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Case Report

Improvement of pulmonary arterial hypertension following medication and shunt closure in a *BMPR2* mutation carrier with atrial septal defect

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ABSTRACT

Mutation of the *BMPR2* gene is the most common genetic cause of pulmonary arterial hypertension (PAH). Although there have been some reports of *BMPR2* mutation carriers among PAH patients with congenital heart disease, there have been few reports of their treatment. Here, we describe a 13-year-old female *BMPR2* mutation carrier who presented with heritable PAH and atrial septal defect (ASD). She complained of fatigue, and cardiac catheterization showed a mean pulmonary artery pressure (PAP) of 56 mmHg, a pulmonary vascular resistance (PVR) of 8 Wood units and a pulmonary to systemic blood flow ratio (Qp/Qs) of 1.3. Following 2 years of medication therapy, the mean PAP had decreased to 30 mmHg, the Qp/Qs had increased to 2.7, and her symptoms persisted. We closed the ASD interventionally, and her symptoms improved after closure. Medication therapy was continued. Four years after closure, the PAH had improved with a mean PAP of 20 mmHg and a PVR of 3.1 Wood units. To the best of our knowledge, this is the first report of PAH improvement following medication and ASD closure in a *BMPR2* mutation carrier with heritable PAH. ASD closure following medication appears to be effective in some ASD patients with heritable PAH.

<**Learning objective:** Mutation of the *BMPR2* gene is the most common genetic cause of pulmonary arterial hypertension (PAH). Heritable PAH with *BMPR2* mutations has been reported to have a poorer prognosis once PAH has developed. Recent reports have described treatment of atrial septal defect (ASD) patients with PAH by surgical or interventional ASD closure following medication therapy. This case suggests that medication followed by ASD closure could also be effective for *BMPR2* mutation carriers with ASD and heritable PAH.>

Introduction

Mutation of the *BMPR2* gene is the most common genetic cause of pulmonary arterial hypertension (PAH) and has been detected in approximately 75% of familial PAH and up to 25% of apparently sporadic cases. Moreover, a study of 40 adults and 66 children showed that *BMPR2* mutations were present in 6% of PAH patients with congenital heart disease [1]. However, the prognosis of PAH patients carrying *BMPR2* mutations has not yet been fully elucidated. There have been few reports of treatment of *BMPR2* mutation carriers with PAH accompanied by congenital heart disease. Recent advances in medical therapy have remarkably improved the prognosis of patients with PAH and congenital heart disease, including atrial septal defects (ASD). Several reports have described treatment of PAH patients with ASD by surgical or interventional ASD closure following medication [2–5]. Here, we report ASD closure following medication therapy in a *BMPR2* mutation carrier with heritable PAH and ASD.

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Table 1 Plasma BNP levels and hemodynamic parameters obtained from cardiac catheterization.

	At diagnosis	Time after initiation of medication				Time after ASD closure	
		7 months	1 year	2 years		1 year	4 years, 9 months
				Before occlusion	After occlusion		
PAP, mmHg	78/42	59/29	53/19	42/19	36/16	36/10	29/12
Mean PAP, mmHg	56	42	39	30	25	24	20
PVR, Wood units	8	4.6	3.8	3.7		4.1	3.1
PVR/SVR	0.47	0.31	0.16	0.14		0.27	0.19
Qp/Qs	1.3	1.8	2.3	2.7			
BNP, pg/ml	38.7	21.7	17.7			18.9	15.2

ASD, atrial septal defect; BNP, brain natriuretic peptide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PVR/SVR, pulmonary/systemic vascular resistance ratio; Qp/Qs, pulmonary/systemic blood flow ratio.

Case report

A 13-year-old girl was referred to our hospital for further examination of PAH with ASD. A heart murmur was detected during a school health examination. She had a several-month history of fatigue [New York Heart Association (NYHA) class II]. Two of her maternal relatives died in youth due to PAH. A chest X-ray showed the pulmonary knob and a cardiothoracic ratio of 48%. Electrocardiography showed no right ventricular hypertrophy. Transthoracic echocardiography revealed an 11-mm secundum ASD with a left-to-right shunt, and the right ventricular systolic pressure estimated from the tricuspid regurgitation jet velocity was 99 mmHg plus right atrial pressure. The right ventricle and right atrium were enlarged. Cardiac catheterization confirmed PAH with a mean pulmonary artery pressure (PAP) of 56 mmHg, a pulmonary vascular resistance (PVR) of 8 Wood units, and a calculated pulmonary to systemic flow ratio (Qp/Qs) of 1.3 on room air (Table 1). With intravenous infusion of adenosine (200 μg/kg/min), PVR decreased to 5.6 Wood units and pulmonary/systemic vascular resistance ratio increased to 0.72, with a mean PAP 55 mmHg and a Qp/Qs 1.3. The plasma brain natriuretic peptide (BNP) level was 38.7 pg/ml. Genetic analyses of the patient were performed after obtaining written informed consent in accordance with the study protocol approved by the Medical Ethical Committee of Niigata University Graduate School of Medical and Dental Sciences. We found deletion and insertion mutations in exon 5 of the patient's *BMPR2* gene (c.535_547delCGTAAACAAGGT-CinsATG) (Fig. 1). Patients with left-to-right shunt due to isolated medium-sized ASD, such as this patient, rarely develop severe PAH in their early teenage years, implicating *BMPR2* mutation in the accelerated onset. Thus, the patient was diagnosed with heritable PAH and ASD. The patient was started on oral beraprost, bosentan, warfarin, and home oxygen therapy, but her symptoms did not improve. The maximum doses of beraprost and bosentan were 3.2 μg/kg/day and 2.5 mg/kg/day, respectively. Eight months later, the PAH had improved and Qp/Qs had increased. Oral sildenafil at a maximum dose of 1.6 mg/kg/day was added in expectation of further improvement of her hemodynamic state, but her symptoms persisted. Two years after the first cardiac catheterization, the mean PAP and PVR had decreased to 30 mm Hg and 3.7 Wood units, respectively, and the Qp/Qs had increased to 2.7. Balloon occlusion of the ASD further decreased the PAP. We speculated that even though the PAH had improved, the patient's symptoms persisted due to high pulmonary flow. Accordingly, we elected to close the ASD with a 16 mm Amplazter septal occluder, and the patient's symptoms improved soon after closure (NYHA class I). The medications were continued. Four years and nine months after ASD closure, the PAH had improved, with a mean PAP of 20 mmHg and a PVR of 3.1 Wood units. The plasma BNP level had decreased to 15.2 pg/ml.

Discussion

To the best of our knowledge, this is the first report of improved PAH following medication and ASD closure in a *BMPR2* mutation carrier with heritable PAH and ASD.

We speculate that the combination of the *BMPR2* mutation and ASD might have resulted in our patient's severe PAH. The patient carried a frameshift mutation in the *BMPR2* gene, which encodes the type II receptor for bone morphogenetic protein (BMP), a member of the transforming growth factor-β family. BMP signaling regulates cell proliferation, differentiation, and apoptosis in the pulmonary vasculature. Thus, mutations in *BMPR2* may attenuate BMP signaling and lead to PAH. To date, more than 400 mutations in the *BMPR2* gene have been reported in patients with PAH, of which approximately 70% are nonsense or frameshift mutations [6]. Although phenotype–genotype relationships have not yet been elucidated for *BMPR2*, the frameshift mutation detected in this patient is thought to cause nonsense-mediated decay resulting in functional haploinsufficiency. The fact that only 10–27% of individuals with *BMPR2* mutations develop PAH suggests that *BMPR2* mutation is necessary but insufficient to cause PAH. We assume that in our patient, the increased pulmonary flow due to the left-to-right shunt of ASD represents an additional insult.

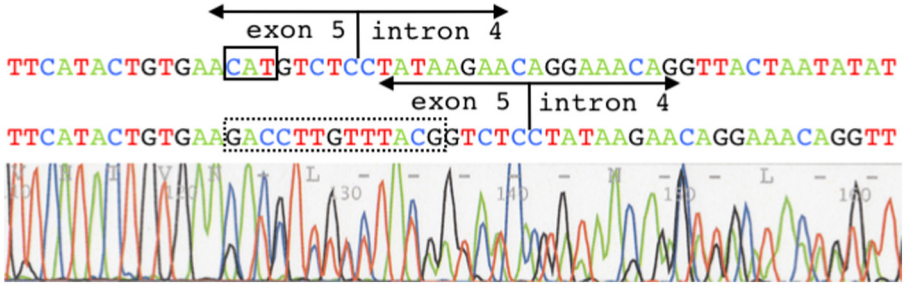

Fig. 1. Polymerase chain reaction sequence electrophoretogram of the intron 4/exon 5 junction of the *BMPR2* gene in our patient. The 13-nucleotide deletion and the 3-nucleotide insertion in exon 5 are outlined with dashed and solid black lines, respectively. The vertical black line indicates the intron/exon junction.

Approximately 5–10% of adults with untreated ASD present with severe PAH at a median age of 51 years [7]. However, it is extremely rare for patients with isolated medium-sized ASD, such as this patient, to develop severe PAH in their early teenage years.

After ASD closure, the patient's condition did not meet the criteria of PAH and her symptoms improved. Subjects with *BMPR2* mutations have been reported to have a poorer prognosis once PAH has developed. A French study of adults with PAH found that patients who carried *BMPR2* mutations were diagnosed and died at an earlier age than patients without mutations [8]. In a Japanese study of childhood PAH, the 5-year survival rate was lower for patients with *BMPR2* mutations than for those with an unmutated gene [9]. However, the number of patients with *BMPR2* mutations was relatively low in these studies. To date, dozens of patients with PAH and ASD have been treated by ASD closure following medication. In each of those cases, the medications were started in adulthood and the disease status was more severe than in our patient. Although their symptoms and hemodynamics improved after ASD closure, residual mild or moderate PAH was still detected in those patients [2–5]. An echocardiographic study of adult patients after percutaneous ASD closure showed that PAH persists in some ASD patients, even when the PAH was not severe [10]. We speculate that the better clinical course in our patient compared with previous cases resulted from a combination of early initiation of medication and correction of the additional insult, ASD. Thus, earlier treatment appears to be more effective, even in heritable PAH patients carrying *BMPR2* mutations.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Roberts KE, McElroy JJ, Wong WP, Yen E, Widlitz A, Barst RJ, et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J 2004;24:371–4.
[2] Tahara N, Mizoguchi M, Honda A, Tahara A, Nitta Y, Kodama N, et al. Successful shunt closure and improvement of hemodynamics in an ASD patient with severe pulmonary arterial hypertension and small shunt following a long-term use of bosentan. Int J Cardiol 2012;158:E38–40.
[3] Bradley EA, Chakinala M, Billadello JJ. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. Am J Cardiol 2013;112:1471–6.
[4] Schwerzmann M, Zafar M, McLaughlin PR, Chamberlain DW, Webb G, Granton J. Atrial septal defect closure in a patient with "irreversible" pulmonary hypertensive arteriopathy. Int J Cardiol 2006;110:104–7.
[5] Hoetzenecker K, Ankersmit HJ, Bonderman D, Hoetzenecker W, Seitelberger R, Klepetko W, et al. Atrial septal defect repair after a 10-month treatment with bosentan in a patient with severe pulmonary arterial hypertension: a case report. J Thorac Cardiovasc Surg 2009;137:Error: FPage (760) is higher than LPage (–761)!.
[6] Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. Circ Res 2014;115:115–30.
[7] Engelfriet P, Meijboom F, Boersma E, Tijssen J, Mulder B. Repaired and open arterial septal defects type II in adulthood: an epidemiological study of a large European cohort. Int J Cardiol 2008;126:379–85.
[8] Sztrymf B, Coulet F, Gired B, Yaici A, Jais X, Sitbon O. Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. Am J Respir Crit Care Med 2008;177:1377–83.
[9] Chida A, Shintani M, Yagi H, Fujiwara M, Kojima Y, Sato H, et al. Outcomes of childhood pulmonary arterial hypertension in BMPR2 and ALK1 mutation carriers. Am J Cardiol 2012;110:586–93.
[10] Balint OH, Samman A, Haberer K, Tobe L, McLaughlin P, Siu SC, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous arterial septal defect closure. Heart 2008;94:Error: FPage (1189) is higher than LPage (–1193)!.