

Neonatal Chylothorax and Dysmorphic Phenotype: A Noonan Syndrome?

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Abstract

Congenital chylothorax is an abnormal accumulation of chyle in the pleural space. Most are idiopathic, but it may be a characteristic of Down, Turner and Noonan syndromes.

We report the case of a 4 y old female with a history of polyhydramnios, hydrops fetalis and bilateral congenital chylothorax. She had a pulmonary valve stenosis, short stature (<P3), psychomotor delay, and distinctive facial features. Karyotype and cerebral magnetic resonance were normal. She was diagnosed with Noonan syndrome according to Van der Burgt criteria. Molecular genetic studies were undertaken and a p.Glu139Asp mutation was found in PTPN11.

This report illustrates that NS should be suspected in patients presenting with congenital chylothorax, dysmorphic phenotype and a normal karyotype. Based on the proportion of Noonan syndrome attributed to a mutation in each gene, we recommend the sequence analysis of PTPN11 as the first step in the testing strategy.

Keywords: Noonan syndrome; Congenital chylothorax; Chylothorax; PTPN11; Dysmorphic features; Facial dysmorphism; Prenatal diagnosis; Prenatal ultrasound; Hydrops fetalis

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Introduction

Congenital chylothorax is an abnormal accumulation of chyle in the pleural space. Pleural fluid is filtered into the pleural space by both the parietal and visceral pleura and is reabsorbed, mostly by the lymphatics. Fluid accumulation occurs when the rate of filtration increases, lymphatic clearance decreases, or both [1]. Its prevalence is low (1 per 10000 - 15000 births). Most are idiopathic, but some have been consistently associated with lymphatic system malformations or abnormalities of the thoracic duct. It may be a characteristic of Down and Turner syndromes, but it has also been reported in individuals with Noonan syndrome (NS) [2, 3].

NS is the most common rasopathy. The rasopathies are a group of syndromes caused by mutations in genes encoding proteins participating in signaling through the RAS/mitogen-activated protein kinase (RAS-MAPK) pathway and include NS, Noonan syndrome with multiple lentigines (formerly LEOPARD syndrome), Costello syndrome and cardiofaciocutaneous syndrome [4].

NS is characterized by characteristic facies, short stature,

congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, varied coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 50%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Up to one fourth of affected individuals have mild intellectual disability, and language impairments in general are more common in NS than in the general population [5].

Here, we report on a patient with a de novo PTPN11 mutation, which is associated with Noonan syndrome. Congenital chylothorax was the first sign of the syndrome

Case Report

We report the case of a 4-year-old female with a history

of polyhydramnios, hydrops fetalis and bilateral congenital chylothorax (**Figure 1**).

Hydrothorax was observed as a prenatal ultrasound finding at 20 weeks' gestation. Polyhydramnios, increased intrathoracic pressure and prehydropic signs were detected at 33 week obstetrical ultrasound evaluation. Thoracoamniotic shunt placement was attempted but finally she was delivered by an emergency cesarean section at 33 weeks gestation secondary to placental abruption as a complication during intrauterine pleural drainage.

Postnatal therapy included pleural bilateral fluid drainage, immediate ventilation, and total parenteral nutrition followed by median chain triglyceride (MCT) enriched formula. Diagnosis of chylothorax was confirmed by analysis of the pleural fluid. Pleural fluid triglyceride level was greater than 110 mg/dl, with a predominance of lymphocytes (>80%). Chylothorax and edema were solved within a week. No other lymphatic disorders have been observed.

Moreover, our patient had a pulmonary valve stenosis, short stature (<P3), psychomotor delay, and distinctive facial features (**Figure 1**). Karyotype and cerebral magnetic resonance were normal. She was diagnosed with NS according to Van der Burgt criteria (**Table 1**) [6]. Molecular genetic studies were undertaken and a p.Glu139Asp mutation was found in PTPN11.

Discussion

This report illustrates that NS should be suspected in patients

presenting with congenital chylothorax, dysmorphic phenotype and a normal karyotype.

Lymphatic dysplasia has been reported in NS and may occur anywhere in the body including lung [7]. Pulmonary lymphatic dysplasia may result in lymph flow obstruction resulting in development of fistulas between thoracic duct and pleural space or in rupture of thoracic duct and chylothorax. Thoracentesis is required for definitive diagnosis. In our patient, thoracentesis and analysis of fluid confirmed chylothorax.

Prenatal findings of polyhydramnios, hydrops fetalis and cystic hygroma in combination with an increased nuchal translucency have been found most frequently in NS [8-10]. Hydrops fetalis and polyhydramnios were observed in our patient, but neither cystic hygroma nor increased nuchal translucency.

Fetal pleural effusion at >34 weeks of gestation is recommended to be treated with immediate thoracocentesis and delivery. In pleural effusion identified before 34 weeks of gestation, presenting with mild-to-moderate unilateral effusions without hydrops, serial weekly ultrasonography follow ups is preferred. In cases where the pleural effusion progresses or where hydrops develops, thoracocentesis or thoracoamniotic shunting should be considered [11]. Postnatal therapy in congenital chylothorax involves pleural bilateral fluid drainage, immediate ventilation, and total parenteral nutrition followed by median chain triglyceride (MCT) enriched formula [12]. In majority, these measures result in complete resolution of the effusion without subsequent recurrence as happened in our case. The early

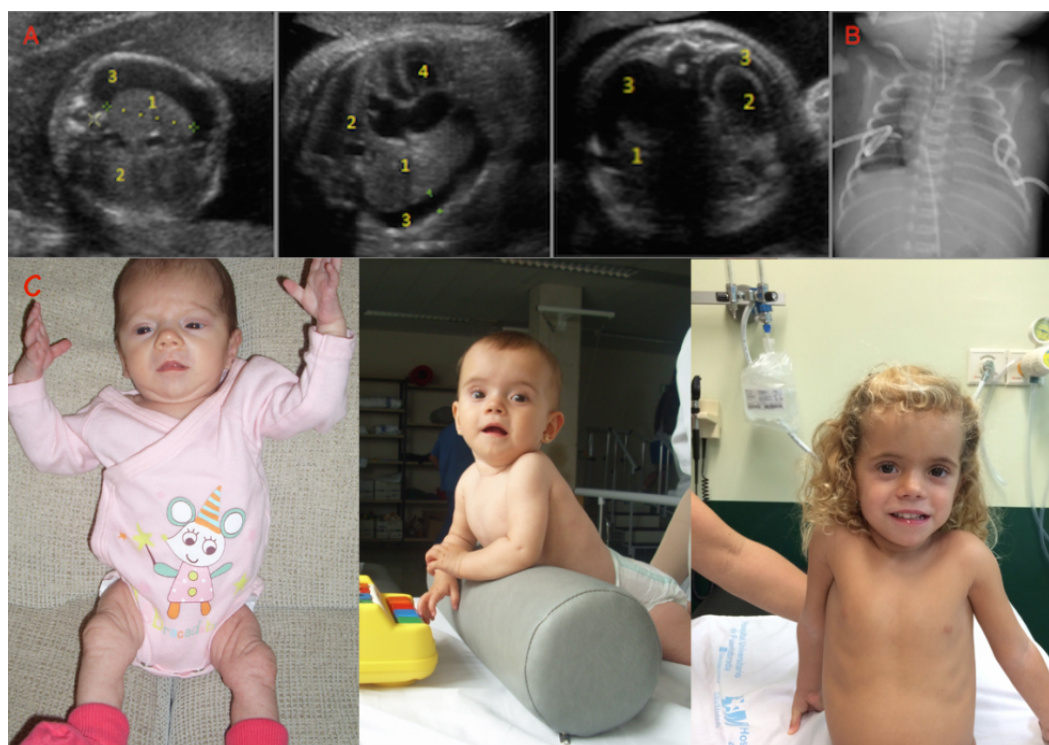


Figure 1 (A) Prenatal ultrasound (transverse view) at 20, 32 and 33 weeks of gestation. Note pleural effusion. 1: Right lung; 2: Left lung; 3: Pleural effusion; 4: Heart. (B) Anteroposterior chest radiography during neonatal period. Note bilateral pleural effusion, larger in the right side. (C) Frontal view of the female at 1.5 month old, 12 month old, and 4 y old, respectively. Note hypertelorism, low set ears, short and webbing neck, and pectum carinatum.

diagnosis and prompt management is essential for survival of such neonates.

The cardinal features of NS are short stature, congenital heart defect (dysplastic/stenotic pulmonic valve, hypertrophic cardiomyopathy and septal defects are most common), developmental delay, webbed neck, scoliosis, pectus carinatum or excavatum, low-set nipples and cryptorchidism in males. The facial features in neonates consists of a broad and high forehead, hypertelorism, epicanthal folds, low-set posteriorly rotated ears, micrognathia, short neck and low posterior hairline [3]. There have been diagnostic criteria developed by van der Burgt to help in the investigation and management of patients with Noonan syndrome [6]. She describes six major criteria: typical face dysmorphology, pulmonary valve stenosis/hypertrophic cardiomyopathy/typical ECG, percentile of height according to age<P3, pectus carinatum/excavatum, first-degree relative with definitive NS and mental retardation/cryptorchidism/lymphatic dysplasia. The minor criteria consist of suggestive facial dysmorphology, another cardiac defect not previously described, percentile of height according to age<P10, broad

thorax, first-degree relative with suggestive NS and one of either mental retardation, cryptorchidism and/or lymphatic dysplasia. In addition to the diagnostic criteria, other associated features in NS include renal and genitourinary anomalies, coagulation-factor deficiencies, lymphoproliferative disorders, ocular abnormalities, and sensorineuronal hearing loss, among others [13].

Although NS is still diagnosed on clinical grounds by observation of key features, molecular genetic testing can provide confirmation in 70% of cases. A missense mutation in PTPN11 is found in approximately 50% of the patients. Activating mutations in other gene associated with the Ras pathway (SOS1, RAF1, KRAS, NRAS, BRAF, MAP2K1) have also been described⁶. Based on the proportion of NS attributed to a mutation in each gene, we recommend the sequence analysis of PTPN11¹³ as the first step in the testing strategy.

Early, accurate diagnosis of NS is important because each patient requires an individual treatment regimen and has a different prognosis and recurrence risk [14]. A scoring system has been devised to help diagnose patients with the condition [6].

Table 1 Scoring system for Noonan syndrome (NS), Adapted from Van der Burgt I [6].

Feature	A=Major	B=Minor
1. Facial	Typical face*	Suggestive face
2. Cardiac	Pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy and/or typical ECG findings **	Other cardiac defect
3. Height	<3th centile	<10th centile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First degree relative with definite NS	First degree relative suggestive of NS
6. Other	Mild developmental delay, cryptorchidism AND lymphatic dysplasia	Mild developmental delay, cryptorchidism, OR lymphatic dysplasia
* <i>Typical face</i> : hypertelorism, epicanthus, antimongoloid palpebral fissure, low set ears, arched palate, micrognathia, short neck with low hairline. Older children may present with protrusion of the ocular globes, ptosis, lip widening with deep nasolabial furrow, wide neck, pronounced trapezius.		
** <i>Typical ECG findings</i> : left axis deviation, low voltage R wave in precordial leads (low R/S), broad QRS, pathologic Q waves (>25% the amplitude of the R wave and more than 0.04 ms duration).		
1A+1 major criteria or 2 minor criteria		
1B+2 major criteria or 3 minor criteria		

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