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Male infant with Noonan syndrome with *RAF-1* gene mutation who survived hypertrophic cardiomyopathy-induced fatal heart failure and uncontrollable arrhythmias

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SUMMARY

Noonan syndrome (NS) is a congenital disease with characteristic facial features as well as heart disease, short stature and thoracic abnormalities. More than eighty per cent of patients with NS show several cardiac disorders including pulmonary valvular stenosis, hypertrophic cardiomyopathy (HCM) and/or atrial septal defects. HCM is a serious cardiac comorbidity in patients with NS, especially in those who are diagnosed within 6 months of age with congestive heart failure. Arrhythmia with or without HCM in NS is a rare comorbidity with a complicated clinical course and poor prognosis.

In this manuscript, we present the case of a male infant with NS with *RAF1* gene mutation, who showed various types of arrhythmias. He developed life-threatening heart failure and uncontrollable arrhythmias. We attempted several antiarrhythmic agents and finally controlled the arrhythmias to establish a normal sinus rhythm with a combination of amiodarone and flecainide.

BACKGROUND

Noonan syndrome (NS) is a congenital disease caused by the activation of the rat sarcoma (RAS)/mitogen activated protein kinase (MAPK) signal transduction system. The patients present characteristic facial features such as ocular hypertelorism, narrowing of the palpebral fissure, ptosis, a flat nasal bridge and low-set ears, as well as heart disease, short stature and thoracic abnormalities.[1] Eighty per cent of patients with NS show several cardiac disorders including pulmonary valvular stenosis (PS), hypertrophic cardiomyopathy (HCM) and/or atrial septal defects.[2] HCM is a serious cardiac comorbidity in patients with NS, especially in those who are diagnosed within 6 months of age with congestive heart failure.[3] Arrhythmia with or without HCM in NS is a rare comorbidity with a complicated clinical course and poor prognosis.[3]

At present, 13 genes are known as the causative genes of NS in the RAS/MAPK signal transduction system, and these are collectively called RASopathies.[4] Disease-causing mutations usually enhance the signal flow through this pathway. *RAF1* gene mutations have been detected in 5% of patients with NS, *SOS1* gene mutations in approximately 10%, *RIT1* gene mutations in 5% and *KRAS* gene mutations in less than 5%, whereas *PTPN11* gene mutations are found in more than half of all cases, although the detection rate of major gene mutations in NS varies depending on the report. The incidence of common cardiac symptoms in NS depends on the major causative genes. PS is predominant in patients with *PTPN11*, *SOS1* and *RIT1* gene mutations. HCM is common in patients with *RAF1* and *RIT1* gene mutations and rare in patients with *PTPN11* and *SOS1* gene mutations.

We present the case of a male infant with NS with *RAF1* gene mutation, who showed various types of arrhythmias along with HCM and mild PS. He developed life-threatening heart failure due to uncontrollable arrhythmias. We attempted several antiarrhythmic agents and finally controlled the arrhythmias to establish a normal sinus rhythm with a combination of amiodarone and flecainide.

CASE PRESENTATION

A woman in her late 20s was referred to our hospital in week 14 of pregnancy because of nuchal fold thickness. Chromosome analysis based on Giemsa banding and fluorescence in situ hybridisation did not detect any karyotypic abnormalities. In week 31, polyhydramnios due to fetal hydrops led to a risk of premature delivery. Fetal ultrasonography detected macrocephaly and venous defects. A male baby was born at 32 weeks and 2 days of gestation by emergency caesarean section due to endometrial infection with a 5-min Apgar score of 8. His birth weight, height and head circumference were 1793 g (0 SD), 40.1 cm (−0.91 SD) and 32.0 cm (+1.58 SD), respectively. Postnatal respiratory distress syndrome was treated with mechanical ventilation for 2 days followed by high-flow nasal cannula oxygen therapy for 33 days. He received a clinical diagnosis of NS based on (1) facial features, such as intereye dissection, flat nasal bridge and low-set ears; (2) heart disease, such as HCM and mild PS and (3) cryptorchidism. In addition, a missense mutation (c.770C<T, p.Ser257 Leu) due to a single-nucleotide substitution of the *RAF1* gene was detected on genetic diagnosis which confirmed the diagnosis of NS. There were no mutations in the *PTPN11*, *SOS1*, *RIT1*, *KRAS*, *NRAS*, *SHOC2*, *CBL* or *BRAF* genes.

At around 1-month-old, the patient was admitted to our department from the neonatal care unit with poor feeding, apnoeic attacks and transient supraventricular tachycardia (SVT). He had no family history of heart disease including arrhythmias. On admission, chest radiography showed an enlarged

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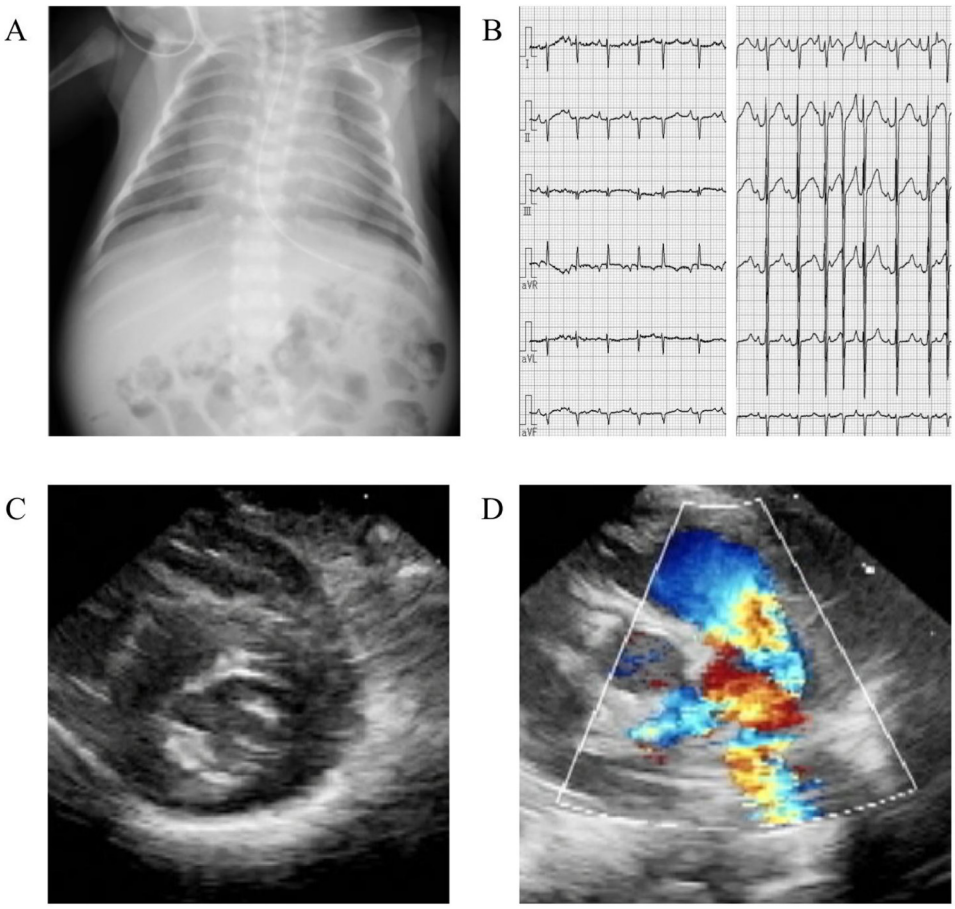

Figure 1 (A) Chest and abdominal radiography on admission. (B) ECG on admission. (C) Parasternal short axis view (papillary muscle level) of transthoracic echocardiography (TTE). (D) Parasternal short axis view (pulmonary artery bifurcation level) of TTE.

cardiothoracic ratio of 60% (figure 1A). ECG revealed premature atrial contractions (PACs) with left axis deviation (figure 1B). Transthoracic echocardiography (TTE) showed myocardial hypertrophy with 6 mm of interventricular septum thickness (Z score = +5.3) and 4 mm of left ventricular posterior wall thickness (Z score = +2.8) without left ventricular outflow tract stenosis (figure 1C) and mild PS (peak velocity = 1.58 m/s and estimated pressure gradient = 10 mm Hg) (figure 1D). We administered propranolol for SVT for 3 days and discontinued the medication because there was no recurrence. In the subsequent 2 weeks, he gained weight without any signs of heart failure, respiratory distress or persistent arrhythmia except for sporadic PACs (figure 2A). The level of brain natriuretic peptide (BNP) was 80 ng/L (normal range <18.4 ng/L). However, on day 55, the monitor ECG suddenly presented 30 s of torsade de pointes (TdP) while sleeping (figure 2B). We then resumed propranolol and subsequently added sotalol, a potassium channel blocker, for consecutive premature ventricular contractions (PVCs) at 2 months of age (figure 2C). However, the PVCs did not decrease with propranolol and sotalol; instead, atrial fibrillation (AF) appeared at 2.5 months of age (figure 2D) with a significant increase in the BNP level to 2000 ng/L. We then performed several attempts of cardioversions that failed to terminate AF while infusion of flecainide, a sodium channel blocker, finally terminated AF. However, 20 min later, he experienced cardiopulmonary arrest after transient bradycardia and apnoea. After successful resuscitation, he was admitted to the intensive care unit (ICU) at our hospital. He showed marked atrial enlargement by TTE (figure 2E) and decreased ventricular contractility with various origins of arrhythmias including ventricular tachycardia (VT) and recurrent AF (figure 2F).

TREATMENT

He was treated with respiratory support composed of deep sedation, diuretics, catecholamine infusion and antiarrhythmic agents such as amiodarone and flecainide. His haemodynamics were unstable even with the support for the first week in the ICU. However, his condition gradually improved even with continued arrhythmias in the second week. He was extubated at about 3 months old and returned to the general paediatric ward with several types of arrhythmias (figure 2G). We administered several combinations of antiarrhythmic agents, such as amiodarone alone, amiodarone with sotalol, amiodarone with propranolol and amiodarone with flecainide. Finally, a combination of amiodarone with flecainide terminated AF, PVCs and PACs at around 4 months of age (figure 2H). His heart failure further attenuated with a BNP level of approximately 100 ng/L after the termination of the arrhythmias (figure 3).

OUTCOME AND FOLLOW-UP

He was discharged from the hospital around 5 months of age with flecainide and amiodarone. We have been following him for 1½ years and gradually decreasing the amount of the drugs. He showed HCM without any recurrence of arrhythmia.

DISCUSSION

In the present case, a missense mutation (c.770C<T, p.Ser257 Leu) of the *RAF1* gene was detected. RAF1 is a MAPK which

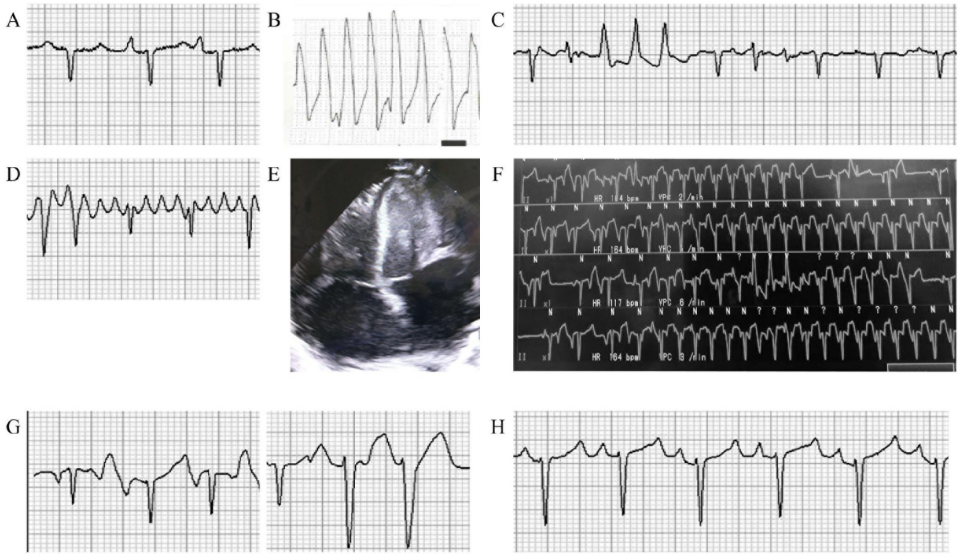

Figure 2 (A) ECG with sporadic premature atrial contractions on admission. (B) ECG with torsade de pointes on day 55. (C) ECG with consecutive premature ventricular extrasystole contractions on day 63. (D) ECG with atrial fibrillation on day 75. (E) Apical four chamber view of transthoracic echocardiography with marked atrial enlargement. (F) Monitor ECG in the intensive care unit with various origins of arrhythmias. (G) ECG in the general paediatric ward on day 95. (H) ECG with sinus rhythm on day 123.

belongs to the RAS family of membrane-bound GTPases in the RAS/MAPK signalling pathway. In NS, mutations are concentrated in the CR2 region of a phosphorylation site that suppresses RAF1 activity.[5] This case also involved a mutation in the CR2 region. In patients with NS with a *RAF1* gene mutation, the frequency of heart disease is high. Arrhythmia is a relatively rare cardiac complication in NS, while more than half of the patients with *RAF1* mutations have arrhythmia.[3 5] Mutations in *RAF1* behave as gain-of-function mutants and induce high levels of phosphorylation of mitogen-induced extracellular kinase (MEK) and extracellular signal-regulated kinase (ERK), which are downstream targets of the RAS/MAPK pathway. Activated ERKs regulate cellular proliferation, apoptosis, differentiation and migration of cardiomyocytes which lead to cardiac hypertrophy in NS.[5–7] Furthermore, mutations in *RAF1* are associated with the activation of Ca^{2+}/calcineurin through the RAF-calcineurin-nuclear factor of activated T cells pathway.[7] This pathway causes arrhythmia and cardiac hypertrophy due to pathological cardiac remodelling.[8] In our case, the patient had already presented with moderate-to-severe HCM soon after birth. Therefore, it was difficult to determine whether the arrhythmia was associated with HCM, NS-related or both. The types of arrhythmia in our patient were SVT, AF and VT, which are common in RAS/MAPK-associated arrhythmia due to the aforementioned mechanisms and as well as HCM-induced arrhythmia due to myocardial fibrosis and left atrial enlargement.[9] His arrhythmia terminated after the treatment of heart failure with catecolamine support in the ICU in combination with antiarrhythmic agents, and his heart failure further attenuated after arrhythmia termination; thus, his condition may have been complicated by the HCM and several types of arrhythmia-related injury in cardiomyocytes.

We administered several combinations of antiarrhythmic drugs, including propranolol alone, propranolol with sotalol, sotalol with flecainide, amiodarone alone, amiodarone with sotalol, amiodarone with propranolol and amiodarone with flecainide. It was very difficult to choose the antiarrhythmic drugs for this

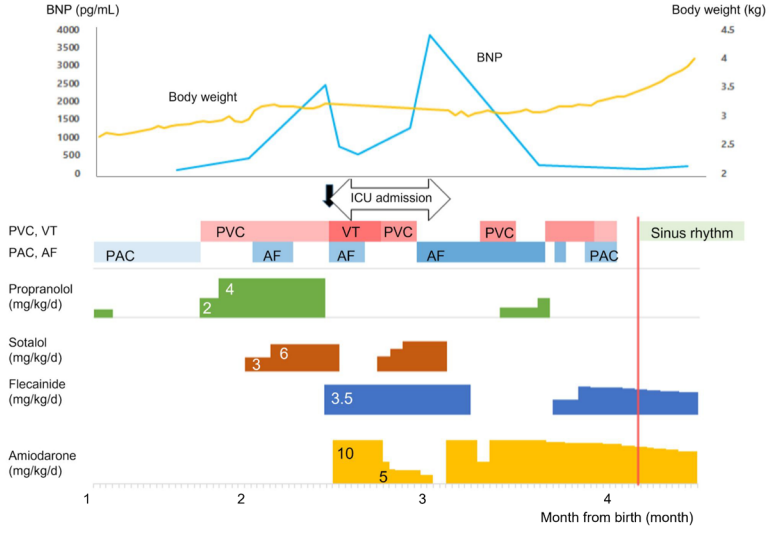

Figure 3 Clinical course of the patient with the combinations of antiarrhythmic drugs (illustrated by Hagino M).

patient because the types of arrhythmia changed during the clinical course. In addition, there are no consensus guidelines for the arrhythmia of the preterm infants, the patients with neonatal HCM or NS.[10] In our case, we finally found the combination of amiodarone with flecainide which ceased the long-lasting arrhythmia. However, we should have paid more attention to the possible exacerbation caused by the several combinations of the drugs, that is, TdP with sotalol plus amiodarone, heart failure with flecainide or overlapped β-blocking effects of sotalol and propranolol. Levin *et al* reported 11 cases of non-re-entrant atrial tachycardia in NS occurring independently of HCM.[3] They reported that propranolol alone and/or with digoxin failed to control NS-associated arrhythmia, while flecainide alone and/or with propranolol, amiodarone alone or propranolol with verapamil successfully attenuated the arrhythmia. Flecainide suppressed the increase of the action potential by suppressing the increase in intracellular Na^+ concentration, amiodarone inactivated K channels, sympathetic nerves and Ca channels as a multichannel blocker. Although we avoided administering verapamil because of the risk of worsening cardiac function in the infant, calcium blockers may be a good choice to block the Ca^{2+}/calcineurin pathway.[11] Cyclosporine was also a candidate to suppress the RAF1-associated Ca^{2+}/calcineurin activation and cardiomyocyte remodelling as shown in in vivo studies.[7 11]

In conclusion, we attempted several antiarrhythmic agents and finally controlled the arrhythmias to establish a normal sinus rhythm with a combination of amiodarone and flecainide in a male infant with NS with HCM.

Patient's perspective

Parents' perspective: When he was in the ICU, we spent very hard time because of the uncontrollable arrhythmia. Therefore we were very happy when he could discharge from the hospital. However, we are still worried about his condition with HCM and heart failure.

Learning points

- *RAF1* is associated with hypertrophic cardiomyopathy and refractory arrhythmia in Noonan syndrome.
- The combination of amiodarone and flecainide was effective in life-threatening arrhythmias in an infant.
- It is important to choose the best combination of antiarrhythmic drugs with the balance of the effects and the patients' conditions.

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REFERENCES

1 van der Burgt I, Burgt vander I. Noonan syndrome. *Orphanet J Rare Dis* 2007;2:4.
2 Marino B, Digilio MC, Toscano A, *et al*. Congenital heart diseases in children with noonan syndrome: an expanded cardiac spectrum with high prevalence of atrioventricular canal. *J Pediatr* 1999;135:703–6.
3 Levin MD, Saitta SC, Gripp KW, *et al*. Nonreentrant atrial tachycardia occurs independently of hypertrophic cardiomyopathy in RASopathy patients. *Am J Med Genet A* 2018;176:1711–22.
4 Aoki Y, Niihori T, Inoue S-ichi, *et al*. Recent advances in RASopathies. *J Hum Genet* 2016;61:33–9.
5 Kobayashi T, Aoki Y, Niihori T, *et al*. Molecular and clinical analysis of Raf1 in noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation. *Hum Mutat* 2010;31:284–94.
6 Limongelli G, Sarkozy A, Pacileo G, *et al*. Genotype-phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome. *Am J Med Genet A* 2008;146A:620–8.
7 Dhandapany PS, Fabris F, Tonk R, *et al*. Cyclosporine attenuates cardiomyocyte hypertrophy induced by RAF1 mutants in noonan and LEOPARD syndromes. *J Mol Cell Cardiol* 2011;51:4–15.
8 Wu X, Simpson J, Hong JH, *et al*. MEK-ERK pathway modulation ameliorates disease phenotypes in a mouse model of noonan syndrome associated with the Raf1(L613V) mutation. *J Clin Invest* 2011;121:1009–25.
9 Patten M, Pecha S, Aydin A. Atrial fibrillation in hypertrophic cardiomyopathy: diagnosis and considerations for management. *J Atr Fibrillation* 2018;10:1556.
10 Brugada J, Blom N, Sarquella-Brugada G, *et al*. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-arrhythmia working group joint consensus statement. *EP Eur* 2013;15:1337–82.
11 Li S-jun, Sun N-ling, Li S. Regulation of intracellular Ca2+ and calcineurin by NO/PKG in proliferation of vascular smooth muscle cells. *Acta Pharmacol Sin* 2005;26:323–8.