Surgical Repair of Left Ventricular Noncompaction in a Patient with a Novel Mutation of the Myosin Heavy Chain 7 Gene

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Left ventricular noncompaction (LVNC) represents arrest of the normal process of myocardial compaction process and results in the persistence of multiple prominent ventricular trabeculations and deep intertrabecular recesses. LVNC can be classified into 2 forms: isolated LVNC in the absence of other cardiac anomalies and non-isolated LVNC associated with congenital heart disease. The clinical presentation and the natural history of LVNC are highly variable, ranging from no symptoms to congestive heart failure, arrhythmias, and systemic thromboemboli. LVNC is genetically heterogeneous and can be inherited as an autosomal dominant or X-linked recessive disorder. It is also linked to mutations in several genes, encoding the sarcomeric proteins, such as myosin heavy chain 7 (MYH7). MYH7 encodes the β-myosin heavy chain, expressed in the cardiac muscle. The operative indication for patients with non-isolated LVNC is unclear. Here, we report the first successful case of surgical repair of a ventricular septal defect (VSD) in an infant with non-isolated LVNC associated with a novel MYH7 mutation. This mutation leads to the substitution of 7 amino acid residues (671-677) in the actin-binding region of the protein. After the VSD operation, the patient’s congestive heart failure and pulmonary hypertension improved. His condition has remained stable for 18 months with pharmacotherapy comprising diuretics, an angiotensin converting enzyme inhibitor, and a β-blocker. Although the postsurgical observational period was short, the findings indicate that LVNC mutation analyses may facilitate surgical decisions and help predict clinical courses.

Keywords: β-myosin heavy chain; cardiomyopathy; left ventricular noncompaction; MYH7; ventricular septal defect


Left ventricular noncompaction (LVNC) represents arrest of the normal process of myocardial compaction process and results in the persistence of multiple prominent ventricular trabeculations and deep intertrabecular recesses (Ichida 2009). The clinical presentation and natural history of LVNC are highly variable, ranging from no symptoms to disabling congestive heart failure, arrhythmias, and systemic thromboemboli (Ichida 2009).

LVNC is genetically heterogeneous and can be inherited as an autosomal dominant or an X-linked recessive disorder. It has been linked to mutations in several genes, including LIM domain-binding protein 3 (LDP3), dystrobrevin-α (DTNA), tafazzin/protein G4.5 (TAZ/G4.5), laminin A/C (LMNA), and genes encoding sarcomeric proteins such as myosin heavy chain 7 (MYH7), actin-α cardiac muscle 1 (ACTC1), and troponin T type 2 (TNNT2) (Ichida et al. 1999, 2001; Klaassen et al. 2008). Two forms of LVNC have been described: isolated LVNC in the absence of other cardiac anomalies, and non-isolated LVNC associated with congenital heart disease (Chin et al. 1990). Intracardiac repair of congenital heart disease in cases of non-isolated LVNC has rarely been reported (Çakmak et al. 2007; Sasaki et al. 2010).

Here, we report a case where surgical repair was used to repair a ventricular septal defect (VSD) in a young boy with non-isolated LVNC associated with a missense mutation of the MYH7 gene.

Clinical Findings

An 11-day-old boy born normally to healthy Japanese parents after an uneventful pregnancy was referred to our group for loud systolic heart murmurs. Ultrasound cardiology (USCG) performed at an outpatient clinic revealed a VSD located at the perimembranous trabecular outlet (Fig. 1), and diuretic administration (furosemide, 2 mg/kg daily) was initiated. However, the patient was admitted for con-
gestive heart failure when he was 15 days old. USCG showed a left ventricular end-diastolic diameter of 27.8 mm (140% of normal) and a left ventricular ejection fraction (LVEF) of 52%. Color Doppler echocardiography showed prominent trabeculations and blood flow into the deep intertrabecular recesses in continuity with the left ventricle. Furthermore, the ratio between the thickness of the non- compacted layer and that of the myocardial layer was 2.5:1 (normal ratio in children, < 1.4). Non-isolated LVNC was diagnosed on the basis of these findings (Fig. 2).

Soon after admission, administration of an angiotensin converting enzyme inhibitor (ACEI; enalapril, 0.1 mg/kg daily) successfully improved his clinical condition and LVEF (63%). To evaluate the indication for operative repair of the large VSD, cardiac catheterization was performed when the patient was 2 months old. Left ventricular angiography showed the VSD and a wide spongy-like layer in the left ventricle; the right ventricle pressure and pulmonary artery pressure were both confirmed to have increased (systolic/diastolic/mean pressure: 70/0/10 mmHg and 55/18/30 mmHg, respectively); the massive left-to-right shunt was also ascertained (pulmonary flow/systemic flow, 4.6; pulmonary vascular resistance, 1.3 WU*m²; L-R shunt ratio, 78%).

Based on these findings, intracardiac repair of the VSD patch closure was performed to relieve the cardiac volume...
overload and pulmonary hypertension (PH). The VSD was closed using a 0.4-mm GORE-TEX patch. Surgical repair of the VSD improved the patient’s clinical conditions and cardiac function (LVEF, 68%), and pharmacotherapy consisting of a diuretic (furosemide 1 mg/kg daily), an ACEI (enalapril, 0.1 mg/kg daily), and a β-blocker (carvedilol, 0.1 mg/kg daily) maintained his condition for 18 months after surgery.

**Gene mutation screening for LVNC**

Mutational analysis for the candidate gene for LVNC was performed before the surgery. Genomic DNA was extracted from the peripheral blood and was used for polymerase chain reaction (PCR) amplification of the main sar-
comere genes such as MYH7, myosin-binding protein C (MYBPC3), TNN2, ACTC1, and α-tropomyosin (TPM1). DNA sequence analysis revealed a heterozygous 22-nucleotide deletion, and a 22-nucleotide insertion of inverted complementary DNA strand sequence in the MYH7 exon 18 c.2010_2031 (Fig. 3A). This mutation was not detected in the 100 healthy volunteers. This finding was confirmed by cloning and subsequent sequencing of the PCR products (Fig. 3B). No mutation was found in MYBPC3, TNN2, ACTC1, or TPM1. The MYH7 mutation should result in the substitution of 7 amino acid residues (671-677) in the actin-binding region of the MYH7 protein. The amino acid sequence of the actin-binding region is conserved among the mammalian homologs (human, NP_000248.2; chimpanzee, XP_001150786.2; dog, NP_001107183.1; cow, NP_777152.1; mouse, NP_542766.1; rat, NP_058936.1) (Fig. 3C), indicating that mutations in this region could affect the function.

Discussion

Mutations in several gene encoding sarcomeric proteins, including those in MYH7, ACTC1, and TNN2, were first identified in familial hypertrophic cardiomyopathy and have also been implicated in dilated cardiomyopathy (Kamisago et al. 2000). Thus, it has become possible to provide genetic diagnosis by using DNA sequence analysis in suspected cases.

In adult patients with the MYH7 mutation, dyspnea is the most commonly observed symptom, followed by atypical chest pain and palpitations (Klaassen et al. 2008). Life-threatening arrhythmias and sudden cardiac deaths have not been reported. One study has described 2 asymptomatic patients, a 2-year-old boy and an 8-year-old boy, both of whom had been diagnosed with LVNC at an early age (Klaassen et al. 2008).

However, it remains difficult to estimate the prognosis and to identify the operative indications in infants with LVNC due to its highly variable clinical presentation. Therefore, intracardiac repair of congenital heart disease in children with non-isolated LVNC has rarely been reported (Çakmak et al. 2007; Sasaki et al. 2010). In particular, successful surgical repairs in infants with non-isolated LVNC and mutations in the causative genes have not been reported.

Because the present case of non-isolated LVNC demonstrated the progression of PH, surgical repair of the VSD was performed irrespective of the presence of an MYH7 mutation. The patient’s clinical condition and cardiac function improved drastically after surgery with pharmacotherapy consisting of diuretics, an ACE-I, and a β-blocker.

To the best of our knowledge, this is the first report of successful surgical repair of VSD in an infant with non-isolated LVNC and an associated genetic abnormality, although a few cases of surgical treatment of congenital heart diseases without the identification of associated genetic abnormalities have been reported. Sasaki et al. (2010) reported the first case of successful VSD repair in an infant with non-isolated LVNC, while Çakmak et al. (2007) described a neonate who had non-isolated LVNC and had a fatal outcome after surgical treatment for complex aortic coarctation and VSD.

In summary, this is the first successful case of surgical repair for VSD in an infant with non-isolated LVNC associated with a novel MYH7 gene mutation. Although the post-surgical observation period was short in this case and long-term follow-up is mandatory, the findings indicate that mutation analysis for patients with LVNC may help facilitate surgical decisions and predict clinical courses.

Conflict of Interest

The authors have no conflict of interest to declare.

References


