFC are Noonan syndrome and Costello syndrome. The most common heart defects associated with CFC syndrome are pulmonic stenosis (PS) and atrial septal defects (ASD)[1-5]. Few patients with CFC syndrome have exhibited cardiomyopathy, and to our knowledge, no patient has been diagnosed as having both CFC syndrome and tetralogy of Fallot (TOF). In this report, we describe a male infant with CFC syndrome and TOF, in addition to a small secundum ASD, patent ductus arteriosus (PDA), and subsequent hypertrophic cardiomyopathy.

Case Report

This patient, an 11-month-old infant, was the second child of nonconsanguineous parents. He was born during the 36th week of pregnancy to a mother aged 34 years and a father aged 33 years, and prenatal and family histories were insignificant. His weight was 2460 g at birth, at which time he was admitted to the neonatal intensive care unit for the treatment of respiratory distress. Auscultation revealed a 3/6-grade systolic murmur. Echocardiography indicated TOF, a small secundum ASD, and PDA. In addition to his heart disease, he exhibited an atypical facial appearance.

The results of routine hematologic examination, blood biochemistry analysis, urinalysis, cranial ultrasonography, chromosomal analysis, thyroid function tests, serum zinc level assessment, and tandem mass spectrophotometry were within the normal ranges. Fluorescent *in situ* hybridization analysis did not show 22q11 deletion. The results of abdominal ultrasonography revealed bilateral hydronephrosis that resolved spontaneously during his 10th month of life.

At the patient's two-month follow-up examination, growth deceleration was identified. Results of physical examination when the patient was 11 months old revealed a weight of only 5000 g, a length of 65 cm, and a head circumference of 41 cm (values below the 3rd percentile). The patient's achievement of developmental milestones was also delayed.

His facial dysmorphism was more apparent when he was 11 months old. Bitemporal narrowing, decreased eyebrow and eyelash,

hypoplasia of the supraorbital ridges, low-set and posteriorly angulated ears with prominent helices, depressed nasal bridge, telecanthus, hypertelorism, down-slanted palpebral fissures, hypoplastic maxilla, a broad nasal tip, prominent filtrum and short neck were seen (Figs. 1, 2). Mild

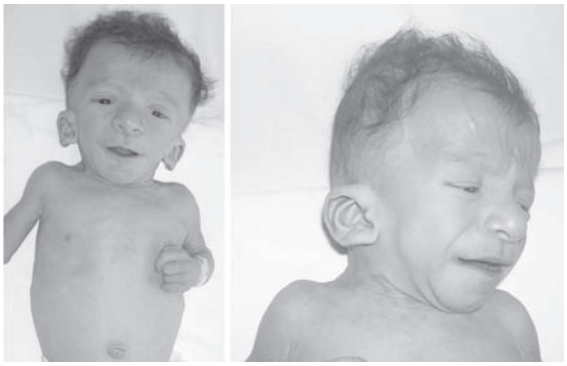

Fig. 1-2. Phenotypic features of the patient.

pectus carinatum and persistent cryptorchidism were also identified. His hair was thin and sparse, and both temporal and occipital baldness was noted. His skin was dry and mildly hyperkeratotic. Eczematous lesions were found on his neck, keratosis pilaris on his arms, seborrheic dermatitis on his scalp, and miliaria on his back. Two melanocytic nevi were also identified. The skin of his palmoplantar regions was slightly loose. Café-au-lait spots, papillomas, hemangiomas, and acanthosis nigricans were not detected. The patient was diagnosed as having CFC syndrome. Soon after that diagnosis was made, follow-up echocardiography showed hypertrophic cardiomyopathy additional to TOF (Fig. 3).

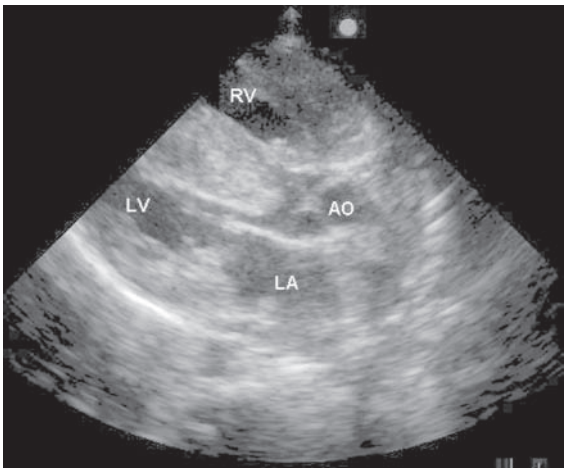

Fig. 3. Parasternal long axis echocardiographic view of the heart. LA: Left atrium. LV: Left ventricle. RV: Right ventricle. AO: Aorta.

At this time, echocardiographic measurements of diastolic interventricular septum diameter, systolic interventricular septum diameter, end-diastolic ventricular diameter, systolic ventricular diameter, diastolic left ventricular posterior wall thickness and systolic right ventricular posterior wall thickness were 13.7, 18, 17, 3.3, 8.2 and 11.1 mm, respectively. These measurements at 3 months were 6, 9, 13.1, 9.3, 6.2, and 10.6 mm, respectively. The patient died early after the heart surgery.

Discussion

The typical facial features associated with CFC syndrome are a large prominent forehead, bitemporal narrowing, relative macrocephaly, shallow orbital ridges, low-set posteriorly rotated ears, a short upturned nose, down-slanted palpebral fissures, hypertelorism, ptosis, prominent philtrum, and exophthalmos[2].

The common ectodermal abnormalities described in patients with CFC syndrome include abnormal hair, which is sparse, curly, fine, and thin with abnormal growth; sparse eyelashes and eyebrows; dry eczematous skin; hyperkeratosis; keratosis pilaris; seborrheic dermatitis; and hemangiomas. Rare abnormalities are loose skin on the hands and feet, acanthosis nigricans, pigmented nevi, and café-au-lait spots[4]. The ectodermal abnormalities noted in our patient were thin and sparse hair, temporal and occipital baldness, dry and mildly hyperkeratotic skin with regional eczema, keratosis pilaris on his arms, seborrheic dermatitis on his scalp, loose skin on his palmoplantar regions, miliaria on his back, and two melanocytic nevi.

We established the diagnosis in our patient based on typical dysmorphic features concordant with CFC syndrome. The characteristic abnormalities and facial features of individuals with CFC syndrome are similar to those of people with Noonan syndrome or Costello syndrome.

Kavamura and colleagues[2] created a CFC index to confirm the diagnosis of typical and severe cases of CFC syndrome. They also suggested that this index could be used to differentiate CFC syndrome from Costello syndrome or Noonan syndrome. Ninety-five percent (54 patients) of the population studied by those authors had CFC indices between 9.5 and 19.9 (mean±2 SD). We calculated a CFC index of 11.5 for our patient.

Cardiac findings in the CFC syndrome are also remarkably similar to those noted in the Noonan and Costello syndromes. Pulmonary valve stenosis is common in these three syndromes. The incidence of pulmonary valve stenosis and hypertrophic cardiomyopathy are similar in CFC and Costello syndromes, whereas Noonan syndrome has a considerably higher incidence of pulmonary valve stenosis and a much lower incidence of hypertrophic cardiomyopathy[6].

Pulmonary stenosis is the most common heart defect associated with CFC syndrome. ASD, ventricular septal defect (VSD), PDA, mitral valve prolapse and insufficiency, thickened and dysplastic valves, and aortic valve stenosis were also reported[7-9]. Our patient's initial cardiac findings were TOF, a small secundum ASD, and PDA. When he was 11 months old, cardiac examination exhibited hypertrophy of the interventricular septum and the unrestrained ventricular walls suggesting hypertrophic cardiomyopathy[8,10-12]. As mentioned earlier, hypertrophic cardiomyopathy has been identified in a few patients with CFC syndrome. However, to our knowledge, TOF has never been reported in association with CFC syndrome; thus, this is the first report of a patient with both TOF and CFC syndrome.

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