H116 Neonatal Pulmonary Arterial Hypertension (PAH): A Fatal Case of Noonan Syndrome (NS)

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Learning Overview: After attending this presentation, attendees will better understand the effects of NS on the respiratory system in association with PAH, which is an uncommon histological feature.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by suggesting that molecular genetic testing should be performed when newborns develop early severe PAH, an aggressive and often fatal condition.

NS is an autosomal dominant disorder characterized by congenital heart defects, facial dysmorphism, and intellectual disability caused by mutations in genes encoded by proteins of the RAS/MAPK pathway that regulate cellular cycle, differentiation, migration, and apoptosis.[1] This malformation syndrome has an estimated prevalence of 1:1,000–2,500.[2] The main feature of NS is a large spectrum of cardiac defects, including Pulmonary Valve Stenosis (PVS) and Hypertrophic Cardiomyopathy (HCM); the prevalence of cardiac defects in NS is about 80%–90% of cases.[3] Cardiac disease tends to be more progressive in infants with NS, and the earlier the presentation, the more severe the phenotype and the worse the long-term prognosis. Among those patients, there is substantial early mortality, with most deaths occurring during infancy.[4]

The prevalence of pulmonary pathologies in RASopathies is not as well-established as the cardiac and neurocognitive impairments. The development of pulmonary hypertension is generally a gradual and secondary effect of heart malformations.[5] Reported here is a case of uncommon association between NS and early-onset neonatal PAH due to a specific molecular alteration that primarily affects the arterial vessels of the lung.

A 2,150g female newborn was delivered at 34 weeks gestation to a 32 year-old primigravida. Cranio-facial anomalies were found at physical examination. Prenatal routine ultrasound detected polydramnios and biventricular hypertrophy. Family history was negative for congenital anomalies and consanguinity, and exposure *in utero* to teratogens was excluded. Over the next two months, the newborn developed significant hypoxia resulting from recurrent episodes of pulmonary atelectasia with gradual impairment of cardiac function. Echocardiogram and Computed Tomography (CT) scan showed severe HCM with evidence of PAH. Despite intensive neonatal care, the newborn succumbed to complications of acute respiratory failure at four months of age.

The external examination revealed a weight of 4,065g, length of 64cm, and head circumference of 36cm. Multiple dysmorphic anomalies were identified, including dolichocephaly with a square forehead, flat nasal bridge, low-set and posteriorly angulated ears, short neck, and nuchal edema. The internal examination showed severe right and left ventricular hypertrophy of the heart and enlargement of the pulmonary artery and its branches. The histologic examination of the lungs showed pathological changes of pulmonary arterial vessels, including medial hypertrophy, intimal proliferation with plexogenic arteriopathy, and angiomatosis. These findings were consistent with PAH. A comprehensive panel of genetic testing on blood samples revealed that the infant was heterozygous for the c770C>T mutation in RAF1, which is frequently associated with NS.

Several studies have reported that the RAF1 mutation produces a constitutive activation of the RAS/MAPK pathway with abnormal artery smooth muscle cell proliferation. While patients with this specific mutation are very likely to develop HCM (~85%), it also contributes to the development of an early onset of PAH.[3]

This presentation will provide a better knowledge on the pathogenesis of PAH in NS. An early onset of PAH, especially in newborns, is consistent with a primary genetic alteration of the pulmonary vessels rather than a progressive effect of heart malformation. Comprehensive prenatal screening for RAS/MAPK pathway mutations could allow for possible therapies targeted at the involved pathway, potentially capable of reversing HCM and delaying PAH development.[6]

Reference(s):

1. Rachel K. Hopper, Jeffrey A. Feinstein, Melanie A. Manning, William Benitz, and Louanne Hudgins. Neonatal Pulmonary Arterial Hypertension and Noonan Syndrome: Two Fatal Cases with a Specific RAF1 Mutation. *American Journal of Medical Genetics Part A* 167, no. 4 (Apr. 2015): 882-5. https://doi.org/10.1002/ajmg.a.37024.
2. Surasak Puvabanditsin, Rosanna Abellar, Adaora Madubuko, Rajeev Mehta, and Lauren Walzer. Pulmonary Vasculitis and a Horseshoe Kidney in Noonan Syndrome. *Case Reports in Pathology* 2018, (Jan. 2018). https://doi.org/10.1155/2018/6829586.
3. Angela Myers et al. Perinatal Features of the RASopathies: Noonan Syndrome, Cardiofaciocutaneous Syndrome and Costello Syndrome. *American Journal of Medical Genetics Part A* 164, no. 11 (Nov. 2014): 2814-2. https://doi.org/10.1002/ajmg.a.36737.
4. R. Karnik and M. Geiger. Cardiac Manifestations of Noonan Syndrome. *Pediatric Endocrinology Reviews* 16, Suppl 2 (May 2019): 471-476. https://doi.org/10.17458/per.vol16.2019.
5. Krishna S. Vyas and Jacqueline A. Noonan. Pulmonary Hypertension in the RASopathies. *Journal of Cardiology and Vascular Medicine* 1, (Dec. 2013): 1-6.
6. Bruce D. Gelb, Amy E. Roberts, and Marco Tartaglia. Cardiomyopathies in Noonan syndrome and the other RASopathies. *Progress in Pediatric Cardiology* 39, no. 1 (Jul. 2015): 13-19. https://doi.org/10.1016/j.ppedcard.2015.01.002.

Noonan Syndrome, Pulmonary Arterial Hypertension, Genetic Testing

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