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Case Report

Successful Bailout of Noonan Syndrome with Obstructive Hypertrophic Cardiomyopathy During Percutaneous Intramyocardial Septal Radiofrequency Ablation

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Abstract

Background: Cardiac disorders such as hypertrophic cardiomyopathy (HCM) are common in patients with Noonan syndrome (NS). Some patients can develop heart failure associated with HCM, and the long-term outcome of patients with NS with HCM is reported to be worse.

Case presentation: We report three patients diagnosed with NS. We initially thought that three patients were diagnosed with only HCM. Three patients' facial features were concealed, making it difficult for us to make a differential diagnosis of NS. Finally, genetic testing identified three patients as NS with HCM. Owing to these patients' conditions, medical treatment was not effective. Patients were treated with percutaneous intramyocardial septal radiofrequency ablation (PIMSRA). Three patients recovered well, and there was no complication.

Conclusions: We describe 3 patients with NS and HCM treated with PIMSRA. PIMSRA is a new therapeutic tool for treating NS with HOCM that can decrease the left ventricular wall thickness, reduce wall stress, and improve cardiac function. Early identification of congenital heart abnormalities and genetic testing are important in diagnosing NS with HCM.

Keywords: noonan syndrome; hypertrophic cardiomyopathy; pimsra

Introduction

Noonan syndrome (NS) is a common genetic disorder characterized by multiple congenital abnormalities, among which the most common cardiac abnormalities notably include pulmonary stenosis and hypertrophic cardiomyopathy (HCM) [1]. The long-term prognosis of patients with NS depends on the severity of cardiac complications. Some patients can develop heart failure associated with HCM, and the long-term outcome of patients with NS with HCM, especially obstructive hypertrophic cardiomyopathy (HOCM), is reported to be worse than that of patients without HCM [2]. Over 80% of patients with NS have cardiac involvement and require complex cardiac operations [3]. Here, we report three cases where NS patients with HOCM were treated with percutaneous intramyocardial septal radiofrequency ablation (PIMSRA).

Methods

Transthoracic echocardiography (TTE)-guided PIMSRA was performed as described previously [4]. Under TTE guidance, a radiofrequency electrode needle was inserted into the hypertrophied interventricular septum (IVS) via the percutaneous intramyocardial approach, with its tip at the region of the IVS basal segment 8 to 10 mm from the subaortic valve. The ablation power started at 60 W, the mean duration was 5 min, and a hyperechoic region was visible on the echocardiogram. If the vital signs were stable and the ablation range was not large enough, as assessed by TTE, we gradually increased the ablation power to 100 W. Each application lasted up to 12 min. The ablation needle was then withdrawn to 10 mm to prepare for the next application. After ablation, we performed a final hemodynamic assessment. The patients were then transferred to the cardiac intensive care unit and were monitored continuously for at least 24 hours.

Case presentation

Patient 1

Patient 1 (Pedigree 1 III3, Figure 1A) was a 15-year-old male. At 2 years of age, Patient 1 underwent cardiac surgery for the Fallot trilogy in 2007, and her echocardiography was reviewed regularly thereafter. In 2017, an ultrasonic cardiogram (UCG) revealed significant thickening of the ventricular septum, up to 15-16 mm, with no obvious symptoms. Since 2020, Patient 1 has presented with fatigue and asthenia. We identified a missense mutation in patient 1: c.755T>A/p. S259T in exon 7 of RAF1 (Figure 1B, C). According to the genetic variant guidelines of the American College of Medical Genetics and Genomics (ACMG), the variant (RAF1 c.755T>A/p. S259T) was predicted to be pathogenic (PS4+PM1+PM2+PM5+PP3). The patient did not undergo magnetic resonance imaging (MRI) after the Fallot trilogy. UCG revealed that the left ventricular wall thickness (LVWT), left ventricular intraventricular gradient, left ventricular ejection fraction (LVEF), stroke volume index (SVI), left atrial volume index (LAVI) and E/e' were 39 mm, 38 mmHg, 65%, 26.6 mL/m2, 23.9 mL/m2 and 32, respectively (Figure 3A). NT-proBNP was 5323 pg/nl. The HCM risk-sudden cardiac death (SCD) score was 2.66%. Patient 1 underwent PIMSRA in 2021. Three months after the PIMSRA procedure, UCG confirmed that Patient 1 had a reduction in the LVWT (26 mm), left ventricular intraventricular gradient (10 mmHg) and E/e' (25.0), with an increase in the SVI (36.1 mL/m2), LVEF (67%) and LAVI (27.1 mL/m2) (Figure 3B).

Patient 2

Patient 2 (Pedigree 2 III1, Figure 1A) was an 18-year-old female. At 15 years of age, Patient 2 had a heart murmur during a physical examination in 2019. Patient 2 presented with chest discomfort and stress-induced dyspnoea in 2021. We initially found that patient 2 had myocardial hypertrophy and was diagnosed with HCM. Genetic testing identified a missense mutation in patient 2: c.768G>T/p. R256S in exon 7 of RAF1 (Figure 1B, C). Patient 2 was ultimately diagnosed with NS with HOCM. According to the genetic variant guidelines of the ACMG, the variant (RAF1 c.768G>T/p. R256S) was predicted to be pathogenic (PS4+PM1+PM2+PM5+PP3). MRI revealed LVH and myocardial fibrosis (Figure 2). UCG revealed that the LVWT, left ventricular outflow tract (LVOT) gradient, LVEF, SVI, LAVI and E/e' were 29 mm, 92 mmHg, 57%, 16.9 mL/m2, 32.4 mL/m2 and 23.8, respectively (Figure 3A). NT-proBNP was 11874 pg/nl. The HCM risk-sudden cardiac death (SCD) score was 4.58%. Patient 2 underwent PIMSRA in 2022. Twelve months after the PIMSRA procedure, the patient's clinical status significantly improved (NYHA class II). UCG confirmed that Patient 2 had a reduction in the LVWT (16 mm), LVOT gradient (10 mmHg), LAVI (26.2 mL/m2) and E/e' (13.0) with an increase in the SVI (27.0 mL/m2) and LVEF (60%) (Figure 3B). Postoperatively, her NT-proBNP level was reduced to 4619 pg/nl.

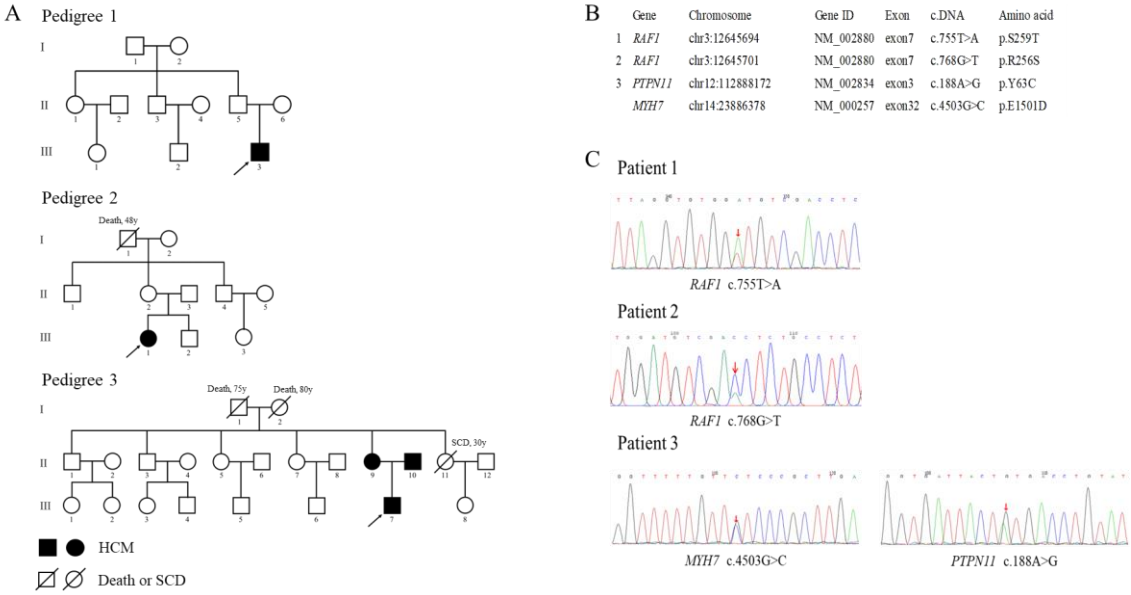

Figure 1: Pedigrees and gene mutations detected in patients. A: the pedigree chart of the family in three patients; B: the gene mutations detected in three patients; C: the mutated site of the gene in three patients

Patient 3

Patient 3 (Pedigree 3 III7, Figure 1A) was a 27-year-old male. At 16 years of age, Patient 3 had a heart murmur during a physical examination in 2009, and Patient 3 was subsequently examined by UCG and diagnosed with HCM. Patient 3 presented with presyncope, chest tightness and exercise-induced shortness of breath in 2020. We identified two missense mutations in patient 3: c.4503G>C/p. E1501D in exon 32 of MYH7 and c.188A>G/p. Y63C in exon 3 of PTPN11 (Figure 1B, C). According to the genetic variant guidelines of the ACMG, the variant (MYH7 c.4503G>C/p. E1501D) was predicted to be pathogenic (PS4+PM1+PM2+PM5+PP3), and the variant (PTPN11 c.188A>G/p. Y63C) was predicted to be pathogenic (PS3+PS4+PM1+PP1+PP2+PP3). MRI revealed LVH and myocardial fibrosis (Figure 2). UCG revealed that the LVWT, LVOT gradient, LVEF, SVI, LAVI and E/e' were 22 mm, 111 mmHg, 58%, 24.8 mL/m2, 42.9 mL/m2 and 12, respectively (Figure 3A). Patient 3 had nonsustained ventricular tachycardia. NT-proBNP was 1492 pg/nl. The HCM risk-sudden cardiac death (SCD) score was 9.33%. Patient 3 underwent PIMSRA in 2022. Twelve months after the PIMSRA procedure, the patient's clinical status significantly improved (NYHA class I). UCG confirmed that Patient 3 had a reduction in the LVWT (17 mm), LVOT gradient (28 mmHg), LAVI (30.3 mL/m2) and E/e' (9.8), with an increase in the SVI (28.5 mL/m2) and LVEF (61%) (Figure 3B). Postoperatively, her NT-proBNP concentration was reduced to 137 pg/nl.

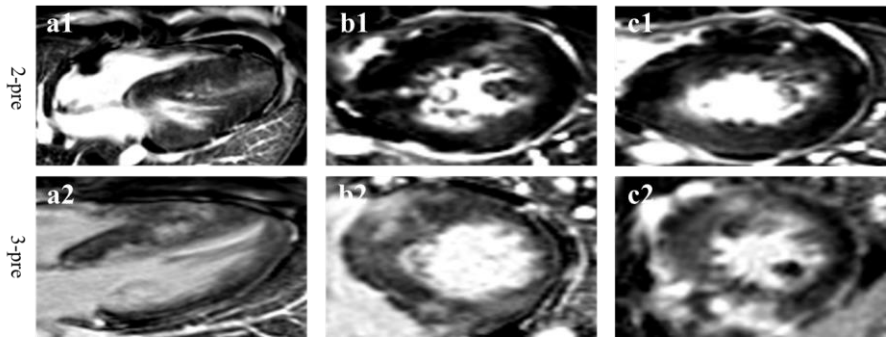

Figure 2: Examples of cardiac cine-MR images among patients

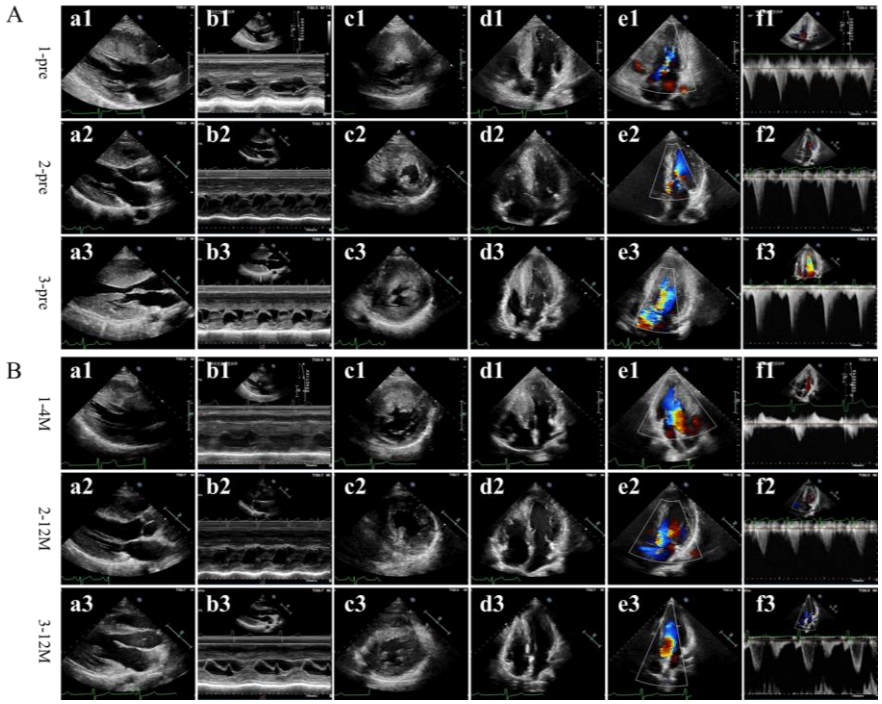

Figure 3: Examples of echocardiographic images among patients. A: preoperative echocardiographic images; B: echocardiographic images during the follow-up period

Discussion

Moreover, NS may be considered when myocardial hypertrophy is associated with other congenital heart abnormalities, such as atrial and ventricular septal defects [5]. Facial features are also classic manifestations of NS, but the facial features of three patients were concealed, making it difficult for us to make a differential diagnosis of NS. Thus, genetic testing of patients with HCM is necessary to distinguish NS.

However, there may be no good treatment for NS complicated with myocardial hypertrophy. Recent studies have shown promise for the use of repurposed antineoplastic drugs, such as rapamycin, an AKT inhibitor, a MEK inhibitor, and recombinant human growth hormone, which target the RAS/MAPK signalling pathway for the treatment of NS-associated HCM [6,7]. In addition, surgical treatments, such as septal myectomy, the modified Konno procedure, mitral valve replacement and transmitral myectomy, could be effective [8]. However, early-stage children with NS who undergo surgery could be at increased risk of early mortality. Therefore, more attention should be given to patients with NS and HCM when they are undergoing surgical treatment.

Conclusions

We assessed changes in patients' clinical features before and after PIMSRA. We confirmed that PIMSRA can decrease left ventricular wall thickness, reduce wall stress, and improve cardiac function. These findings underscore the importance of the early identification of congenital heart abnormalities and genetic testing in diagnosing NS with HCM and demonstrate that PIMSRA is a new therapeutic entity for treating NS in patients with HOCM that is safe, effective, minimally invasive, and easy to use without leaving any scar.

Availability of data and materials

All the data are available in the manuscript.

Authors' contributions

JZ was involved in the clinical management of the case and in manuscript redaction and correction. BW and LL assisted in manuscript redaction and correction. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

Statement of Ethics Study protocol was approved by the Ethics Committee of Xijing Hospital and conformed to the principles of the Declaration of Helsinki, approval number: KY20150120-1. Written consent was obtained from all patients. Written informed consent was obtained for participation in this study.

Consent for publication

Written informed consent was obtained from the patient or patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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