Cardiology in the Young

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Efficacy of cibenzoline for hypertrophic obstructive cardiomyopathy in paediatric patients with RAS/MAPK pathway syndromes

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Brief Report

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Abstract

RASopathies – caused by mutations in the RAS/MAPK signaling pathway – are frequently associated with cardiac diseases, such as hypertrophic obstructive cardiomyopathy. Although cibenzoline is useful for adult hypertrophic obstructive cardiomyopathy patients, little is known about its effect in children. Here, we report two paediatric cases of hypertrophic obstructive cardiomyopathy associated with RASopathies where the condition was improved by cibenzoline.

RASopathies comprise syndromes with overlapping phenotypes caused by germline mutations in the components of the RAS/MAPK signalling pathway, which regulate cell proliferation. Representative syndromes of RASopathies include Noonan syndrome and Noonan syndrome with multiple lentigines, which are known to be associated with cardiac diseases including hypertrophic obstructive cardiomyopathy.[1] Recently, the anti-arrhythmic drug cibenzoline was found effective in adult patients with hypertrophic obstructive cardiomyopathy. Herein, we report two paediatric cases of hypertrophic obstructive cardiomyopathy with RASopathies that have been well controlled with cibenzoline.

Case reports

Case 1

A 2-year-old Japanese boy was admitted to Hokkaido University Hospital for cardiac catheterisation to evaluate hypertrophic obstructive cardiomyopathy. He was born at 39 weeks of gestation without asphyxia. He was not a child of a consanguineous marriage, but his grandmother had a medical history of hypertrophic cardiomyopathy. Soon after birth, a systolic heart murmur was found, and echocardiography showed hypertrophic cardiomyopathy with asymmetrical septal hypertrophy. At 1 year of age, propranolol (daily administration of 1 mg/kg/day) was started because of progressive left ventricular outflow tract stenosis with an estimated pressure gradient of 68 mmHg by echocardiography. Although propranolol dose was subsequently increased up to 2 mg/kg/day, left ventricular outflow tract stenosis did not improve. On admission, his physical examination was unremarkable except for auscultation of Levine 3/VI systolic murmur at the left lower sternum. Echocardiography at admission showed systolic anterior movement of the mitral valve, and the estimated pressure gradient in the left ventricular outflow tract was 87 mmHg. Simultaneously, multiple lentigines were observed, which led to the suspicion of Noonan syndrome with multiple lentigines. Genetic testing found mutated *PTPN11*: p.Y279C, commonly identified pathogenic variant of Noonan syndrome with multiple lentigines leading to loss of function of SHP2, involved in the RAS/MAPK signaling pathway, and the diagnosis of Noonan syndrome with multiple lentigines was confirmed.

Cardiac catheterisation demonstrated that the left ventricular and aortic systolic pressures were 170 mmHg and 84 mmHg, respectively. Cibenzoline (1.4 mg/kg) was injected intravenously while simultaneously measuring left ventricular and aortic pressures, and 5 min later, the pressures decreased to 94 mmHg and 71 mmHg, respectively (Fig 1).

Based on the results, cibenzoline was administered orally after fully explaining to the parents that its use was off-label for obstructive hypertrophic cardiomyopathy in children while monitoring the drug concentration. The estimated pressure gradient of the left ventricular outflow tract was only 12 mmHg after 8 years of cibenzoline administration (Fig 2a).

Case 2

A 6-year-old Japanese boy was followed up because of hypertrophic obstructive cardiomyopathy detected by echocardiography at birth. Minor malformations, such as shortened limbs and short

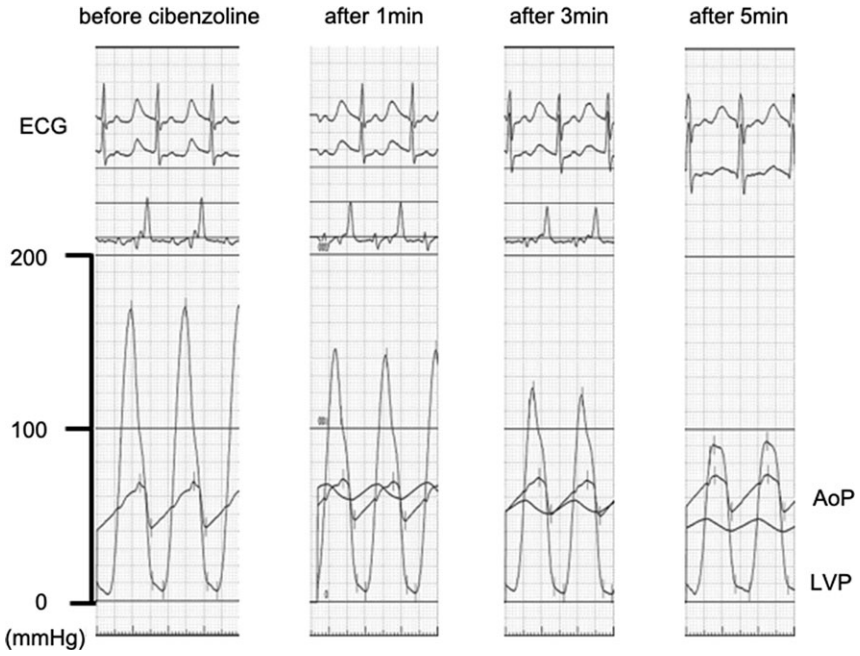

Figure 1. The results of cardiac catheterization in case 1. Effect of cibenzoline administration on the LVP gradient. The maximum LVP gradient attenuated from 86 mmHg to 23 mmHg following intravenous injection of cibenzoline. No QT prolongation was observed in the ECG. ECG, electrocardiogram; AoP, aortic pressure; LVP, left ventricular pressure.

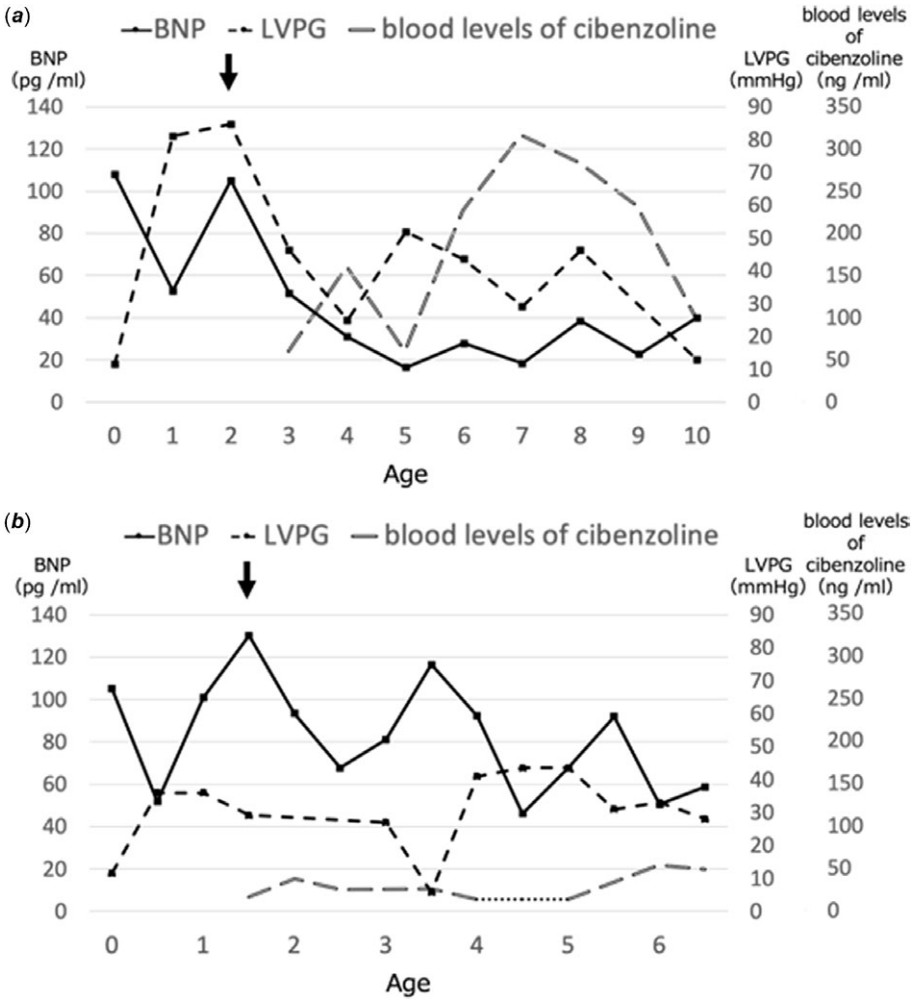

Figure 2. The clinical course of case 1 (a) and 2 (b). The arrow indicates the point of cibenzoline initiation. The dotted portion of the line indicating the blood levels of cibenzoline was below the sensitivity of the measurement. LVPG, left ventricular pressure gradient; BNP, brain natriuretic peptide.

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stature (−3.5 standard deviation), were also observed. Along with the neonatal onset of hypertrophic cardiomyopathy, a RASopathy-related disease was also suspected.

At 5 months of age, he was administered propranolol because of progressive left ventricular outflow tract stenosis with an estimated pressure gradient of 33.6 mmHg measured using echocardiography. At 19 months of age, oral cibenzoline (1.0 mg/kg/day) was included in the prophylaxis to prevent further left ventricular outflow tract stenosis progression after fully explaining to the parents that its use was off-label for obstructive hypertrophic cardiomyopathy in children.

He is now 6 years old and is being treated with cibenzoline (3.1 mg/kg/day) and propranolol (1.9 mg/kg/day); no progressive left ventricular outflow tract stenosis has been observed to date (Fig 2b). His genetic analysis at 6 months of age revealed a *RAF1* mutation :p.S257L, commonly identified pathogenic variant of Noonan syndrome leading to paradoxical activation of ERK signalling involved in the RAS/MAPK signalling pathway, confirming the diagnosis of Noonan syndrome. For his short stature, the indication of growth hormone therapy was once considered. However, we have been withholding this therapy owing to possible worsening of left ventricular outflow tract stenosis.

Discussion

The efficacy of disopyramide, a class Ia anti-arrhythmic drug, has been previously reported in adult patients with hypertrophic obstructive cardiomyopathy,[2] and that of cibenzoline, belonging to the same class, was compared with that of a lesser anticholinergic agent, in adult patients.[3]

Cibenzoline alleviates left ventricular outflow tract stenosis through a negative inotropic action.[4] A decrease in intracellular Na^+ concentration and inhibition of depolarisation in cardiomyocytes activate the myocardial Na^+/Ca^{2+} exchanger, resulting in an increase in Na^+ concentration and a decrease in Ca^{2+} concentration. The relief of the left ventricular outflow tract stenosis in the acute phase is possibly related to the decrease in Ca^{2+} concentration. Elevated Ca^{2+} concentration in cardiomyocytes in hypertrophic obstructive cardiomyopathic patients is closely associated with left ventricular dysfunction and left ventricular myocardial hypertrophy.[4,5,6] The myocardial Na^+/Ca^{2+} exchanger is vital in maintaining Ca^{2+} homeostasis and preventing Ca^{2+} overload. These effects of cibenzoline may be useful in the relief of left ventricular outflow tract stenosis.[3]

Although reports on cibenzoline therapy in children with hypertrophic obstructive cardiomyopathy are limited, continuous improvement can be expected with long-term administration in adult patients.[3] Long-term observation is required to understand the relief of left ventricular outflow tract stenosis following oral cibenzoline administration; however, the present case report presents evidence in paediatric cases.

Cibenzoline is known to cause adverse event like arrhythmia, hypoglycaemia, and hepatic dysfunction, but none of these adverse event were observed in the two cases.

Growth hormone therapy is widely used for the short stature associated with RASopathies.[7] However, growth hormones stimulate the RAS/MAPK cascade, and this therapy can induce the progression of myocardial hypertrophy.[8] While growth hormone therapy does not appear to have any adverse effects on the heart,[9] there have been some reports where hypertrophic obstructive cardiomyopathy worsened after the initiation of growth hormone therapy.[10] Such reports should be considered when considering growth hormone therapy for to patients with hypertrophic obstructive cardiomyopathy. Although case 2 has not received growth hormone therapy yet, if the left ventricular outflow tract stenosis is well controlled by cibenzoline, he may exhibit adaptation to growth hormone therapy in the future.

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Conflicts of interest. None.

Ethical standards. The authors declare that all procedures used in this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the respective institutional committees.

References

1. Wolf CM, Zenker M, Burkitt-Wright E, et al. Management of cardiac aspects in children with Noonan syndrome - results from a European clinical practice survey among paediatric cardiologists. Eur J Med Genet 2021; 65: 104372.
2. Sherrid M, Delia E, Dwyer E. Oral disopyramide therapy for obstructive hypertrophic cardiomyopathy. Am J Cardiol 1988; 62: 1085–1088.
3. Hamada M, Shigematsu Y, Ikeda S, Nakamura M, Ohshima K, Ogimoto A. Impact of cibenzoline treatment on left ventricular remodeling and prognosis in hypertrophic obstructive cardiomyopathy. ESC Heart Fail 2021; 8: 4832–4842.
4. Hamada M, Shigematsu Y, Ikeda S, et al. Class Ia antiarrhythmic drug cibenzoline: a new approach to the medical treatment of hypertrophic obstructive cardiomyopathy. Circulation 1997; 96: 1520–1524.
5. Gwathmey JK, Warren SE, Briggs GM, et al. Diastolic dysfunction in hypertrophic cardiomyopathy. Effect on active force generation during systole. J Clin Invest 1991; 87: 1023–1031.
6. Palmiter KA, Solaro RJ. Molecular mechanisms regulating the myofilament response to Ca2+: implications of mutation causal for familial hypertrophic cardiomyopathy. Basic Res Cardiol 1997; 92: 63–74.
7. Noordam C. Growth hormone and the heart in Noonan syndrome. Horm Res 2009; 72 Suppl, 2: 49–51.
8. Seo GH, Yoo HW. Growth hormone therapy in patients with Noonan syndrome. Ann Pediatr Endocrinol Metab 2018; 23: 176–181.
9. Noonan JA, Kappelgaard AM. The efficacy and safety of growth hormone therapy in children with noonan syndrome: a review of the evidence. Horm Res Paediatr 2015; 83: 157–166.
10. Jo KJ, Kim YM, Yoon JY, et al. Comparison of effectiveness of growth hormone therapy according to disease-causing genes in children with Noonan syndrome. Korean J Pediatr 2019; 62: 274–280.

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