Congenital Contractural Arachnodactyly without *FBN1* or *FBN2* Gene Mutations Complicated by Dilated Cardiomyopathy

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Abstract

Congenital contractural arachnodactyly (CCA) is a rare connective tissue disorder characterized by marfanoid habitus with camptodactyly. However, cardiac features have rarely been documented in adults. We herein report a sporadic case of CCA in a 20-year-old woman who developed decompensated dilated cardiomyopathy. The patient did not have any mutations in the *FBN1* or *FBN2* genes, which are most commonly associated with Marfan syndrome and CCA, respectively. Although whether these two diseases are caused by a mutation(s) in the same gene or two different genes remains unknown, this case provides new clinical insight into the cardiovascular management of CCA.

Key words: congenital contractural arachnodactyly, connective tissue disease, dilated cardiomyopathy, heart failure, fibrillin-2

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Introduction

Congenital contractural arachnodactyly (CCA, also known as Beals syndrome) is an autosomal dominant heritable disorder affecting the connective tissue (1, 2). CCA patients present with marfanoid habitus characterized by long slim limbs (dolichostenomelia) and long spider-like fingers (arachnodactyly). Such patients are also likely to display external ear abnormalities, such as a crumpled appearance of the ear helix, as well as flexion contractures of multiple joints, and the *FBN2* gene on chromosome 5q23-q31 is the only causative gene of CCA identified to date. In addition, aortic dilatation/dissection and ectopic lentis, the most com-

mon features in patients with Marfan syndrome (MFS), which is caused by a mutation in the *FBN1* gene on 15q15-21.3 encoding fibrillin-1, have only rarely been documented in CCA patients.

According to recent reports, a considerable number of MFS patients exhibit subclinical cardiac dysfunction without apparent valvular abnormalities (3-5). However, there is currently only one published case of cardiomyopathy complicated by CCA (6), in which a newborn boy presented with a transient dilated left ventricular chamber composed of noncompaction-like structures that improved spontaneously. We herein present a sporadic case of CCA without *FBN1* or *FBN2* gene mutations complicated by severe dilated cardiomyopathy (DCM). Although the underlying mechanism con-

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necting these two diseases is unknown, this case provides valuable insight into the development of connective tissue disease (CTD)-related cardiomyopathy, as the association between CTD and heart failure without valvulopathy is of current research interest.

Case Report

Mutation analyses of the *FBN1* and *FBN2* genes

The genetic analyses for MFS-related disorders and familial thoracic aneurysm/dissection were approved by the Institutional Ethics Committee of the University of Tokyo Hospital (G-1538), and written informed consent was obtained from the patient after providing a detailed explanation of the purpose and protocol of the examinations. A mutation analysis of the *FBN1* gene was performed as previously described (7). Genomic DNA and mRNA isolated from white blood cells were utilized for genetic testing of *FBN2* gene mutations. In order to amplify exons 1 and 22-36 (mutation hotspots) of the *FBN2* gene, intron-specific primers flanking exons for polymerase chain reaction (PCR) were designed. In addition, the full protein-coding region of complementary DNA (cDNA) between exons 2 and 65 was amplified and separately subdivided into 20 fragments via PCR. The PCR-products were then sequenced using the BigDye Terminator v3.1 cycle-sequencing system on an ABI Prism 3100xl Genetic Analyzer (Applied Biosystems Waltham, USA). All sequencing analyses were carried out using forward and reverse primers, and all primer sequences are available on request.

Case report

The patient was a 20-year and 4-month-old woman with no apparent relevant family history who had developed severe and persistent heart failure two years previously and was subsequently referred to our hospital for the management of refractory cardiac dysfunction.

At 2 months of age, the patient was found to have bilateral contractures of the fingers (camptodactyly), which was followed up at her local orthopedic hospital along with progressive scoliosis. During her high school years, she sat out from gym classes due to lumbago; however, no cardiovascular abnormalities had been detected on school physical examinations. At 18 years and 4 months of age, she suffered from progressive dyspnea, and an cardiac echocardiogram obtained on the first hospital admission to a local general hospital revealed left ventricular (LV) dilatation and severely decreased LV contractions, with a normal structure and function of the valves. The LV diastolic diameter (LVDd) and ejection fraction (EF) were 58 mm and 18%, respectively. Her blood pressure was low, and she was diagnosed with DCM. Treatment with the beta-blocker carvedilol was titrated to a dose of 10 mg daily, which resulted in temporal and partial improvements in her subjective symptoms and echocardiographic findings (LVDd: 57 mm, EF: 25%).

At 20 years and 1 month of age, the patient's symptoms were exacerbated and she was readmitted to the local hospital. At that time, the serum N-terminal pro-brain natriuretic peptide (BNP) (NT-proBNP) level was increased at 6,414 pg/mL. Despite receiving intensive care for two months, she remained catecholamine-dependent and was therefore transferred to our hospital for an evaluation of the differential diagnosis and treatment. An echocardiographic examination revealed enlargement of the LV chamber with diffuse hypokinesis of the LV wall (LVDd: 58 mm, EF: 22%) (Fig. 1A-D), although no mitral valve prolapse (MVP) or aortic root dilatation were observed [sinus of Valsalva: 20 mm, Z score: -2.54 (8)]. The plasma BNP level was 451.2 pg/mL. The patient's coronary arteries were normal, whereas endomyocardial biopsy specimens showed significant interstitial fibrosis, which was not specific for secondary cardiomyopathy (Fig. 1E). In addition, all blood tests for well-known chronic systemic disorders causing cardiomyopathy were negative (Table).

We thus suspected a possible association between the cardiac dysfunction and skeletal abnormalities, based on the concept that cardiovascular disorders may be caused by CTD, such as MFS. The patient was 149.0 cm in height, 39.2 kg in weight (BMI 17.7) and 142 cm in arm span (span/height ratio = 0.95). Walker (wrist) and Steinberg (thumb) signs were both negative, although she exhibited severe camptodactyly (hands and feet) (Fig. 2A, B), a small kink in each ear helix (Fig. 2C) and scoliosis with a Cobb angle of 36 degrees (Fig. 2D). The patient's skeletal disorder was therefore diagnosed as CCA by staff of the "Marfan clinic" at our institute according to the constellation of her clinical features (9). Finally, we performed genetic analyses of the *FBN1* and *FBN2* genes among her unaffected family members (father, mother and elderly brother); however, none of her family members were found to have any causative mutations in their DNA sequences.

Since the cause of the patient's heart failure was not determined clinically or genetically, she was diagnosed with idiopathic DCM. After providing aggressive treatment for three months, the catecholamines were withdrawn. Right heart catheterization performed in the absence of inotropic support revealed a low output (cardiac index: 1.85 L/min/m²) without pulmonary congestion (pulmonary capillary wedge pressure: 11 mmHg). The dose of carvedilol was ultimately titrated to 25 mg daily in addition to a prescription of 1.25 mg of enalapril and 50 mg of spironolactone daily. However, no remarkable improvements were noted in the LV size and contractions (LVDd: 58 mm, EF: 26%) or plasma BNP level (533.1 pg/mL). The patient was discharged and subsequently readmitted to our hospital four months later due to the exacerbation of heart failure. She is currently considered a potential recipient for cardiac transplantation.

Figure 1. Cardiac findings consistent with dilated cardiomyopathy. (A-D) Two-dimensional echocardiogram obtained on admission to our hospital showing dilatation of the LV chamber with a poor LV systolic function. (A, B) Parasternal long-axis view of the LV at end-diastole (A) and end-systole (B). (C, D) Parasternal short-axis view of the LV at end-diastole (C) and end-systole (D). LVDd: 58 mm, LVDs: 52 mm, LVEF: 22%. (E) Endomyocardial biopsy specimens of the LV with interstitial fibrosis on Azan staining (original magnification: $\times 100$).

Table. Laboratory Data on Admission to Our Hospital.

Parameters		normal range	
Adrenocorticotrophic hormone (ACTH)	28.91	7.2-63.3	pg/mL
Cortisol	3.3	4.0-19.3	μ g/dL
Aldosterone	243	36.0-240.0	pg/mL
Plasma renin activity (PRA)	4.3	0.2-2.7	ng/mL/hr
Angiotensin converting enzyme (ACE)	15	8.3-21.4	U/L
Adrenaline	5	0-100	pg/mL
Noradrenaline	97	100-450	pg/mL
Dopamine	5	0-20	pg/mL
Growth hormone	0.356	0.01-3.607	ng/mL/hr
Somatomedin-C	200	119.0-389.0	ng/mL/hr
Antidiuretic hormone	3.5	0.0-4.2	pg/mL
Thyroid stimulating hormone (TSH)	1.65	0.38-4.31	μ U/mL
Free triiodothyronine (fT3)	2	2.1-3.8	pg/mL
Free thyroxine (fT4)	1.29	0.82-1.63	ng/dL
Vitamin B1	44	24-66	ng/mL
Fe	93	40.0-162.0	μ g/dL
Ferritin	38	5.0-152.0	ng/mL
Antinuclear antibody (ANA)	(-)	(-)	

Discussion

We herein describe a case of CCA in a woman with no apparent family history who developed severe DCM without valvulopathy or aortopathy. *FBN2* is the only gene in which a mutation is causative for CCA (1, 2). However, the current patient did not have any mutations in the *FBN1* or *FBN2* genes. Whether these two diseases are caused by a mutation(s) in the same gene or two different genes remains unknown, and this case may provide new clinical insight into the management of CCA, which is thought to have a relatively favorable prognosis (1, 2).

An increasing number of papers have reported that CCA

patients exhibit cardiovascular manifestations. For example, Su et al. reported that approximately one-third of 28 Taiwan patients with CCA had congenital heart disease (10), and Matsumoto et al. described the case of a CCA newborn boy who developed transient cardiomyopathy with LV noncompaction-like structures (6). In addition, two CCA Western families (1, 11) and one Japanese family (N. Takeda, unpublished data 2014) with exon 32 deletions of the *FBN2* gene were reported to be affected by progressive aortic root dilatation and/or dissection. The prevalence of clinical or subclinical heart failure in CCA patients has not been reported, and further cardiovascular studies are needed in adults with CCA.

Recent advances in molecular and genetic analyses have

Figure 2. Skeletal findings consistent with congenital contractural arachnodactyly. (A, B) Bilateral contractures of the hands and feet (camptodactyly). (C) Small kink in the right ear helix (arrowhead). (D) Scoliosis with a Cobb's angle of 36 degrees (rear view), formed by the two dotted lines.

improved the pathophysiological understanding of the cardiovascular features of CTD, and it has become clear that the dysregulation of TGF β signaling is profoundly involved in the pathogenesis of such disorders (12-14). In human patients and mouse models, the loss-of-function of fibrillin-1 results in the aberrant release of TGF β into the extracellular matrix, thus inducing the overactivity of TGF β signaling. Recently, mutations in *TGFB2*, *TGFB1*, *TGFB2* and *SMAD3* were also reported to be responsible for the onset of MFS-related diseases, such as Loeys-Dietz syndrome (15-19). The local dysregulation of TGF β signals may contribute to aortic dilatation/dissection as well as cardiac dysfunction, even in the absence of severe valvulopathy. Treatment with losartan, an angiotensin II blocker, inhibits TGF β signaling activation and is expected to provide clinical benefits for MFS-related disorders (3, 20-23).

Indeed, the overactivity of TGF β signaling is also observed in the osteoblasts of *Fbn2*-deficient mice (24, 25); however this phenomenon does not fully recapitulate the clinical characteristics of CCA in humans (26) and the cardiac performance of these mice has not yet been evaluated. In the present case, the patient did not have any mutations in the *FBN1* or *FBN2* genes. We withheld using losartan and determined the initiation and uptitration of carvedilol using small doses of enalapril and spironolactone, although we did not entirely follow any clear treatment strategies.

FBN2 mutations are detected in 27-43% of CCA patients with a definitive clinical diagnosis (1, 27). There are two possibilities of how the critical gene(s) mutation occurred in the present case. One is that only a single gene affecting both the patient's skeletal and cardiac features was mutated, and the other is that two distinct genes that affected her skeletal and/or cardiac features independently were mutated. Although it is currently difficult to confirm these two interpretations, the application of emerging next-generation sequencing (NGS) is expected to enhance our current understanding of connective tissue diseases complicated by cardiac dysfunction in the near future.

In conclusion, we herein reported a sporadic case of CCA complicated by severe DCM in which the patient did not have any mutations in the *FBN1* or *FBN2* genes. Although the underlying mechanism connecting these two diseases is

unknown, the current case may provide valuable insight into the development of CTD-related cardiomyopathy without valvulopathy and highlights the importance of providing cardiovascular follow-up in CCA patients, who are thought to have a relatively favorable prognosis.

The authors state that they have no Conflict of Interest (COI).

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