Hospitalists Should Have Increased Suspicion for Primary Ciliary Dyskinesia in Patients With Congenital Heart Disease

Case: An infant boy with a prenatal diagnosis of congenitally corrected transposition of the great arteries (CC TGA, also known as L-transposition) was born at an outside hospital. Delivery was at term and via cesarean delivery for nonreassuring fetal heart rate. He was the first infant of a 22-year-old mother with no family history of heart disease, and the delivery was otherwise uncomplicated, with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. He was admitted to a NICU for observation, where he was noted to desaturate to 80% oxygen saturation when agitated. The care team chose to electively intubate, start him on prostaglandin E, and transfer to a tertiary care children’s hospital for further evaluation.

On arrival, the patient had a white blood cell count of $18 \times 10^3 / \mu L$ with 76% neutrophils and 14% lymphocytes, a hematocrit of 55%, normal chemistry values, and a capillary blood gas analysis showing a pH of 7.4 and PCO$_2$ of 41. He was stable on the ventilator with saturations in the high 90s on 30% fractional inspired oxygen content. Chest radiography showed clear lungs and mild cardiomegaly. At this point, it was presumed there must be additional occult cardiac lesions in addition to the CC TGA leading to the infant’s hypoxia.

Question: What other cardiac conditions are associated with CC TGA, and what is the natural course of this anomaly?

Discussion: In CC TGA, the heart twists abnormally during embryogenesis, and the right ventricle supplies blood to the body instead of the left. It represents only 0.05% of all congenital heart diseases and is usually associated with other morphologic cardiac defects. The most commonly associated malformations are an interventricular communication (60%), obstruction of the pulmonary outflow tract (40%), and abnormalities of the morphologically tricuspid valve (90%). Another important consideration is that misalignment leads to abnormal position of the cardiac conduction system. Due to this, 10% of patients may have heart block at birth, with the risk increasing by 2% per year to a maximum of 30% with complete heart block by adulthood.1

However, in the rare isolated cases without other morphologic or conduction defects, infants are asymptomatic, until over many years, the weaker right ventricle pumping to the systemic circulation leads to heart failure. These patients may present initially with exercise intolerance. The presence of CC TGA alone is not considered an indication for surgery, but repair of associated malformations or a “double-switch” procedure to reroute the blood flow back to the morphologically appropriate ventricle will eventually be needed in most patients.
Case Continuation: An echocardiogram confirmed the CC TGA and identified a secundum atrial septal defect that was shunting left to right with a small patent ductus arteriosus. The electrocardiogram was normal with no heart block or arrhythmia. Cardiology consultations felt these minor lesions would not explain the infant’s desaturations; he was therefore weaned from prostaglandin E, extubated, and transitioned to the general pediatric hospitalist team for further evaluation.

The patient continued to have tachypnea, intermittent increased work of breathing, and oxygen requirement. On the fourth day of life, a chest radiograph showed right upper lobe atelectasis that progressively worsened to collapse of the right lung (Fig 1). He was started on acetylcysteine, albuterol, chest physiotherapy, and both right side-up and prone positioning with minimal improvement. He was noted to be afebrile but to have thick secretions and noisy breathing. Laboratory test results were pertinent for capillary blood gases showing pH of 7.4 with PCO₂ retention to 56, a normal white blood cell count of 11×10³/μL, and a negative respiratory viral panel by multiplex polymerase chain reaction from respiratory secretions. Pneumonia was suspected, and ceftriaxone and vancomycin were started; however, his symptoms did not improve over the next several days.

At this point, the differential diagnosis was broadened to include possible airway or vascular malformations. A chest computed tomography and magnetic resonance imaging scan with intravenous contrast showed atelectasis of the right upper and middle lobes but no tracheal or bronchial obstruction and no vascular rings or slings. Abdominal sonogram showed the liver, kidneys, and spleen to be within normal size range and in the normal positions. Otolaryngology and pulmonology were consulted for bronchoscopy to further attempt re-expansion of lung, assess airway anatomy, and obtain culture and biopsy specimens. Bronchoalveolar lavage fluid was sent for culture, fungal culture, pertussis, and Pneumocystis testing; the results were all negative. Ultimately, pathology from a nasal biopsy specimen showed cilia with defective inner dynein arms and microtubular disorganization, confirming a diagnosis of primary ciliary dyskinesia (PCD) (Fig 2).

Question: What is the relationship between PCD and congenital heart disease?

Discussion: Defects in motile cilia, grouped under the term “primary ciliary dyskinesia,” lead to impaired airway clearance and recurrent lung, ear, and sinus infections. PCD is believed to affect 1 in every 10 to 20,000 persons, which is likely an underestimate. Although symptoms begin in infancy, the disease is often missed because of overlap with common childhood illnesses and because definitive diagnosis can be challenging. Approximately 50% of affected patients will also have mirror-image position of the thoraco-abdominal organs (situs inversus totalis) because motile cilia help to determine laterality in the developing embryo. When coupled with sinusitis and bronchiectasis, this phenotype is known as Kartagener syndrome. In the remaining PCD patients, there may be no rotational defects (situs solitus) or there may be a gradient of less extreme rotational defects with only 1 or a few organs affected (situs ambiguous). Cardiologists frequently use the term “heterotaxy” to describe certain cardiac lesions associated with extracardiac anomalies such as asplenia or a midline liver. Heterotaxy and situs anomalies occasionally overlap, although the terms are not interchangeable, and the terminology can be confusing. Isolated corrected transposition, as in our patient, is considered a mild form of heterotaxy in which the heart is the only affected organ.

Although it makes sense, cilia defects could lead to abnormal rotation of the embryonic heart; historically, PCD has not been associated with a higher risk
of congenital cardiac disease. In 1976, an 18-year-old male, thought to have Kartagener syndrome due to recurrent respiratory infections and an affected sibling, developed heart failure; on autopsy, the patient was discovered to have situs solitus and corrected transposition, similar to our patient. The authors felt congenital heart disease was “uncommon” in Kartagener syndrome, and found only 5 other cases in the literature, 2 of which also had transposition of the great vessels as 1 of several defects. Since that time, an 8-year old girl with dextrocardia, corrected transposition, ventricular septal defect, and pulmonary stenosis and a 14-year old boy with dextrocardia, corrected transposition, and atrial septal defect were the only similar cases reported.

In 2007, a large retrospective review of 337 patients with PCD greatly added to our understanding of the interplay between cilia and the heart. In the subset of patients with heterotaxy, there was a 200-fold higher prevalence of congenital heart disease compared with the general population. Patients within this group who need to undergo cardiac surgery for their lesions also are known to have worse outcomes than patients with similar heart disease but without heterotaxy. Could it be that patients with heart disease and heterotaxy fare worse because they also have underlying ciliary dysfunction that leads to perioperative respiratory distress and infections? A recent study assessed 43 patients with congenital heart disease and heterotaxy for ciliary dysfunction by using video-microscopy of ciliary motion in nasal tissue, genetic analysis, and nasal nitric oxide (NO) testing; they found 42% had evidence of ciliary dysfunction. Taking together, these findings point to an increased need for echocardiography in patients with known PCD and increased PCD screening in preoperative heart disease patients. Broader distribution of this knowledge may lead to earlier diagnosis in patients such as presented in the current article.

Case Continuation: For further confirmation of diagnosis, the patient’s DNA was sent for sequencing analysis of 11 PCD-related genes. The results showed no mutations known to be associated with disease. He gradually improved on supportive therapy and was discharged from the hospital with oxygen, budesonide, albuterol, chest physiotherapy, and pulmonary follow-up. Parents were counseled on increased risk for infections and infertility.

Question: What should be done in terms of diagnosis and health maintenance counseling for children with suspected PCD?

Discussion: If PCD is suspected, the diagnosis can still be challenging. Commercial genetic testing is available but detects only 50% to 60% of cases. The most common gene mutations associated with the inner dynein arms and microtubular disorganization phenotype seen in our patient are in CCDC39 and CCDC40, neither of which was tested. Since the time of this case, these genes are now included in several available panels. Another potential aid to diagnosis is measurement of nasal NO production. Nasal NO values, in children aged >5 years with PCD, are often <100 nL/min, whereas levels in healthy control subjects are often >250 nL/min. Therefore, measurement of nasal NO is beginning to emerge as a screening test. The gold standard for diagnosis is nasal brush biopsy with electron microscopy to look for changes in cilia ultrastructure, but this process requires a specialized center, and results may be normal in up to 30% of patients with PCD.

When a biopsy is performed, defects in ciliary outer dynein arms are most commonly seen regardless of situs anomaly. However, because central apparatus and radial spoke defects do not occur in embryonic monocilia, they are never seen in situs ambiguous, which makes cases of PCD with situs anomalies have proportionally more outer dynein arms defects. Interestingly, this patient’s cilia had defects in the inner dynein arms with microtubule disorganization (Fig 2), and he had L-transposition but normal situs of the extracardiac organs.

This patient was also interesting given his extremely young age at presentation. As previously stated, diagnosis of PCD is usually delayed due to the nonspecific nature of symptoms while young, until lung damage builds up over time. It has been previously thought that lung disease occurs late in PCD. However, up to 80% of children with PCD have neonatal respiratory distress. Even in young infants, chest radiograph (Fig 1), high-resolution computed tomography, or infant lung function test results may show evidence of lung disease. Clinical suspicion should be raised when given a history with chronic wet cough, chronic nasal congestion, neonatal respiratory distress despite term gestation, persistent otitis media, bronchiectasis, or a laterality defect.

Early recognition and treatment before progression to bronchiectasis are ideal. No therapy to correct ciliary dysfunction at the cellular level exists. Patients
are treated similarly to those with cystic fibrosis, with regular airway clearance and aggressive treatment of upper and lower airway infections with antibiotics. Bronchodilators, hypertonic saline, and inhaled recombinant human deoxyribonuclease are also sometimes used. Patients far from major pulmonary centers should be directed to www.pcdfoundation.org for education and referrals.

In addition to education on respiratory disease, the families of newly diagnosed patients should receive counseling on the likelihood of infertility. Up to 50% of male patients with PCD will be infertile due to poor motility of sperm. Female patients have reduced fertility and higher risk of ectopic pregnancy. However, both male and female subjects with PCD have successfully had children.10 The variability in clinical expression will likely be better understood with future genetic research. For now, children with PCD should be encouraged to participate in all activities of normal daily living to their best ability.

**CONCLUSIONS**

PCD is a disorder of ciliary function. It causes impaired clearance in the airways and leads to recurrent lung, ear, and sinus infections. Although symptoms begin in infancy, the disease is often missed because of overlap with common childhood illnesses and because definitive diagnosis can be challenging. Approximately one-half of affected patients have the triad of situs inversus totalis, sinusitis, and bronchiectasis classically known as Kartagener syndrome. This case reports a patient who is both very young and whose corrected transposition is the sole manifestation of laterality defect. Clinicians should have increased suspicion for PCD in infants with respiratory findings and screen PCD patients for congenital heart disease.

**REFERENCES**