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CASE REPORT

Neonatal Presentation of Noonan Syndrome Type 2 with Severe Airway Obstruction and Gastroesophageal Reflux Disease: A Case Report

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Abstract:

Background: Noonan syndrome is a heterogeneous RAS-MAPK pathway disorder presenting with craniofacial dysmorphism, congenital heart disease, lymphatic abnormalities, short stature, and variable neurodevelopmental impairment. In neonates, respiratory distress due to airway anomalies and severe feeding intolerance may be early but under-recognized manifestations. Noonan Syndrome Type 2, caused by *LZTR1* variants, can exhibit more severe airway symptoms and feeding pathology.

***Case Report*:** We describe a term female neonate born via elective caesarean section (38+6 weeks, 2.3 kg) who developed immediate upper airway obstruction requiring CPAP support. Feeding attempts failed, and a nasogastric tube was placed; contrast esophagogram revealed Grade IV gastroesophageal reflux disease (GERD). At 17 days of life, she developed acute respiratory collapse with bradycardia requiring resuscitation and mechanical ventilation. Flexible laryngoscopy confirmed laryngomalacia and tracheomalacia. CT of the neck demonstrated subglottic stenosis and tracheal narrowing (2.1 cm segment). Genetic testing identified a heterozygous pathogenic *LZTR1* variant confirming Noonan Syndrome Type 2, along with a VUS in *BRPF1* associated with intellectual developmental disorder with ptosis and dysmorphic facies. USG abdomen revealed umbilical granuloma, USG cranium showed bilateral caudothalamic groove cysts, and MRI brain was normal. Despite multidisciplinary NICU care, gastrostomy placement, and ventilatory support, the infant succumbed to progressive respiratory failure. This case represents a rare and severe neonatal presentation of Noonan Syndrome Type 2 with life-threatening airway obstruction and Grade IV GERD. Early genetic evaluation, aggressive airway assessment, and coordinated multidisciplinary management are critical in neonates presenting with unexplained respiratory distress and feeding failure.

Keywords: Noonan Syndrome Type 2, LZTR1, Neonate, Airway Obstruction, GERD Grade IV, Tracheomalacia, Subglottic Stenosis

INTRODUCTION

Noonan syndrome (NS) is a genetically heterogeneous multisystem developmental disorder belonging to the group of conditions known as RASopathies, caused by dysregulation in the RAS–MAPK signalling pathway. With a birth prevalence of 1 in 1,000 to 2,500 live births, NS represents one of the most common non-chromosomal genetic syndromes associated with congenital heart disease, craniofacial dysmorphism, growth abnormalities, and variable neurodevelopmental delay (1). Although classically associated with *PTPN11* mutations, recent genomic advances have identified several additional causative genes including *SOS1, RAF1, RIT1,* and *LZTR1*, the latter being implicated in Noonan Syndrome Type 2 (NS2). *LZTR1*–related NS often exhibits autosomal dominant inheritance and is increasingly recognized for its distinct phenotypic patterns, including more pronounced airway abnormalities and craniofacial structural variations (2).

The neonatal presentation of NS can be subtle or atypical, contributing to underdiagnosis during early infancy. While some infants present with recognizable facial features such as hypertelorism, low-set posteriorly rotated ears, high-arched palate, or webbed neck, others may initially manifest nonspecific symptoms such as feeding difficulties, respiratory distress, hypotonia, or poor weight gain (3). Severe airway involvement although well documented in older children remains an underreported neonatal feature. Airway anomalies such as laryngomalacia, tracheomalacia, subglottic stenosis, choanal abnormalities, and tracheal narrowing may arise from intrinsic cartilage weakness, neuromuscular hypotonia, or craniofacial disproportion associated with NS (4). These abnormalities can significantly compromise neonatal respiration, leading to inspiratory stridor, recurrent desaturations, and progressive respiratory failure if not promptly recognized (5).

Gastrointestinal manifestations, particularly feeding intolerance and gastroesophageal reflux, are common in NS due to hypotonia, delayed gastric emptying, or impaired autonomic regulation. However, severe presentation such as Grade IV gastroesophageal reflux disease (GERD) with repeated aspiration is extremely rare in the neonatal period (6). GERD-related aspiration significantly worsens respiratory morbidity by triggering recurrent pneumonitis, apnea, or acute respiratory decompensation. Recognition of this association is crucial because persistent feeding difficulties and aspiration may mask underlying structural airway disease or signal the presence of an unrecognized genetic condition such as NS2 (7).

Advances in molecular diagnostics, especially whole exome sequencing, have transformed the approach to infants presenting with complex multisystem involvement. Genetic confirmation not only supports clinical diagnosis but also guides prognostication, anticipatory guidance, and family counselling. Importantly, identification of *LZTR1* variants carries clinical implications due to emerging evidence linking this subtype to severe neonatal presentations, including airway malacia and dysphagia (8).

Early diagnosis and multidisciplinary management involving neonatology, otolaryngology, gastroenterology, pulmonology, neurology, cardiology, and genetics are essential for improving outcomes. For neonates presenting with unexplained respiratory distress, feeding difficulty, and recurrent desaturations, the coexistence of airway anomalies and severe GERD should prompt consideration of an underlying syndromic aetiology such as NS2 (9).
The case reports a neonate with genetically confirmed Noonan Syndrome Type 2 presenting with severe airway obstruction due to laryngomalacia, tracheomalacia, and subglottic stenosis, compounded by Grade IV GERD and aspiration. This case underscores the critical importance of early airway evaluation and genetic testing in infants with atypical or severe neonatal respiratory presentations.

CASE REPORT

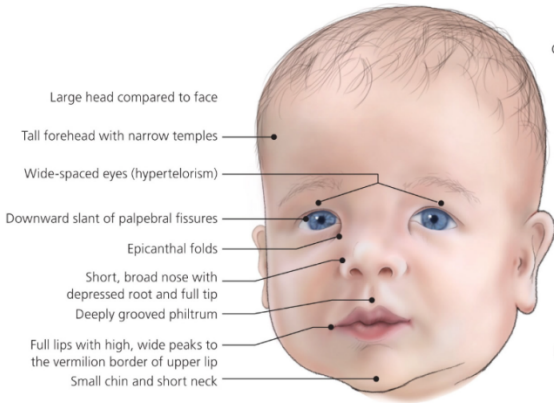

Figure 1. Characteristic Facial Features in Noonan Syndrome

Patient Information- A term female neonate was born at 38+6 weeks of gestation via elective caesarean section to a primigravida mother. Her birth weight was 2.3 kg, and she did not require immediate resuscitation. Within minutes of birth, the infant developed tachypnoea, inspiratory stridor, and persistent upper airway obstruction, prompting transfer to the neonatal intensive care unit (NICU). Initial concerns included poor respiratory effort, intermittent desaturation, and difficulty maintaining oxygenation without continuous positive airway pressure (CPAP). There was no significant antenatal history, and the pregnancy was otherwise uneventful.

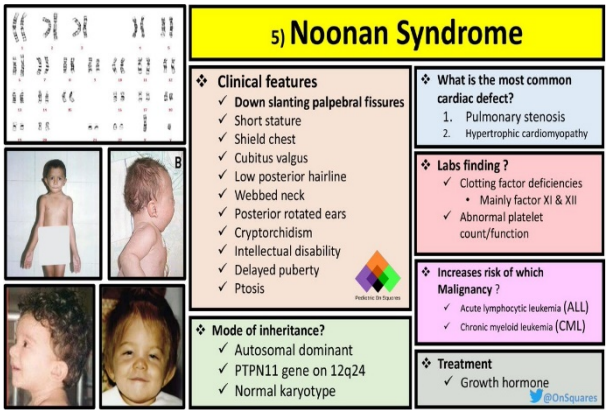

Figure 2. Overview of Clinical, Genetic, and Systemic Features of Noonan Syndrome Clinical Presentation and Initial Management

On admission, the neonate demonstrated laboured breathing with subcostal retractions and required CPAP for stabilization. Feeding attempts were poorly tolerated, with choking, regurgitation, and repeated desaturation episodes. As oral feeds remained unsuccessful, a nasogastric tube was inserted for enteral feeding. Despite supportive care, the infant continued to exhibit noisy breathing, recurrent bradycardic spells during feeds, and progressive intolerance to oral and nasogastric feeding.

Respiratory Deterioration and Airway Evaluation-At 17 days of life, the neonate experienced an acute episode of respiratory collapse characterized by severe desaturation and bradycardia, requiring immediate cardiopulmonary resuscitation and escalation to mechanical ventilation. Once stabilized, flexible laryngoscopy was performed and revealed significant airway abnormalities, including laryngomalacia and tracheomalacia. Further evaluation using computed tomography (CT) of the neck demonstrated subglottic stenosis and diffuse tracheal narrowing involving a 2.1 cm segment beginning at the C5 vertebral level. These findings confirmed multiple levels of airway obstruction contributing to her persistent respiratory distress. Chest imaging revealed intermittent right lower lobe opacities consistent with aspiration pneumonitis.

Feeding Difficulties and Gastrointestinal Evaluation- A contrast esophagogram was conducted to assess persistent feeding intolerance. The study revealed Grade IV gastroesophageal reflux, with rapid retrograde flow of contrast from the stomach into the cervical oesophagus. This severe reflux placed the infant at high risk for recurrent aspiration events and contributed to repeated respiratory decompensation. Due to poor feeding coordination, inability to tolerate oral feeds, and ongoing aspiration risk, a surgical gastrostomy tube was placed for long-term nutritional support.

Figure 3. Neonate with Dysmorphic Features and Respiratory Support

Neurological and Systemic Evaluation- Given cranial shape abnormalities, including scaphocephaly and overriding sutures, a neurological opinion was sought. Cranial ultrasonography showed bilateral caudothalamic groove cysts and a persistent cavum septum pellucidum, while MRI of the brain was unremarkable with no evidence of structural malformations or white matter injury. Ultrasonography of the abdomen revealed a small umbilical granuloma but was otherwise normal. Serial laboratory investigations revealed episodes of metabolic alkalosis and a culture-positive methicillin-resistant Staphylococcus aureus (MRSA) umbilical infection, which was treated appropriately.

Genetic Findings-Due to the combination of airway anomalies, dysmorphic features, feeding difficulties, and developmental concerns, whole exome sequencing was performed. The infant was found to carry a heterozygous pathogenic variant in the LZTR1 gene, confirming the diagnosis of Noonan Syndrome Type 2. Additionally, a variant of uncertain significance (VUS) was identified in the BRPF1 gene, which has been associated with intellectual developmental disorder with ptosis and dysmorphic facies (IDDDFP). Cardiac evaluation including echocardiography revealed no congenital heart defects.

Clinical Course- Despite multidisciplinary care involving neonatology, otolaryngology, gastroenterology, neurology, radiology, and genetics, the infant continued to show severe respiratory instability. Persistent airway malacia, subglottic narrowing, and repeated aspiration events led to prolonged ventilatory dependence. Although gastrostomy improved nutritional stability, respiratory complications persisted due to the severity of airway involvement and recurrent pneumonitis. Over the following days, the infant experienced progressive respiratory failure refractory to maximal supportive measures.

Outcome-Despite comprehensive medical and surgical interventions, the neonate's respiratory status continued to deteriorate. The combination of profound airway obstruction, severe GERD, aspiration pneumonitis, and underlying genetic pathology contributed to a poor prognosis. The infant ultimately succumbed to refractory respiratory failure despite intensive NICU support.

DISCUSSION

Noonan syndrome represents one of the most clinically diverse RASopathies, with phenotypes ranging from mild dysmorphism and cardiac anomalies to severe neonatal complications involving multiple organ systems. Although respiratory and feeding difficulties are recognized in infancy, severe airway abnormalities and life-threatening gastroesophageal reflux disease (GERD) in the neonatal period remain relatively uncommon presentations (10). This case illustrates a particularly severe neonatal form of Noonan Syndrome Type 2 (NS2), associated with a pathogenic LZTR1 variant, manifesting through profound airway obstruction, severe GERD, repeated aspiration, and ventilatory dependence that ultimately proved fatal.
Airway involvement in NS is an under-appreciated yet clinically significant manifestation. Laryngomalacia and tracheomalacia are believed to occur due to intrinsic cartilage weakness, abnormal connective tissue formation, or hypotonia associated with the underlying genetic defect. Subglottic stenosis, as seen in this infant, is even more unusual and contributes to fixed as well as dynamic airway obstruction (11). The coexistence of multilevel airway disease laryngomalacia, tracheomalacia, and subglottic narrowing creates a critical respiratory compromise that is often unresponsive to conventional supportive care. The resulting inspiratory stridor, desaturations, and difficulty maintaining oxygenation frequently necessitate early invasive ventilation (12). In this case, the acute respiratory arrest at 17 days of life reflected the severity of dynamic airway collapse exacerbated by aspiration events.

Feeding difficulties are also common in NS but typically manifest as poor suck, hypotonia, or mild

reflux. Grade IV GERD, however, is rare and represents a severe dysfunction of the lower esophageal sphincter with continuous retrograde flow of gastric contents into the esophagus (13). In neonates with airway malacia, such severe reflux creates a vicious cycle: recurrent aspiration worsens pulmonary inflammation, promotes atelectasis, and increases ventilatory requirements, while positive pressure ventilation may further exacerbate reflux. The combination of severe GERD with compromised airway structure significantly contributed to recurrent pneumonitis and the infant's rapid respiratory deterioration (14).

The neurological findings in this case, including scaphocephaly and bilateral caudothalamic groove cysts, expand the spectrum of potential early brain involvement in NS2, although MRI brain revealed no major structural abnormalities. Caudothalamic cysts may be benign or developmental variations but require close follow-up due to their association with motor delay and prematurity. The identification of a *BRPF1* variant of uncertain significance adds complexity, as *BRPF1*-related disorders are associated with dysmorphic features, ptosis, and intellectual developmental delay. Though its clinical significance cannot be definitively established, dual genetic influence may have contributed to the infant's craniofacial morphology and potential developmental vulnerability (15).

The absence of congenital heart disease in this case is notable, as cardiac anomalies remain the most frequently recognized hallmark of NS. This highlights the importance of avoiding diagnostic anchoring; lack of cardiac defects should not exclude the possibility of NS, particularly in neonates with unexplained airway and feeding pathologies.

Despite early recognition of severe airway malacia and GERD, as well as timely gastrostomy placement and multidisciplinary involvement, the infant's condition continued to worsen. This underscores the limitations of therapeutic interventions in cases where structural airway deficiencies are profound and compounded by severe gastroesophageal dysfunction (14). Mechanical ventilation, although life-saving, may further destabilize an already compromised airway in tracheomalacia due to dynamic airway collapse during expiration (16).

This case reports the crucial role of genetic testing in neonates presenting with persistent, unexplained respiratory distress and feeding difficulty. Early diagnosis of NS2 enables families and clinicians to anticipate complications, plan interventions, and make informed decisions regarding prognosis and long-term care. Additionally, it contributes to the expanding understanding of genotype-phenotype variations in LZTR1-related Noonan syndrome, particularly in the context of severe neonatal airway disease.

CONCLUSION

This case reports a rare and severe neonatal presentation of Noonan Syndrome Type 2 caused by an *LZTR1* pathogenic variant, characterized by multilevel airway obstruction, severe Grade IV gastroesophageal reflux, and progressive respiratory failure. The coexistence of laryngomalacia, tracheomalacia, and subglottic stenosis created a profound airway compromise that was further exacerbated by recurrent aspiration events. Despite early recognition, advanced airway assessment, gastrostomy placement, and dedicated multidisciplinary care, the infant's respiratory condition continued to deteriorate, ultimately leading to a fatal outcome. The case underscores the importance of considering genetic etiologies in neonates with persistent respiratory distress and feeding intolerance, particularly when standard management fails. Early genetic testing, comprehensive airway evaluation, and coordinated multidisciplinary intervention are essential to improving diagnostic accuracy and guiding clinical decision-making. Awareness of such severe neonatal presentations broadens the understanding of Noonan Syndrome Type 2 and emphasizes the need for heightened vigilance in similar clinical scenarios.

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