

Symptomatic hypertrophic cardiomyopathy in 2 infants with Noonan-syndrome and RIT1-mutation: Successful treatment with the MEK inhibitor trametinib

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Introduction: Noonan syndrome (NS) belongs to the spectrum of RASopathies caused by germline mutations of genes involving the RAS/MAPK pathway. NS is frequently associated with cardiovascular involvement including hypertrophic cardiomyopathy (HCM) in 20% of the patients; some mutations are associated with a higher risk of HCM, such as RIT1 mutations. Symptomatic HCM in infants with NS carries a poor prognosis (31% first year survival). So far therapeutic options are limited. We report successful treatment of severely symptomatic infants with trametinib, a MAPK-pathway inhibitor.

Patients: Pregnancy in patient 1 was complicated by polyhydramnios requiring repeat amnioreduction procedures. Following delivery at 36 weeks the girl required mechanical ventilation due to respiratory insufficiency. Genetic testing confirmed the diagnosis of NS with RIT1 F82L de novo mutation.

Echocardiography showed biventricular HCM and pulmonary stenosis. HCM progressed with increasing subvalvular obstruction despite treatment with propranolol up to 10mg/kg/day. Clinical deterioration at the age of 3 months required resuscitation, mechanical ventilation and chest tubes for bilateral chylothoraces. In patient 2 fetal echocardiography showed mild hydramnios, cardiac valve dysplasia and hypertrophic cardiomyopathy. Neonatal echocardiography confirmed prenatal findings. Genetic testing revealed NS with de novo RIT1 S35T mutation. Despite propranolol treatment up to 10mg/kg/day the patient showed rapid aggravation of HCM with significant increase of intracavitary gradients.

Due to the dismal prognosis and in the absence of further alternatives we opted for treatment with a MEK inhibitor. Following discussion with our clinical ethics boards and informed parental consent we started trametinib with 0.025 mg/kg/d at the age of 13 and 14 weeks respectively. Treatment resulted in dramatic clinical and cardiac improvement in both patients with regression of hypertrophy and intraventricular gradients. Side effects were limited to transitory acneiform skin rash in patient 1 and accentuation of physiological alopecia in patient 2. Clinical improvement persists in both patients at the age of 12 months.

Conclusions: Treatment with trametinib in 2 infants with RIT1-associated severe progressive hypertrophic cardiomyopathy resulted in dramatic cardiac and clinical improvement persisting to the end of the first year of life. According to this experience MEK-inhibition might represent a completely new treatment option for these patients.