VACTERL-associated bilateral bronchial stenosis with concomitant spinal muscular atrophy

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Abstract

VACTERL association is linked to multiple congenital anomalies including tracheoesophageal fistula. In rare cases, VACTERL has been complicated by other airway malformations including severe bronchial stenosis or unilateral pulmonary agenesis. We report a child who developed episodes of oxygen desaturation during sleep associated with high pressure support requirements to maintain ventilation. He was known to have VACTERL association as well as spinal muscular atrophy (SMA) type II, a genetic neuromuscular disorder. Children with SMA can show progressive respiratory symptoms, including intercostal muscle weakness and accompanying paradoxical abdominal breathing with sparing of diaphragm function. Our patient was very difficult to ventilate non-invasively despite high pressures. CT chest with dynamic airway evaluation showed bilateral bronchial stenosis. High inspiratory pressures with non-invasive ventilation as seen in our case are required to overcome stenotic airways but are not expected in neuromuscular respiratory failure.

Introduction:

VACTERL association is linked to multiple congenital anomalies including vertebral anomalies (V); anal atresia or anogenital malformations (A); cardiac malformations (C), tracheoesophageal fistula (TE) with or without esophageal atresia; renal-urinary (R) and limb (L) anomalies.[1] Although there is no consensus regarding specific diagnostic criteria for VACTERL association, most clinicians require at least two or three of the above features to be present[1,2] with tracheoesophageal fistula (TEF) and anogenital malformations being the most common malformations.[3,4] The term "association" is applied as there is no causative gene or environmental exposure linked to this disorder.

Tracheoesophageal fistula (TEF) occurs in 60-80% of children with VACTERL association.[3,4] In rare cases VACTERL has been complicated by severe bronchial stenosis[5,6] or unilateral pulmonary agenesis.[7]

We report a child who developed episodes of oxygen desaturation during sleep. He was known to have VACTERL association as well as spinal muscular atrophy (SMA) type II, a genetic disorder associated with biallelic *SMN1* variants. While children with SMA can show progressive respiratory symptoms, he was very difficult to ventilate non-invasively despite high pressures.[8] As he was a high-risk patient for flexible bronchoscopy with anesthesia, a CT chest with dynamic airway evaluation was done which showed bilateral bronchial stenosis.

Case Presentation:

Our patient was born at 34 weeks gestation via a planned caesarean section. His mother had longstanding Crohn's disease managed with infliximab. She was diagnosed with rectal cancer during pregnancy, necessitating the premature delivery to facilitate maternal chemotherapy. An antenatal ultrasound at 28 weeks' gestation had previously noted polyhydramnios, a two-vessel umbilical cord and a right pelvic kidney. No

resuscitation was required at birth. His birth weight was 1,783 g (10^{th}%ile) and head circumference 31 cm (10-50^{th}%ile). He was diagnosed with VACTERL association based on clinical manifestations. The two-vessel umbilical cord was confirmed at birth and subsequent ultrasound noted a horseshoe kidney, with his low-lying right kidney fused to the inferior pole of the left kidney. His family history was otherwise unremarkable, and he had one older half-sister who was healthy.

Challenge Point: A preterm male infant has suspected VACTERL association and is admitted to the NICU for ongoing care.

Learner Reflection:

What congenital malformations seen in VACTERL association can present with respiratory dysfunction?

What imaging would you order to investigate?

Case Progression:

After attempts to pass a nasal gastric (NG) tube were unsuccessful, a chest x-ray and bronchoscopy confirmed esophageal atresia, proximal tracheoesophageal fistula (TEF) and a T5 hemivertebrae. He also had an inferior iris and chorioretinal coloboma affecting his left eye as well as a small atrioseptal defect (ASD). He had single palmar creases but no limb anomalies and he did not show anal atresia. His TEF was repaired on the second day of life. Microarray and *CHD7* sequencing were unrevealing. He was discharged home at 3-1/2 months old on NG feeding. He was re-admitted at 8 months old for investigation of vomiting and noted to have a hiatal hernia and dilation of his distal esophagus requiring surgical repair. A gastrostomy tube was inserted at this time, and he was subsequently transitioned to continuous gastro-jejunal (GJ) feeds to improve tolerance.

At 15 months old (13-1/2 months corrected gestational age) he was reassessed for developmental delay. He was able to roll to each side, but not completely over. He was able to remain sitting independently for up to 2 minutes when placed in a seated position. He was not able to bear weight on his legs or take independent steps. He had a bilateral pincer grasp and could bring a spoon to his mouth. He babbled but did not yet have any spoken words. His examination showed decreased muscle bulk, hypotonia and areflexia. Subsequent testing confirmed spinal muscular atrophy (SMA) with 0x*SMN1* and 3x*SMN2* copies. He was started on salbutamol as a treatment for SMA at 21 months old.

Challenge Point: The patient was subsequently noted to have developmental delay. Examination was notable for decreased muscle bulk, hypotonia, and areflexia. Genetic testing confirmed the diagnosis of SMA, and he was started on salbutamol.

Learner Reflection:

What is the proposed mechanism of action of salbutamol in SMA?

What newer treatments are available for SMA? What impact do these treatments have on respiratory status?

Case Progression:

At 2 years of age, he developed respiratory distress due to rhinovirus bronchiolitis requiring intubation and ventilation for 2 weeks. He was discharged home on overnight non-invasive ventilation having not required ventilator support prior to that time. At 3 years old, he had a three-week admission for aspiration pneumonia. At 3-1/2 years old he again developed respiratory distress and fever due to RSV bronchiolitis requiring 24 h BiPAP support for several weeks before returning to his baseline settings.

At 7-1/2 years old he underwent a sleep study when his mother noted a 6 week history of nocturnal, self-resolving desaturations to the low 70's, despite consistent overnight non-invasive ventilatory support. On his sleep study, he was found to have increased FiO_2 and pressure support requirements, with inspiratory and expiratory positive airway pressure requirements climbing to 22/10 cmH_2O, respectively, and an FiO_2 reaching the 35-40% range. His transcutaneous CO_2 was in the mid-50s. He was observed to have dysynchrony with the ventilator and to have respiratory distress. This presentation of increased pressure support requirements

was considered atypical for SMA related respiratory disease. The patient was a high risk for flexible bronchoscopy with anesthesia. CT chest with dynamic airway evaluation subsequently showed bilateral bronchial stenosis (Figure 1). These lesions were not amenable to tracheostomy, as a surgical airway would not bypass the anatomic stenosis. Due to the patient's underlying conditions and high risk of morbidity and mortality, surgical intervention for the bronchial stenoses was not pursued. The patient was managed medically with adjustment of non-invasive ventilation settings, and supplemental oxygen. The patient's high risk of aspiration due to bulbar weakness, decreased clearance of secretions, as well as continuous G-J feeds, posed additional challenges when managing his high ventilation pressures and necessitated careful consideration of the risks and benefits of this strategy along with the patient's caregivers.

Challenge Point: The patient developed sleep disordered breathing, with high pressure support requirements out of keeping with his underlying neuromuscular condition and more suggestive of a stenotic airway.

Learner Reflection:

1. What are common respiratory complications of neuromuscular disorders in children?
2. How do we manage these complications?
3. What are the advantages and disadvantages of dynamic airway evaluation in children?

Case Progression:

At 8 years old, he began treatment with nusinersen when this treatment became commercially available for SMA. He received a total of 8 doses. He showed a modest improvement in his Hammersmith Functional Motor Scale Extended (HFMSE) from the baseline of 6 to 9/66 after his first year of therapy. At 9 years old, he was able to remain sitting with one hand used for support and he could roll from his back to his side and flex both hips while supine. The patient passed away at 10 years of age from respiratory failure.

Discussion:

We present the complex case of a patient with VACTERL association, SMA, and pulmonary stenosis. Evaluation of the tracheobronchial system should be considered for all children with VACTERL association who present with respiratory symptoms. Longer-term complications of TEF can include tracheomalacia, TEF recurrence, esophageal stricture, and gastroesophageal reflux disease.[9,10] Congenital tracheal stenosis[5] and bronchial stenosis[6] have been reported in two infants with VACTERL association. There should be a low threshold for investigation when patients with VACTERL association present with persistent or severe respiratory symptoms.[10] Our patient differed from the prior cases as he did not require overnight ventilatory support until 2 years of age and did not show overnight desaturation until 7-1/2 years of age. His clinical presentation was further complicated by his diagnosis of SMA.

Concomitant neuromuscular diseases can present a challenge when evaluating respiratory dysfunction. Patients with progressive neuromuscular disorders demonstrate decline in respiratory status with time. Ineffective cough, weak accessory muscles leading to nocturnal hypoventilation, and sleep-disordered breathing are common.[11] Due to imbalance between respiratory muscle strength and increased respiratory load from scoliosis and chest wall deformities, patients with neuromuscular disorders are at risk for respiratory failure.[12] Specific diseases can show a predilection for specific respiratory muscles. Infants and children with an untreated, severe form of SMA show prominent intercostal muscle weakness with accompanying paradoxical abdominal breathing.[13] In SMA, diaphragm function appears to be relatively spared.[14] Neuromuscular diseases such as Duchenne muscular dystrophy show preferential weakness of expiratory muscles and diaphragm involvement while collagen 6A-related congenital muscular dystrophies may show a restrictive pattern of respiratory weakness resulting from more severe diaphragm weakness.[8] Sitting versus supine forced vital capacity (FVC) testing can be particularly helpful in this regard.[15]

Patients with neuromuscular disease are anticipated to have normal lung parenchyma and airway resistance, at least early in their presentations.[11] The high inspiratory pressure requirements in our patient to overcome his stenotic airway would not be expected in neuromuscular respiratory dysfunction. The anatomic lesion observed also explains the ventilator dysynchrony observed in our patient. Ultimately, both airway and

ventilation issues need to be considered when complex patients present with respiratory dysfunction. In patients with underlying genetic syndromes and neuromuscular conditions, the described specific clinical patterns of respiratory dysfunction combined with polysomnogram data and imaging findings can help clarify the etiology of respiratory dysfunction, and guide management options.

Figure / table legend:

Figure 1

CT of the chest at 7-1/2 years old demonstrates: (A) narrowing of the right mainstem bronchi (RMB) compared to the right pulmonary artery (RPA) as well as the (B) left mainstem bronchi (LMB). CT reconstruction frontal (C) and superior view (D) confirm RMB and LMB narrowing.

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