—Case Reports—

Transient Cardiomyopathy in a Patient with Congenital Contractural Arachnodactyly (Beals Syndrome)

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Abstract

We report on an infant with Beals syndrome (congenital contractural arachnodactyly [CCA], MIM 121050) with transient cardiomyopathy showing ballon-like dilatation of the left ventricle that was similar to noncompaction. The patient's father and two of his brothers were also found to have CCA without cardiovascular complications. CCA, which is caused by a mutation of the gene for fibrillin 2 protein is similar to Marfan syndrome (MIM 154700), which is caused by a mutation of fibrillin 1 but produces a life-threatening cardiovascular complications. This is the first report of CCA with transient cardiomyopathy. We discuss the mechanism of the spontaneous improvement of cardiomyopathy in this case on the basis of expression of the responsible gene.
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Key words: Beals syndrome (congenital contractural arachnodactyly; CCA), cardiomyopathy, noncompaction

Introduction

Beals syndrome (congenital contractural arachnodactyly [CCA]) is an autosomal dominant disorder of connective tissues, which is similar to Marfan syndrome (MFS) but is believed not to produce the ocular and life-threatening cardiovascular complications observed in MFS[1–4]. Genetic analysis has shown that CCA is caused by a mutation of the gene for fibrillin 2 protein (FBN2) on chromosome 5q23～q31[5], whereas MFS results from a mutation of FBN1 on 15q15～21.3[6]. FBN1 and FBN2 show high homology with each other, but the mechanism of the cardiovascular involvement in MFS remains unclear. We have observed the spontaneous improvement of cardiomyopathy in an infant with CCA which may help clarify the above question.

Case Report

The patient was the 2,786 g male born at a gestational age 38 weeks 5 days after a normal pregnancy. He had arachnodactyly, dolichostenomelia, metatarsus varus, contraction of the elbows and knees, and thin extremities, and ears with flattered helices and crumpled antihelices (**Fig.**

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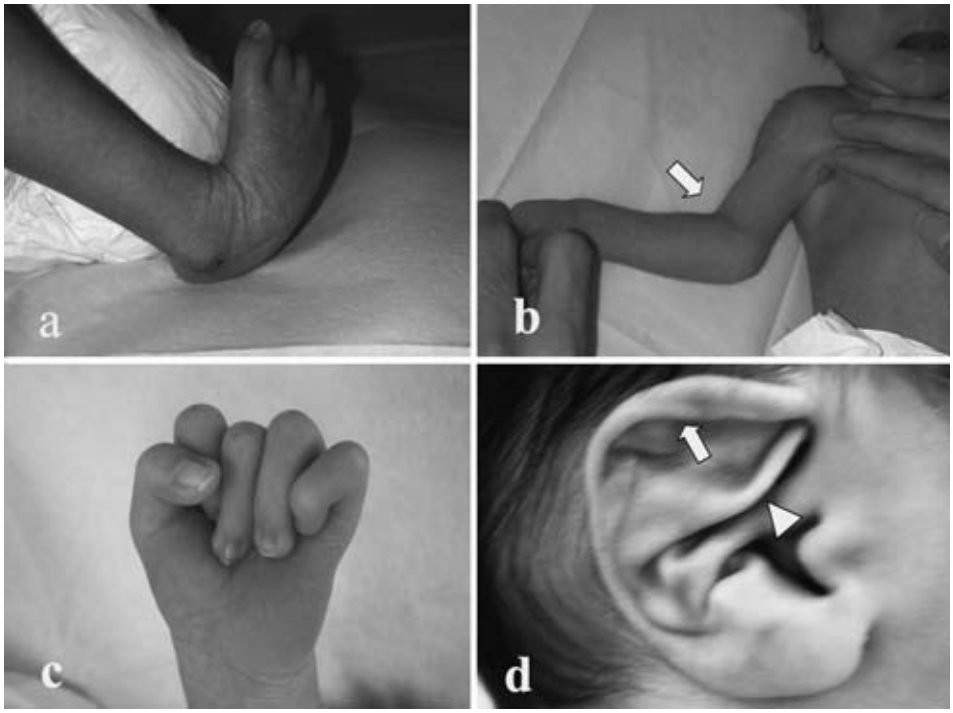

Fig. 1

a Metatarsus varus with long digits.
b Maximum extension of the limb.
c Long digits with contractures at proximal interphalangeal joints, especially that of the index finger.
d The crumpled appearance of the antihelix **(arrow)** with flattenig of the helix **(triangle)**.

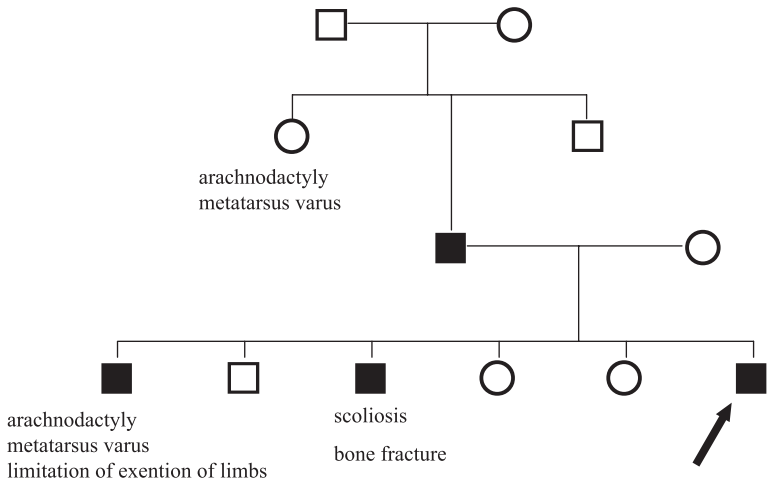

Fig. 2 Pedigree of this family.

1). Ophthalmologic examination did not show lens displacement, and the results of blood and urine examinations were normal. Chromosome analysis showered 46,XY, the normal male pattern. The family history revealed that the patient's father and two of his brothers had strikingly similar deformities: arachnodactyly, dolichostenomelia, thin extremities, and crumpled ears **(Fig. 2)**. They had muscle weakness in childhood, but the muscle weakness gradually improved in all three. One of the brothers had severe scoliosis and had undergone orthopedics surgery at the age of 14 years. No

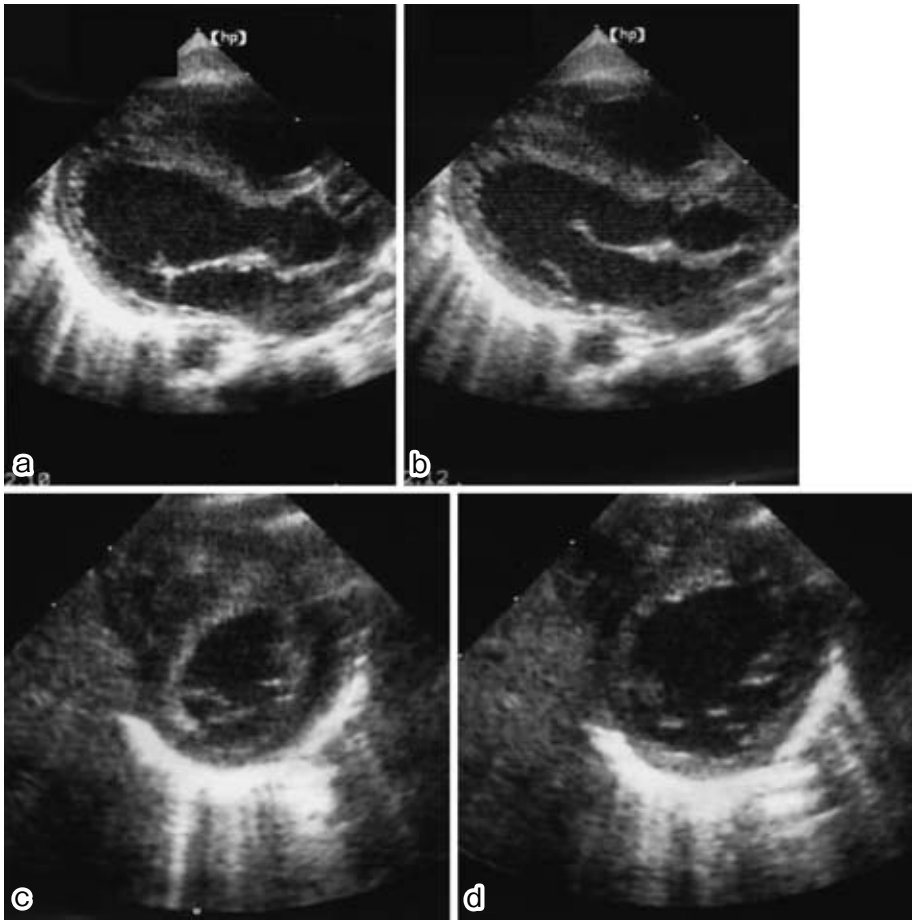

Fig. 3 Two-dimensional echocardiographic view of the heart.
a Long axis view at systole. The left ventricular trabeculations at the apex are impressive and resemble those of noncompaction.
b Long axis view at diastole, showing the balloon-like dilatation of the left ventricle.
c Short axis view at systole. The movement of inferior wall is poor.
d Short axis view at diastole, showing the thin layers of the left ventricular wall.

cardiac involvement was found in the family members. Therefore, CCA was diagnosed in the present patient and the family members. CCA is similar to MFS but CCA does not produce the ocular and life-threatening cardiovascular complications of MFS [1-4]. Interestingly, echocardiographic examinations on the present patient showed that the left ventricle chamber was dilated like a balloon, and its wall had a two-layer structure: a compact epicardial layer and an endocardial layer consisting of a trabecular meshwork with deep intertrabecular spaces, only in the apex region: the left ventricular ejection fraction was 62.1% **(Fig. 3)**. The appearance of the left ventricle was like that of noncompaction, although color Doppler evidence of deep perfused intertrabecular blood flow was not obtained. Moreover, a small type 2 ventricular septal defect with membranous septal aneurysm was found in this patient. To determine the prognosis of cardiac function of the patient, the cardiac function of a brother with the same physical characteristics was examined with echocardiography. This 15-year-old brother had no abnormal findings in echocardiographic findings. Moreover, spontaneous improvement of noncompaction-like area was observed: the prominent trabecula had decreased, and the left ventricular wall looked much smoother. Follow-up echocardiography 1 month later showed over developed trabecula only at the apex of the left ventricle.

Discussion

Fibrillin is a cystein-rich glycoprotein, a major component of the microfibril that is a backbone of extracellular filaments[7]. FBN1 and FBN2 are highly homologous with each other, and both are integral components of microfibrils, which are widely distributed in mammalian tissues that are devoid of amorphous epidermal junction, such as tendons, fascia, and the adventitial layer of blood vessels[8]. Mitral valve prolapse, congenital heart defects, including atrial septal defect and ventricular septal defect, are reported as cardiac complications in CCA[2–4]. This is the first report of a patient with CCA and cardiomyopathy , a left ventricular noncompaction: interestingly, the echocardiographic left ventricular trabeculations decreased as the patient aged, and his 15-year-old brother appeared to have normal left ventricular wall structure.

Gene analysis was not performed in this case because informed consent was not obtained. The reason remains unclear why CCA does not show the aortic dilatation seen in MFS despite the responsible genes, FBN1 and 2, having high homology. FBN2 expression is seen earlier in development in elastic tissues at the elastogenesis, and accumulation of FBN 2 transcripts plateaus before tissue differentiation, then decreases rapidly. As a general rule, FBN1 expression occurs somewhat later in morphogenesis in elastic and nonelastic tissues and persists for a longer period during which it provides force-bearing structural support. Moreover, the amount of FBN1 transcripts increases throughout morphogenesis[9]. Interestingly, the only exception to the general pattern was found in the cardiovascular system, in which the developmental expression of FBN1 gene activity is earlier and higher than that of FBN2[8]. It has been reported that microfibrils in the cardiovascular system are generated and that cardiac function is normal in FBN2 knock-out mice[10]. In the generation of recombinant FBN1 and FBN2 in the mammalian expression system, it has been shown that FBN1 alone can homotypically form the microfibrils without FBN2[9].

These findings suggested that noncompaction, the endocardial morphogenesis disorder, as the patient ages because FBN1 is able to compensate for the absence of FBN2 owing to their high homology. Elucidating the molecular basis of these differences and overlaps will be critical for understanding the pathophysiology of the fibrillin disorders MFS and CCA.

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