Cardiology in the Young

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Noonan syndrome associated with hypoplastic left heart syndrome

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Brief Report

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Abstract

Noonan syndrome is an inherited disorder caused by alterations in the RAS-MAPK pathway. There have been several identified genotype–phenotype associations made with respect to congenital cardiac lesions and Noonan syndrome variants, but limited data exist regarding single ventricle disease in this population. Here, we report two patients with *PTPN11*-related Noonan syndrome and hypoplastic left heart syndrome variants.

Noonan syndrome is an autosomal dominant genetic disorder in which a high percentage of affected individuals have cardiovascular involvement. There are more than 14 described genes in the RAS-MAPK pathway that are associated with Noonan syndrome.[1] There have been several genotype–phenotype associations made with respect to CHD associated with Noonan syndrome.[2,3] Here, we present two cases of *PTPN11* variant Noonan syndrome with hypoplastic left heart syndrome variants. There has been one previous report of hypoplastic left heart syndrome and Noonan syndrome with the *RAF1* mutation but,[4] to our knowledge, a *PTPN11* mutation genotype–phenotype association has not previously been described.

Case 1

A term male with prenatally diagnosed unbalanced atrioventricular canal to the right with arch hypoplasia was born to healthy, non-related parents. Postnatal echocardiography confirmed the prenatal diagnosis and additionally demonstrated mild to moderate right ventricular hypertrophy with normal function and severe left ventricle hypoplasia without pulmonary valve stenosis.

The patient underwent a Norwood procedure with a Blalock–Thomas–Taussig shunt at which time chylous fluid was identified in the pericardium. At 5 months of age, he underwent an elective bidirectional superior cavo-pulmonary connection. His post-operative course was complicated by refractory bilateral chylous effusions requiring multiple thoracostomy tube placements, pleurodeses, and thoracic duct embolisations with eventual takedown of the superior cavo-pulmonary connection and conversion to an aortopulmonary shunt. His post-operative course was further complicated by sepsis and eventual death at 13 months.

Autopsy showed a hypoplastic left heart variant with incomplete common atrioventricular canal with severe imbalance toward the right ventricle, and aortic valve hypoplasia. Additionally, there was evidence of dilated lymphatic channels through multiple organ systems on microscopic analysis.

He was diagnosed with Noonan syndrome shortly before he passed away and found to have a heterozygous pathogenic *PTPN11* variant (c.1507G>C, p. Gly503Arg)[5] with a normal microarray. There was no prior family history of Noonan syndrome.

Case 2

This patient was born at 37 weeks to healthy, non-related parents. He was postnatally diagnosed with unbalanced atrioventricular canal defect toward the right ventricle with aortic arch hypoplasia. Echocardiography also demonstrated moderate right atrioventricular regurgitation and stenosis and moderate right ventricle hypertrophy without pulmonary valve pathology.

On day of life 12, he underwent the Norwood procedure with a Blalock-Thomas-Taussig shunt. Postoperatively, he required chest washout for mediastinal haemorrhage. The postoperative course was further complicated by neuroblastoma, respiratory failure, and cardiac arrest secondary to acute shunt occlusion requiring venoarterial ECMO. Due to failure to wean from ECMO, his care was withdrawn and he passed away at 7 weeks old.

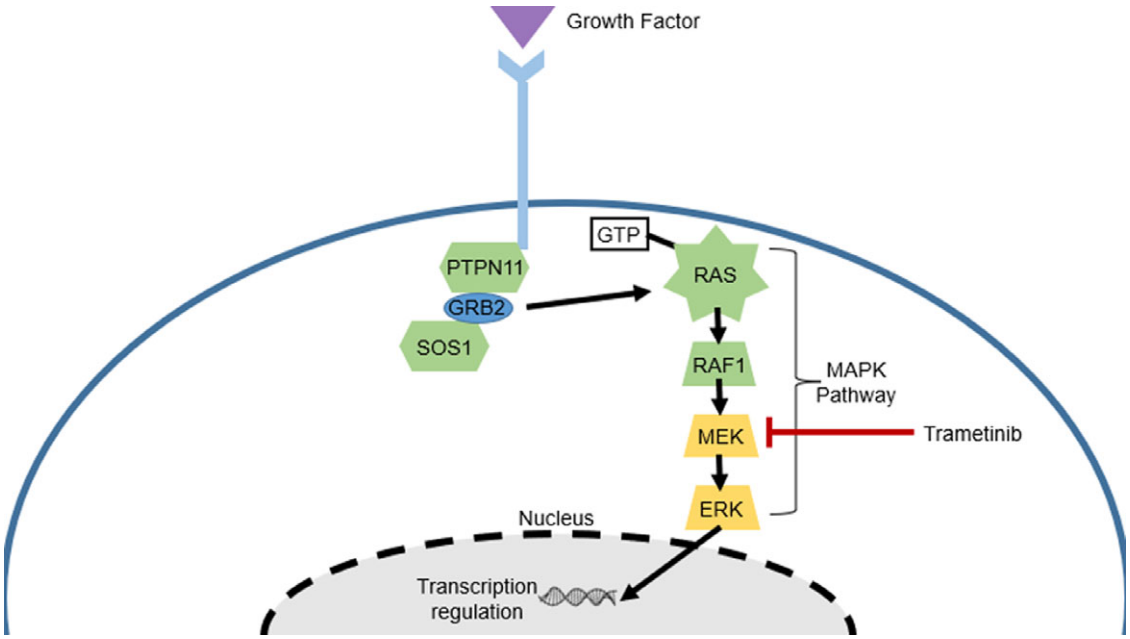

Figure 1. Growth factors bind to a receptor. Through the docking protein GRB2, SOS1, and PTPN11 are recruited which promotes activation of RAS and MAP-K pathway. ERK can enter the nucleus and alter transcription which has downstream effects on cellular proliferation and differentiation. MEK inhibitors, like trametinib, can inhibit this pathway. Gene variants associated with Noonan syndrome are depicted in green.

His autopsy showed a hypoplastic left heart variant with unbalanced atrioventricular canal defect and neuroblastoma with a dominant retroperitoneal mass as well as diffuse liver and lymph node involvement.

He was diagnosed with Noonan syndrome during his hospitalisation and found to have a heterozygous previously-reported pathogenic *PTPN11* variant (c.182A>G, p. Asp61Gly)[5] with a normal microarray. There was no prior family history of Noonan syndrome.

Discussion

Noonan syndrome is an autosomal dominant disorder with a high percentage of affected individuals having cardiovascular involvement. Many Noonan syndrome-associated *PTPN11* pathogenic variants increase signalling through the RAS-MAPK pathway, which can have downstream effects on growth factors that influence cellular proliferation, survival and differentiation (Fig 1).[1] These transcriptional effects can present with wide phenotypic variability which can often lead to a delay in diagnosis, as was seen in our first case. Atrioventricular canal defects can occur in up to 8% of patients with Noonan syndrome, and recent studies show an association with *PTPN11* variants.[3,6] Severely unbalanced atrioventricular defects leading to a hypoplastic left heart syndrome variants, however, have only been described one time in the literature in a patient with a *RAF1* mutation.[4] A better understanding of genotype–phenotype associations can lead to earlier diagnosis and improved care.

In patients with Noonan syndrome and hypoplastic left heart syndrome, there are several important periprocedural considerations. At least 10% of Noonan syndrome patients will have lymphovascular disorders including thoracic duct abnormalities which can be unmasked by cardiac surgery and present as refractory chylothoraces or lymphatic pericardial effusions as was seen in patient 1.[3] Therefore, patients with Noonan syndrome may not tolerate the transition to Glenn or Fontan physiology which can increase venous congestion and exacerbate lymphatic disorders. Therefore, when anatomy permits, a patient with Noonan syndrome may benefit from biventricular repair or hybrid operative approach. Recently severe lymphovascular disorders have been successfully treated with trametinib, a RAS-MAPK pathway inhibitor, in a patient with the *SOS1* variant of Noonan syndrome (Fig 1).[7] This may be an important treatment adjunct for patients with Noonan syndrome that must proceed down the single ventricle pathway, but more studies will need to be done to determine its efficacy in patients with the *PTPN11* mutation.

Noonan syndrome may also affect the haematologic system with up to 65% of patients with Noonan syndrome having bleeding diatheses, including factor deficiencies and qualitative platelet disorders.[8] Patient 2 exhibited numerous haematologic complications including postoperative bleeding and early shunt thrombosis. Haematologic consultation to identify these coagulation disorders, therefore, is recommended prior to surgical intervention in patients with Noonan syndrome and could potentially improve perioperative outcomes. Haematologic malignancies and solid organ tumours can also occur frequently in Noonan syndrome from dysregulation of the RAS-MAPK pathway.[9] For example, 2.9% of patients with neuroblastoma have pathogenic *PTPN11* variants, so screening for these and other commonly associated malignancies is an important consideration in the care and prognosis of these patients.

Given these factors that can complicate periprocedural care, prognosis of patients with Noonan syndrome and hypoplastic left heart syndrome is poor. Both patients in this series, as well as the only other patient reported in the literature,[4] suffered early death. Recently RAS-MAPK pathway inhibitors have been used to successfully manage lymphovascular complications and hypertrophic cardiomyopathy-related heart failure.[10] In the future, other similar targeted therapies may be developed for patients with the *PTPN11*-related Noonan syndrome. We hope that a better understanding of

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the genotype–phenotype association between *PTPN11* variant Noonan syndrome and hypoplastic left heart syndrome variants may lead to earlier diagnosis, more informed decisions around periprocedural care, and the potential for earlier availability of targeted therapies.

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References

1. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013; 381: 333–342. DOI 10.1016/S0140-6736(12)61023-X.
2. Pierpont ME, Digilio MC. Cardiovascular disease in Noonan syndrome. Curr Opin Pediatr. 2018; 30: 601–608. DOI 10.1097/MOP.0000000000000669.
3. Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: diagnosis, management, and treatment. Am J Med Genet C Semin Med Genet. 2020; 184: 73–80. DOI 10.1002/ajmg.c.31765.
4. Schulz S, Fröber R, Kraus C, Schneider U. Prenatal diagnosis of hypoplastic left heart syndrome associated with Noonan Syndrome and de novo RAF1 mutation. Prenat Diagn. 2012; 32: 1016–1018. DOI 10.1002/pd.3938.
5. Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet. 2002; 70: 1555–1563. DOI 10.1086/340847.
6. Digilio MC, Romana Lepri F, Dentici ML, et al. Atrioventricular canal defect in patients with RASopathies. Eur J Hum Genet. 2013; 21: 200–204. DOI 10.1038/ejhg.2012.145.
7. Dori Y, Smith C, Pinto E, et al. Severe lymphatic disorder resolved with MEK inhibition in a patient with noonan syndrome and SOS1 mutation. Pediatrics 2020; 146: 333. DOI 10.1542/peds.2020-0167.
8. Artoni A, Selicorni A, Passamonti SM, et al. Hemostatic abnormalities in Noonan syndrome. Pediatrics 2014; 133: e1299–e1304. DOI 10.1542/peds.2013-3251.
9. Smpokou P, Zand DJ, Rosenbaum KN, Summar ML. Malignancy in Noonan syndrome and related disorders. Clin Genet. 2015; 88: 516–522. DOI 10.1111/cge.12568.
10. Andelfinger G, Marquis C, Raboisson M-J, et al. Hypertrophic cardiomyopathy in Noonan Syndrome treated by MEK-inhibition. J Am Coll Cardiol. 2019; 73: 2237–2239. DOI 10.1016/j.jacc.2019.01.066.

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