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Case Report

Noonan Syndrome, A Rare Clinical Entity: Case Report

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ABSTRACT

Noonan syndrome (NS) is a rate autosomal dominant developmental disorder, occurring in approximately 1 in 1,000-2,500 live births. A prenatal diagnosis of NS is difficult to establish due to high variability of sonographic findings and differential diagnoses. If considered as a differential diagnosis, it allows for appropriate preparation for delivery and treatment of the neonate. We present a case of a 37 year-old female with sonographic findings in the antepartum period suspicious for multiple diseases including Noonan syndrome. Due to its rarity, Noonan Syndrome was not considered a differential diagnosis until delivery based on clinical features and confirmed with genetic testing.

Keywords: Noonan syndrome; Case report; Women's health

BACKGROUND

Noonan Syndrome (NS) is an autosomal dominant developmental disorder characterised by a wide range of features, including congenital heart defects, short stature and a variable degree of developmental delay [1]. The estimated incidence of NS is approximately 1 in 1,000-2,500 live births [2]. Prenatal surveillance for detection can be based on sonographic findings or genetic testing if warranted. We present a case of a 37 year-old G5P2022 female with delivery of a neonate with Noonan Syndrome with suggestive features in the antepartum period, in the late third trimester.

Case Report

37 year-old female G5P2022 woman of Indian descent initially presented to the Women's health clinic at 9 weeks of gestation. Obstetrical history is significant for a prior full-term caesarean section for arrest of descent and 2 spontaneous abortions within the first trimester. Gynecological history is significant for leiomyomas. Routine prenatal labs were drawn, and the patient was offered additional genetic testing due to advanced maternal age. The Non-invasive prenatal testing (NIPS) indicated the pregnancy is not at an increased risk for trisomies 21, 18, 13 or sex chromosome aneuploidies. She declined invasive testing via amniocentesis. Remainder of genetic testing including smooth muscle antibody (SMA) cystic fibrosis (97 mutations) and Fragile X syndrome (29 & 35 repeats) and maternal serum alpha-feta protein screenings were negative.

At 19 weeks' gestation, an anatomy sonogram revealed two choroid plexus cysts (CPC) at the base of the neck measuring 4 mm with slightly angled feet. She had a fetal echocardiogram performed at 20 weeks to rule out cardiac anomalies in view of the sonogram findings, which was negative for any defects. Follow up sonogram at 21 weeks' gestation was significant for only persistent bilateral choroid plexus cysts at the same previous measurements. At this point, the patient was evaluated by genetics for ultrasound findings and was counselled on risks and benefits of amniocentesis with microarray for further confirmatory testing, however the patient declined. A fetal MRI was planned for further evaluation of bilateral CPCs and was performed at 25 weeks' gestation that revealed no evidence of previous branchial cysts, however was remarkable for an enlarged edematous nuchal fold of 11.4 mm containing a 7 mm central fluid region with an occipitofrontal diameter measuring less than the 1st percentile. Repeat fetal echocardiogram was performed at 30 weeks' gestation for further evaluation of previous findings, significant for thickening of the pulmonary valve leaflets, consistent with valvular Pulmonic Stenosis. At this point, the combination of findings of pulmonary valve stenosis and thickened nuchal fold was concerning for a genetic disorder, differentials including NS, however could only be confirmed after delivery.

The patient presented to the labor and delivery unit in the latent phase of labor at 39 weeks and underwent a repeat caesarean section, which in itself was uncomplicated. Following delivery, the neonate had respiratory distress syndrome with APGAR scores of 8 at 1 minute, and 9 at 5 minutes. The neonate was also noted to have dysmorphic features, including low set ears and a thickened

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neck fold, and was transferred to the neonatal intensive care unit (NICU) for further management.

In the NICU, the male neonate required oxygen supplementation and had abnormal x-ray findings, including bilateral pleural effusions, thickening of both the pulmonic and aortic valves as well as asymmetric left ventricular wall thickening with normal function. A prominent systolic murmur was present on physical examination. He was also found to have polycythemia, based on decreased platelets and hematocrit.

Further genetic testing was performed via a chromosome analysis, which revealed a normal male karyotype of 46 XY with microarray confirming a heterozygous mutation in the gene PTPN11 for Noonan syndrome.

DISCUSSION

NS is carried as an autosomal dominant disorder, genetically heterogeneous, which partially explains its striking clinical variability. It is characterised by a wide range of features including broad-webbed neck, low set ears, short stature, heart defects and vision problems. Although it is an autosomal dominant disorder that has familial recurrence, majority of the cases are denovo mutations [1].

NS has no definitive sonogram criteria for early in utero recognition, therefore it is typically diagnosed during childhood based on phenotypic features. Prenatal suggestive features for diagnosis is based on sonogram findings, features including septated cystic hygroma, hydrothorax, polyhydramnios, and cardiac defects, such as pulmonic stenosis and hypertrophic cardiomyopathy [3,4].

Prenatal features of NS and its prenatal diagnosis have been reported in several studies, but a clear correlation between specific prenatal features and the postnatal phenotype has not been investigated thoroughly [1]. The most common sonographic features of NS are polyhydramnios (58%), cystic hygroma (42%), increased nuchal translucency and fetal hydrops (33%). Cardiac anomalies are present in 60% of cases: including left ventricular hypertrophy (25%), pulmonary stenosis (19%), atrial septal defect (10%) or dysplastic pulmonary valve in 7% [5]. The most consistent sonographic finding is nuchal translucency, where a thickness of >2.5 mm is clinically positive in about 41% of NS cases. Cystic hygromas are also a common sonographic finding in about 50% of chromosomal aneuploidies, including NS [6]. Other sonographic findings of NS itself include femur lengths at or just below the lower end of the normal range, pleural effusions, and renal anomalies.

Our patient initially had routine antepartum surveillance revealing two choroid plexus cysts measuring 4 mm with slightly angled feet at a 19-week anatomy sonogram. She underwent more frequent surveillance, revealing findings of an enlarged edematous nuchal fold containing a central fluid region with an occipitofrontal diameter measuring less than the 1st percentile. A fetal echocardiogram revealed valvular pulmonic stenosis. The combination of findings of congenital heart defect and increased nuchal translucency alludes to a wide variety of diseases, including trisomies, Turner syndrome, Smith-Lemli Opitz syndrome and congenital heart diseases.

The high variability of clinical symptoms, sonographic findings, and genetic heterogeneity makes it difficult to establish a diagnosis of NS. Patients are most frequently diagnosed postnatally, even though prenatal characteristic sonographic findings are often noted, described as above. Other differential diagnoses based on clinical features of NS include Turner Syndrome, Cardio-facio-cutaneous syndrome, Watson syndrome, Costello syndrome, Neurofibromatosis 1, and LEOPARD syndrome (lentigines, electrocardiogram conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness).

In familial cases with known mutations, preimplantation genetic testing could be performed. Our patient has no familiar history of NS, therefore a sporadic mutation could only be diagnostically confirmed after birth. Now, molecular genetic testing can provide confirmation in 70% of cases, where NS mutations occur in the RAS/mitogen-activated protein kinase (MAPK) pathway. Approximately one-half of known mutations are located in the protein tyrosine phosphatase non-receptor, type 11 gene (PTPN 11 gene) [4]. Chromosome analysis with microarray was performed on our male neonate post-delivery, confirming a heterozygous mutation in the gene PTPN11 [7].

CONCLUSION

Overall, it is important to always consider NS as a differential diagnosis when presented with characteristic sonographic features antenatally. In families with known NS, genetic testing is recommended. Our patient had multiple suggestive sonographic features antenatally, however NS was not considered as a differential diagnosis at the time. Even though NS is diagnosed in childhood, awareness of possible NS allows providers to be prepared following delivery for potential neonatal needs, including a birth center equipped with an appropriate level NICU to provide respiratory resuscitation, cardiac support or surgical intervention if needed. There are many differential diagnoses based on common sonographic findings, however with an increased number of confirmed cases of NS, it should always be included as a constituent.

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