Non-invasive management of infants with SFTPC pathogenic variants

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Abstract

Pathogenic variants in the Surfactant Protein C gene (*SFTPC*) result in fibrotic childhood interstitial lung disease (chILD). We previously reported three children with *SFTPC* pathogenic variants with respiratory failure who were supported by chronic invasive ventilation via tracheostomy as an alternative to lung transplantation or comfort care [(1)](#ref-0001). We present two children with *SFTPC* pathogenic variants treated with non-invasive ventilation (NIV) (Figure 1).

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To the Editor:

Pathogenic variants in the Surfactant Protein C gene (*SFTPC*) result in fibrotic childhood interstitial lung disease (chILD). We previously reported three children with *SFTPC* pathogenic variants with respiratory failure who were supported by chronic invasive ventilation via tracheostomy as an alternative to lung transplantation or comfort care (1). We present two children with *SFTPC* pathogenic variants treated with non-invasive ventilation (NIV) (Figure 1).

Case 1

A full-term male with unremarkable pregnancy and birth histories presented at one week of life with tachypnea and hypoxemia that progressed to respiratory failure requiring invasive mechanical ventilation with high frequency oscillatory ventilation (HFOV). Echocardiogram was unremarkable and infectious workup was negative. Chest computed tomography (CT) demonstrated patchy airspace consolidation with diffuse parenchymal ground-glass opacities (Figure 2A). Lung biopsy showed alveolar type II cell (AEC2) hyperplasia, alveolar septal fibrosis, and abundant reactive intra-alveolar macrophages. Genetic testing revealed a *de novo SFTPC*(NM_003018.3) pathogenic variant: c.566G>A,p.Cys189Tyr. This previously reported (2) variant affects a conserved amino acid within the BRICHOS chaperone domain, is not present in large adult genomic databases (3, 4), and is predicted damaging by *in silico*(5, 6).

Following diagnosis, treatment was initiated with high-dose intravenous methylprednisolone (30mg/kg IV daily for three days every month), azithromycin (5mg/kg enterally three times weekly), and hydroxychloroquine (7mg/kg enterally daily). The infant's oxygenation improved following corticosteroid administrations, transitioning sequentially from HFOV to conventional mechanical ventilation, NIV, and ultimately nasal cannula oxygen (Figure 1A). He received feeding supplementation via nasogastric tube for 7 months, and medications at time of hospital discharge included azithromycin and hydroxychloroquine. At 8 months, supplemental oxygen was discontinued. At 2 years, chest CT showed improved parenchymal infiltrates, and enteral medications were discontinued (Figure 2B). At time of last follow-up visit, he remained nonmonic off oxygen and without significant developmental delays.

Case 2

A full-term male with unremarkable pregnancy and birth histories was diagnosed with failure to thrive at his 2-week well child check prompting hospital admission (Figure 1B). Echocardiogram was unremarkable. Infectious workup was remarkable for nonspecific chest radiograph findings. A video fluoroscopic swallow study noted incoordination, and nasogastric feeds were initiated. He desaturated with sleep and was discharged with nasal cannula oxygen.

He was readmitted at 3.5 months for fever, emesis, increased work of breathing, and increased oxygen requirement. Chest CT revealed diffuse ground-glass opacities and right sided lobar cystic structures (Figure 2C). Genetic testing revealed a novel, *de novo SFTPC* variant: c.289G>T;p.Gly97Cys that is not present in adult databases(3, 4), affects a conserved amino acid within the BRICHOS domain, and is predicted deleterious(5, 6).

His respiratory status continued to decline with multiple hospitalizations, requiring maximal respiratory support of NIV. He discharged home at 11 months with nasal cannula oxygen while awake and NIV 15/7 with oxygen bled-in for sleep. Discharge medications included prednisolone 9 mg/kg weekly, azithromycin 10 mg/kg three times per week, and hydroxychloroquine 7mg/kg daily via gastrostomy tube. Growth and development continue to be typical for age. NIV was discontinued at 21 months, and oxygen was discontinued at 2 years. He tolerated respiratory syncytial virus infection without hospitalization or oxygen. At 3 years, he remains on azithromycin and hydroxychloroquine and is normoxic while comfortably breathing room air.

Discussion

We previously reported three term infants with *SFTPC* pathogenic variants who presented with post-neonatal respiratory failure and were supported with tracheostomy and chronic mechanical ventilation(1). At the time, chronic invasive mechanical ventilation was a novel, alternative approach to lung transplantation (12). However, tracheostomy placement carries significant risks including bleeding, infection, and sudden death resulting from tube occlusion and parents assume a huge burden of care(13).

Historically, home NIV was suboptimal for children due to limitations surrounding ventilator size, mask size and fit, skin breakdown, midface hypoplasia, impeding developmental skills, and insurance approval. In two infants with *SFTPC* pathogenic variants, we used NIV which avoided additional medical complexity associated with tracheostomy while still permitting developmental therapies. Infant 2 was treated with enteral corticosteroids (instead of intravenously), further decreasing medical complexity and family burden. As ventilator technology improves with less dead space, better synchrony, and smaller, infant-appropriate masks, NIV may be an effective therapy for infants with respiratory insufficiency.

SFTPC pathogenic variants act in an autosomal dominant manner with variable penetrance or arise *de novo* .(7) Among families with the same inherited *SFTPC* variant, age of presentation varies, ranging from neonatal respiratory failure to adult pulmonary fibrosis(8). *SFTPC* encodes a 191 or 197-amino acid precursor protein (proSP-C), which undergoes proteolytic processing resulting in an extremely hydrophobic, 35-amino mature protein. The c.Gly97Cys and c.Cys189Tyr variants identified in these infants are located within the BRICHOS domain which mediates folding and processing of proSP-C (9-11).*SFTPC* variants within the BRICHOS domain result in retention of mutant proSP-C in the endoplasmic reticulum and subsequent cellular stress, activation of the unfolded protein response, AEC2 apoptosis, increased cytokine production, macrophage recruitment, polycellular alveolitis, and fibrosis (11).

Histologic findings among children with *SFTPC* pathogenic variants include alveolar proteinosis, non-specific interstitial pneumonia or desquamative interstitial pneumonia, depending on timing of biopsy(14). The alveolar proteinosis associated with infantile *SFTPC*pathogenic variants typically will improve with time through macrophage catabolism, visualized with clearance of ground-glass opacities on chest CT (15). *SFTPC* pathogenic variants result in diverse respiratory phenotypes, and affected infants and children may require prolonged hospitalization due to slow improvement: families and care providers should be prepared for this. Like bronchopulmonary dysplasia, infants with *SFTPC* pathogenic variants benefit from higher positive end expiratory pressure (PEEP) to prevent atelectasis, but conversely, may benefit from lower tidal volumes and higher rates to limit further alveolar injury. Clinical phenotype varies dramatically, and discussions of transplantation and comfort care may still be appropriate with treatment course personalized to each child. ChILD Centers of Excellence have expertise with these rare and complex patients and may help guide these decisions. We present two infants with *SFTPC* pathogenic variants managed with NIV as an alternative therapy to transplantation, comfort care, or tracheostomy placement.

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Figure 1. Clinical courses of our two patients with*SFTPC* pathogenic variants

Figure 2. Chest CT imaging from two cases with *SFTPC*pathogenic variants. 2A: Case 1 at 2 weeks of age with diffuse ground-glass opacities. 2B: Case 1 at 2 years of age with clearing of ground-glass opacities. 2C: Case 2 at 3 months of age with diffuse ground-glass opacities.

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