

Genetics Corner: Resolved Fetal Hydrops in a Newborn with Noonan Syndrome

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Case Summary

A 37-week 3-day gestation SGA male was admitted to the NICU because of respiratory distress and small size for gestational age. His prenatal course was complicated by transient fetal ascites, polyhydramnios (AFI 27), bilateral hydroceles, and abdominal wall edema, noted for the first time at 29-week 4-day gestation. Other complications were fetal growth restriction (<3rd %ile), echogenic bowel, liver calcifications, and preeclampsia without severe features. The fetal US at 19 weeks had been normal. A fetal echocardiogram was normal.

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The mother, a 29 yo G₃P₀Ab₂ woman with endometriosis, had conceived this pregnancy spontaneously. Both of her previous pregnancies, which were conceived with IVF, had been unsuccessful—one blighted ovum (twins) and one without a sac. Cell-free DNA screening was negative for common aneuploidies. Maternal blood type was A positive. Her hemoglobin electrophoresis was normal. An amniocentesis was performed at about 30 weeks' gestation. Chromosome microarray was normal. PCR studies were negative in amniotic fluid for Parvovirus B19, CMV, Herpes simplex virus, and Toxoplasma gondii. A gene panel for hydrops fetalis was pending at delivery. Fetal ascites, hydroceles, and polyhydramnios had resolved by the day prior to delivery when the fetal US showed that interval growth was less than expected, estimated fetal weight at the 2nd %ile, amniotic fluid volume was normal, echogenic bowel was slightly improved, and

liver calcifications were present.

Vaginal delivery was induced at 37-week 2-day gestation for fetal growth restriction and preeclampsia. The infant was born in vertex presentation with a tight nuchal cord x2. He was blue, without respiratory effort, with poor tone. He had a weak cry at 1 minute of life. He was resuscitated with positive pressure ventilation for 5 minutes, transitioning to bubble CPAP at 6 minutes of life. Apgar scores were 2¹, 6⁵, and 8¹⁰. Capillary blood gas at 45 minutes: 7.091/64.8/56.7/19.7/–11.8. Lactate 6.1. He did not meet the criteria for therapeutic hypothermia. His highest Sarnat score within 6 hours of life was stage 1, with an improved neurological exam by 2 hours of life. BW 2190 g (0.35th %ile), BL 46 cm (<2nd %ile), HC 29.5 cm (<0.01st %ile).

An echocardiogram showed a small PFO (patent foramen ovale). Head US was normal. US of the abdomen showed left renal calyceal dilations.

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The physical exam showed a small for gestational age newborn male with mildly dysmorphic facial features: hypertelorism, prominent globes, downslanting palpebral fissures, infraorbital creases, and widely spaced, low-set nipples. There was no nuchal webbing, low posterior hairline, or edema.

We informed the parents of the diagnosis and tested them for the variant, which was then identified in the mother. She had not been previously diagnosed with Noonan syndrome. She had a short stature at 4'11". She described having learning problems in school that required extra resources and an individual educational plan. As an adult, she had endometriosis and an ovarian cyst but no known cardiac or other health concerns.

The baby was quickly weaned to ambient air. He had an evaluation for sepsis with negative cultures. Rubella IgG was positive, likely

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from maternal transmission. He achieved full enteral feedings on the second day. At discharge, he was taking breast or bottle on demand with adequate weight gain. He was discharged on the fourth day of life with outpatient follow-up in the Cardiology clinic.

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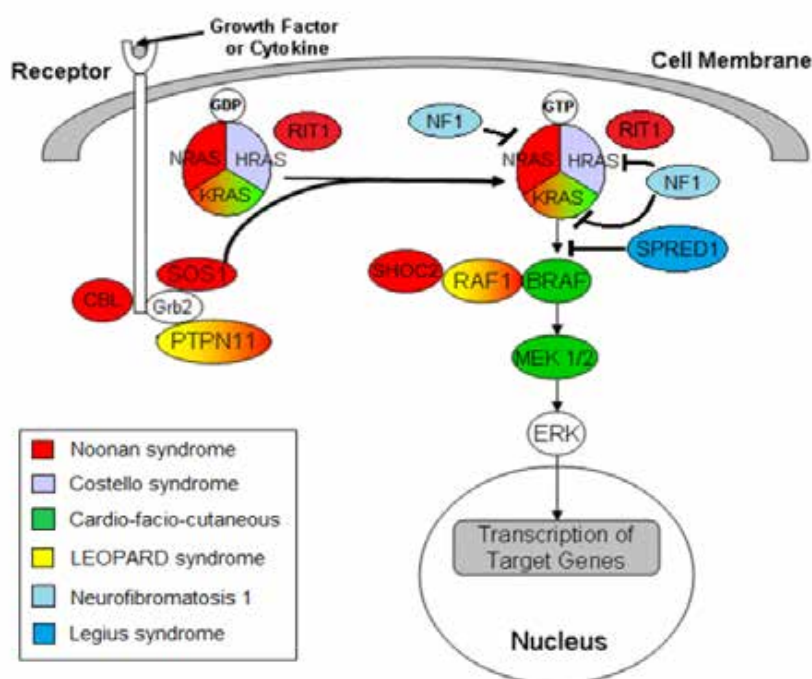
Discussion

Noonan syndrome (NS) is typically an autosomal dominant multisystem disorder with a prevalence of 1/1000 to 1/2500 live births (1). NS is one of six disorders known as RASopathies, caused by gain-of-function variants that activate the RAS-MAP-kinase pathway (2). Heterozygous variants in *PTPN11* are responsible for about half of Noonan syndrome, with the rest caused by other genes in the MAP-Kinase pathway (Figure 1).

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This infant with Noonan syndrome had a severe prenatal phenotype with poor fetal growth and significant, if transient, fetal hydrops. I found it difficult to reconcile my (erroneous) expectation for a poor postnatal outcome based on his prenatal ascites, polyhydramnios, and pleural effusions with the mild appearance of this infant and his affected mother. I wondered, had his mother decided against the amniocentesis, whether the two of them would have been diagnosed with Noonan syndrome postnatally? I had to conclude that probably not. Even though his difficult transition at birth brought him to the NICU, by the second day of life, he was doing well, and he and his mother had mild features of Noonan syndrome. This case offers several lessons. First, Noonan syndrome has a wide range of phenotypes, and many, if not most, mildly affected individuals are probably undiagnosed. Second, the prenatal phenotype of Noonan syndrome does not correlate with the postnatal phenotype.

Figure 1: This diagram (2) of the RAS-MAP kinase pathway illustrates the primary genes responsible for the group of disorders known as RAS-opathies: Noonan syndrome, Costello syndrome, Cardio-facio-cutaneous syndrome, LEOPARD syndrome, Neurofibromatosis 1 and Legius syndrome. Noonan syndrome can be caused by activating variants in several genes in the pathway, of which *PTPN11* is the most common. Note that variants in some genes have been associated with more than one disease phenotype.



Generally, the cardinal signs of syndrome identification rely heavily on a phenotype's more typical and/or more severe aspects. This means that the milder phenotypes associated with a syndrome receive less attention and are underappreciated. It should not be surprising that patients with fewer features of a disorder are less often recognized. It may not be evident that it can be more challenging to diagnose a mildly affected child than a severely affected one.

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Many of the classic features of Noonan syndrome are nonspecific: short stature, hypertelorism, down down-slanting palpebral fissures (Figure 2) (3). Even the more specific features: broad or webbed neck, low set, widely spaced nipples, and pectus carinatum can be seen in other syndromes and are not reliably present in Noonan syndrome. Lymphatic abnormalities, such as chylothorax and protein-losing enteropathy, develop in about 20% of patients with Noonan syndrome after birth. Coagulation defects and speech/language impairment are more common than the general population. About a quarter of individuals have mild intellectual disability (4).

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Figure 2: We could not include a photograph of our patient for this report. However, this image, which appears in an NIH patient recruitment notice for a RASopathy study (3), demonstrates some of the typical facial features of Noonan syndrome: hypertelorism and down-slanting palpebral fissures.



However, children with Noonan syndrome are rarely diagnosed based on their stature, learning disabilities, or dysmorphic features alone. Most patients with Noonan syndrome, 50–84% (4), come to medical attention because of a congenital heart defect. The characteristic cardiac lesion of NS, pulmonary valve stenosis, is present in 20–50%. Hypertrophic cardiomegaly, which occurs in 20–30%, is not always present at birth but can develop in infancy or childhood, so continued cardiac surveillance is necessary even when the initial echocardiogram is normal. Other structural heart defects: ASD, VSD, tetralogy of Fallot, and branch pulmonary artery stenosis can also occur. The math shows that 20–50% of individuals with Noonan syndrome have normal cardiac anatomy. Whether our patient's PFO is considered an ASD or not is a moot point because it was not appreciated as a sign or a possible sign of a multisystem syndrome. A PFO is so commonly encountered in newborns that it does not raise concern for an underlying diagnosis.

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About 21–50% of patients with RASopathy have a prenatal phenotype (5,6). Studies have demonstrated that prenatal ultrasound features of lymphatic dysplasia do not predict an unfavorable postnatal prognosis for Noonan syndrome. The prenatal phenotype of Noonan syndrome includes cardiac and renal anomalies. However, NS can also cause a wide variety of lymphatic abnormalities, from enlarged nuchal translucency (NT), dilated jugular lymph sacs (JLS), cystic hygroma, pleural effusion, and ascites to fetal hydrops, which may resolve.

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Stuurman et al. (7) reviewed the Dutch experience with gene testing in fetal lymphatic anomalies over six years (2011–2016). They identified a variant (likely pathogenic or pathogenic) in one of 14 RASopathy genes in 40/424 fetuses who had one or more of the following: increased NT/cystic hygroma (defined as NT ≥ 3.5 mm), distended JLS, pleural effusion, ascites, polyhydramnios, cardiac defects and/or renal anomalies and a normal chromosomal microarray result. The variant was in

PTPN11 in the majority of cases (27/40). Based on the postnatal phenotype, cardiac anomalies in this group of affected fetuses were less frequent than expected. The authors found that only 40% (16/40) of affected fetuses with RASopathy had a prenatally documented cardiac defect. They explained that “pulmonic valve stenosis and hypertrophic cardiomyopathy, the common cardiac defects described in Noonan syndrome, are difficult to visualise [sic] on fetal ultrasound,” which is a valid explanation for prenatal under-ascertainment. Although a RASopathy cannot be excluded when there is only one anomaly in the fetal US, especially when NT is markedly enlarged (5.5–13.0 mm), the authors found that most mutation-positive fetuses (23/40 fetuses, 57.5%) had more than one abnormality on the US.

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The final lesson that may be taken away from this case is that fetal hydrops that resolves before birth do not rule out a RASopathy. It supports the conclusion that the milder the phenotype, the more challenging the diagnosis.

Practical Applications

1. Recognize that in 21–50% of cases, NS presents prenatally with persistent or transient lymphatic disturbances: increased nuchal translucency, distended jugular lymph sacs, cystic hygroma, pleural effusion, ascites or hydrops fetalis.
 - a. Understand that cardiac anomalies may be under-ascertained prenatally in NS because the characteristic cardiac lesions, pulmonic valve stenosis and hypertrophic cardiomyopathy, are challenging to visualize with fetal ultrasound.
2. Remember that in Noonan syndrome (NS), a severe

prenatal phenotype of lymphatic dysplasia does not predict a poor prognosis after birth.

3. Not all infants with NS have a cardiac defect at birth.
 - a. 50–84% have cardiac anomalies: pulmonic stenosis, hypertrophic cardiomyopathy (which may develop after birth), ASD, VSD, and others.
 - b. 20–50% have no cardiac anomalies at birth.
4. Identify extracardiac features of NS that may be apparent at birth: hypertelorism, downslanting palpebral fissures; low posterior hairline; broad or webbed neck; low-set, widely spaced nipples.
5. Recall that parents of an infant with NS may be affected by NS.
 - a. In at least 1/3 of families, NS is inherited from an affected parent who may not be aware of their diagnosis.
 - b. When NS is diagnosed in an infant, test both parents for the pathogenic variant.

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