Journal of Cardiology Cases 19 (2019) 140–143

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

MYH7 mutation identified by next-generation sequencing in three infant siblings with bi-ventricular noncompaction presenting with restrictive hemodynamics

A report of three siblings with a severe phenotype and poor prognosis

Fumitake Miura (MD)[a,*], Jun Shimada (MD)[a], Yosuke Kitagawa (MD)[a], Katsuki Otani (MD)[a], Takumi Sato (MD PhD)[a], Tsutomu Toki (PhD)[a], Toru Takahashi (MD PhD)[b], Susumu Yonesaka (MD PhD)[b], Hiroki Mizukami (MD PhD)[c], Etsuro Ito (MD PhD)[a]

[a] Department of Pediatrics, Hirosaki University School of Medicine and Graduate School of Medicine, Hirosaki, Japan
[b] Hirosaki University School of Health Sciences and Graduate School of Health Sciences, Hirosaki, Japan
[c] Department of Pathology and Molecular Medicine, Hirosaki University School of Medicine and Graduate School of Medicine, Hirosaki, Japan

ARTICLE INFO

Article history:
Received 23 June 2018
Received in revised form 29 October 2018
Accepted 7 December 2018

Keywords:
Ventricular noncompaction
Next-generation sequencing
MYH7
Sarcomere
Restrictive cardiomyopathy

ABSTRACT

Noncompaction of the ventricular myocardium (NVM) is a genetically heterogeneous cardiomyopathy. Various mutations associated with NVM have been identified in several genes. NVM patients usually present with complications of dilated cardiomyopathy.

We identified a missense mutation, c.5740G>A, p.Glu1914Lys of *MYH7*, by targeted next-generation sequencing in three infant siblings with isolated bi-ventricular noncompaction who presented with restrictive hemodynamics and severe clinical courses. This mutation appears to be associated with a severe phenotype and poor prognosis. Early heart transplantation should be considered in similar cases.

<**Learning objective:** No clear noncompaction of the ventricular myocardium genotype-phenotype correlations have been found to predict the clinical course. This report describes a *MYH7* mutation in three infant siblings with isolated bi-ventricular noncompaction who presented with restrictive hemodynamics and severe clinical courses. Early heart transplantation should be considered in cases with a similar genotype and/or phenotype.>

Introduction

Noncompaction of the ventricular myocardium (NVM) is a cardiomyopathy characterized by prominent left ventricular trabeculations and deep intertrabecular recesses. NVM is genetically heterogeneous and various mutations in several genes have been identified [1]. Patients usually present with hemodynamics characteristic of dilated cardiomyopathy (DCM) [2].

We identified a missense mutation of *MYH7* by targeted next-generation sequencing (NGS) in three infant siblings with isolated bi-ventricular noncompaction who presented with restrictive hemodynamics and severe clinical courses.

Case 1

A 17-month-old boy was referred to our institution due to syncope and heart failure. He had no known family history of heart disease or sudden cardiac death. Echocardiography revealed that both cardiac ventricles had a coarsely trabeculated and spongy appearance in posterior wall, lateral wall, apical segments, and right ventricle, suggestive of bi-ventricular noncompaction (Fig. 1A). Left ventricular ejection fraction (LVEF) was estimated at 51%, with normal left ventricle end-diastolic volume (110%), bi-atrial and right ventricular enlargement, moderate tricuspid regurgitation (velocity 5.0 m/sec), moderate mitral regurgitation, and no other congenital heart disease. E-wave deceleration time at the transmitral level was short (85 msec) with a high E/A ratio (2.1) (Fig. 1B), suggesting restrictive physiology. The ratio between the thickness of the noncompacted layer and the myocardial layer was 3.4:1.

* Corresponding author at: Department of Pediatrics, Hirosaki University School of Medicine and Graduate School of Medicine, 5 Zaifucho, Hirosaki 036-8562, Japan.
E-mail address: f.miura1210@gmail.com (F. Miura).

https://doi.org/10.1016/j.jccase.2018.12.017
1878-5409/

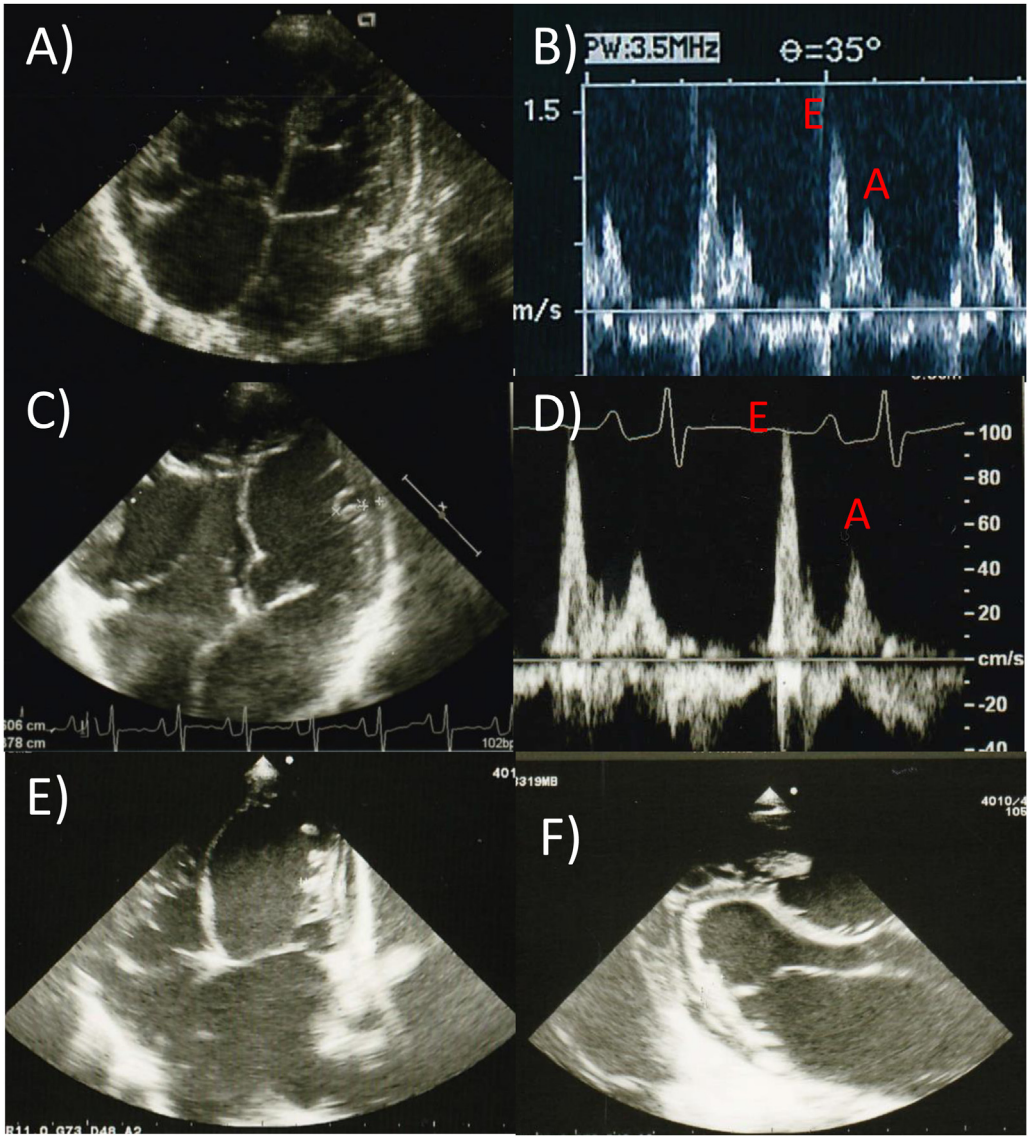

Fig. 1. (A, B) Echocardiography of Case 1 revealed that both ventricles had a coarsely trabeculated and spongy appearance, suggestive of bi-ventricular noncompaction. E-wave deceleration time at the transmitral level was short (85 msec) with a high E/A ratio (2.1), suggesting restrictive physiology. (C, D) Echocardiography of Case 2 revealed that both ventricles had a coarsely trabeculated and spongy appearance, suggestive of bi-ventricular noncompaction. E-wave deceleration time at the transmitral level was short (77 msec) with a high E/A ratio (2.2), suggesting restrictive physiology. (E, F) Echocardiography of Case 3 revealed that both ventricles had a coarsely trabeculated and spongy appearance, suggestive of bi-ventricular noncompaction.

We used the diagnosis criteria of NVM as follows: (1) The characteristic appearance of numerous, excessively prominent trabeculations and deep intertrabecular recesses on echocardiography. Two-layered appearance of the myocardium, with an increased noncompacted to compacted ratio >2.0. (2) Multiple deep intertrabecular recesses communicating with the ventricular cavity, as demonstrated by color Doppler imaging.

He was diagnosed with isolated bi-ventricular noncompaction with restrictive hemodynamics and severe pulmonary hypertension. He next underwent cardiac catheterization. Ventriculography showed a sponge-like layer in both ventricles. Left ventricular systolic pressure and end-diastolic pressure were 95 mmHg and 37 mmHg, respectively. Pulmonary artery pressures were elevated (systolic/diastolic/mean pressure: 61/21/39 mmHg). Mean pulmonary capillary wedge pressure and right atrial pressure were 35 and 10 mmHg, respectively. Pulmonary vascular resistance was 4.0 Wood Unit m^2. Although he was treated for heart failure, his clinical condition did not improve and he died of advanced heart failure at 2 years of age.

Case 2

The second sibling, a female, was born when the proband (Case 1) was 21 months old. Echocardiography in the neonatal period showed bi-ventricular trabeculations in posterior wall, lateral wall, apical segments, and right ventricle (Fig. 1C, Supplementary Video S1a, b) and a depressed LVEF of 38%. She was diagnosed with isolated bi-ventricular noncompaction and gradually developed restrictive hemodynamics. E-wave deceleration time at the transmitral level was short (77 msec) with a high E/A ratio (2.2) (Fig. 1D), the ratio of early transmitral velocity to tissue Doppler lateral and septal mitral annular early diastolic velocity (E/e') were 12.2 and 18.6, suggesting restrictive physiology, when she was 9 months old. Her parents hoped to pursue heart transplantation.

She underwent cardiac catheterization at 3 years 3 months of age. Ventriculography showed a sponge-like layer in both ventricles (Supplementary Video S2a, S2b). Left ventricular systolic pressure and end-diastolic pressure were 64 mmHg and 15 mmHg, respectively. Pulmonary artery pressures were elevated (systolic/diastolic/mean pressure: 58/27/40 mmHg). Mean pulmonary capillary wedge pressure and right atrial pressure were 20 and 9 mmHg, respectively. Pulmonary vascular resistance was 8.6 Wood Unit m^2. She received medication for heart failure as an outpatient, including diuretics, an angiotensin-converting enzyme inhibitor, a ß-adrenergic blocker, and aspirin. However, when she was 4 years old, she suddenly went into cardiac arrest. Echocardiography revealed low echoic lesions in the right atrial and right ventricle, suggesting a thrombotic cause of cardiac arrest. She was resuscitated but developed hypoxic ischemic encephalopathy, which made her ineligible for heart transplantation. When she was 7 years old, she died of advanced heart failure.

Case 3

The youngest sibling, a female, was born when Case 2 was 2 years 4 months old. Echocardiography in the neonatal period showed bi-ventricular trabeculations in posterior wall, lateral wall, apical segments, and right ventricle (Fig. 1E, F) and a depressed LVEF of 35%. She was diagnosed with isolated bi-ventricular noncompaction and gradually developed restrictive hemodynamics. Her heart failure rapidly progressed, and she died of advanced heart failure at 12 months of age. An autopsy was performed with her parents' consent. Grossly, both ventricles showed coarse trabeculations (Fig. 2A, B). Microscopic examination revealed anastomosing endocardial trabeculations with thickened endocardial fibrosis accompanied by insufficient formation of cardiac muscle wall (Fig. 2C, D).

Molecular studies

After informed consent was obtained, genetic analysis of the three siblings was performed. Due to lack of consent, genetic analysis was not performed on the parents. Targeted resequencing was performed using TruSight One sequencing panels (Illumina, San Diego, CA, USA), which included 4813 genes associated with various clinical phenotypes. Variants identified by resequencing were annotated and filtered by VariantStudio (ver 2.2.1, Illumina) (details are included in the Supplementary Text S1). The missense mutation c.5740G>A, p.Glu1914Lys (NM_000257.3) in exon 39 of *MYH7* was identified by NGS in all three siblings (Fig. 3).

Discussion

To date, various genetic causes of NVM have been identified. Mutations in sarcomere genes have been identified in isolated NVM cases [3]. The *MYH7* gene localizes to chromosome 14p12 and encodes a myosin heavy chain beta isoform expressed primarily in cardiac muscle. *MHY7* dysfunction has been shown to cause dilated, hypertrophic, and restrictive cardiomyopathies and/or NVM. In this study, we identified the missense mutation c.5740G>A, p.Glu1914Lys of *MYH7* by NGS in three infant siblings

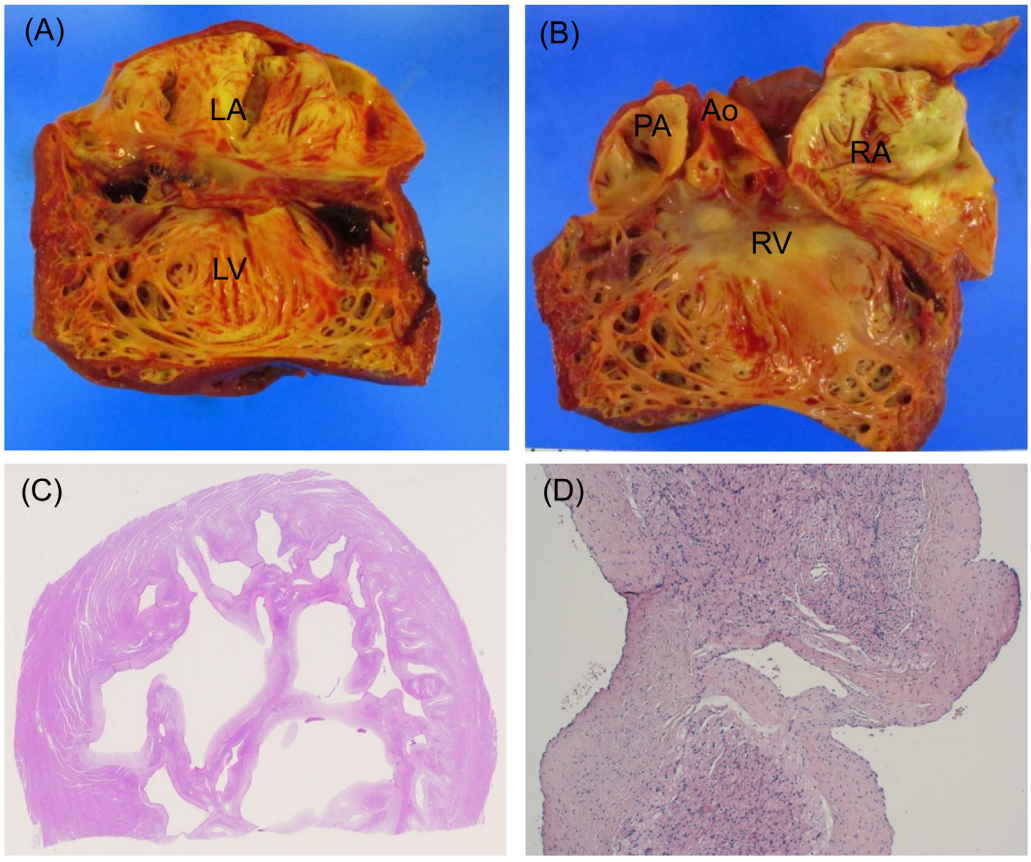

Fig. 2. (A, B) Macroscopic examination revealed bi-ventricular coarse trabeculations. (C, D) Microscopic examination in low magnification revealed anastomosing endocardial trabeculations with thickened endocardial fibrosis accompanied by insufficient formation of cardiac muscle wall.
LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; Ao, aorta; PA, pulmonary artery.

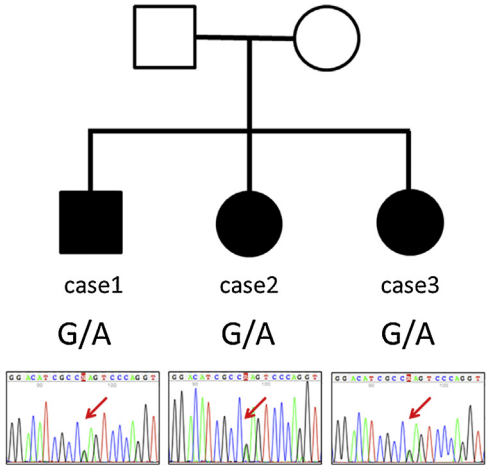

Fig. 3. Locations of the confirmed mutations on the noncompaction of the ventricular myocardium pedigree. Affected individuals are denoted by filled symbols and capillary sequence traces of the *MYH7* variants are shown.

with isolated bi-ventricular noncompaction presenting with restrictive hemodynamics and severe clinical courses.

The clinical course of NVM can vary greatly, from asymptomatic to progressive deterioration in cardiac function [1]. Previous reports noted that NVM patients usually present with decreased LVEF, similar to DCM [2]. On the other hand, NVM patients such as the three current cases, with restrictive hemodynamics, infantile onset, and cardiac dysfunction at initial presentation, have been reported to have a poor prognosis [4–7]. The current three cases all carried the same mutation. Lamont et al. reported two cases with the same *MYH7* mutation that we identified [8]. One case had hypertrophic cardiomyopathy with NVM and the other had DCM. The former case required heart transplantation at 3.5 years of age. This report, together with our experience, suggests that the *MYH7* mutation is associated with a severe phenotype and poor prognosis. Early heart transplantation should be considered in cases with a similar genotype and/or phenotype.

As with other inherited cardiomyopathies, the clinical presentation of NVM can vary, even within a single family carrying the same mutation. Xing et al. suggested that other factors (environment, modifier genes, etc.) might affect the clinical presentation [9]. In addition, only a few causative genetic mutations have been identified, compared to the relatively high number of familial cases, suggesting the presence of other, as yet unidentified, causative genes [1]. No clear NVM genotype-phenotype correlations have been found to predict the clinical course. Furthermore, in our cases, since all three siblings had the same heterozygous mutation, we suspect that the mutation occurred during the developmental stage in one of their parents' germ cell lines.

In conclusion, we identified the missense mutation c.5740G>A, p.Glu1914Lys of *MYH7* by NGS in three infant siblings with isolated bi-ventricular noncompaction who presented with restrictive hemodynamics and severe symptoms. This mutation appears to be associated with a severe phenotype and poor prognosis. Early heart transplantation should be considered in similar cases. Further genetic testing will help elucidate genotype-phenotype correlations in patients with cardiomyopathy.

Conflict of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jccase.2018.12.017.

References

[1] Ichida F. Left ventricular noncompaction. Circ J 2009;73:19–26.
[2] Ritter M, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. Mayo Clin Proc 1997;72:26–31.
[3] Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation 2008;117:2893–901.
[4] Ichida F, Hamamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 1999;34:233–40.
[5] Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. Circulation 2013;127:2202–8.
[6] Zuckerman WA, Richmond ME, Singh RK, Carroll SJ, Starc TJ, Addonizio LJ. Left-ventricular noncompaction in a pediatric population: predictors of survival. Pediatr Cardiol 2011;32:406–12.
[7] Tsai SF, Ebenroth ES, Hurwitz RA, Cordes TM, Schamberger MS, Batra AS. Is left ventricular noncompaction in children truly an isolated lesion? Pediatr Cardiol 2009;30:597–602.
[8] Lamont PJ, Wallefeld W, Hilton-Jones D, Udd B, Argov Z, Barboi AC, et al. Novel mutations widen the phenotypic spectrum of slow skeletal/β-cardiac myosin (*MYH7*) distal myopathy. Hum Mutat 2014;35:868–79.
[9] Xing Y, Ichida F, Matsuoka T, Isobe T, Ikemoto Y, Higaki T, et al. Genetic analysis in patients with left ventricular noncompaction and evidence for genetic heterogeneity. Mol Genet Metab 2006;88:71–7.