Update of Respiratory Tract Disease in Children with Primary Ciliary Dyskinesia

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Primary ciliary dyskinesia (PCD) is a rare genetic disease characterized by abnormal ciliary structure and function leading to impaired mucociliary clearance and chronic progressive sinopulmonary disease. Upper and lower respiratory tract manifestations are cardinal features of PCD. This review summarizes the current state of knowledge of respiratory tract disease in individuals with PCD and highlights the challenges in identifying and quantifying lung disease in very young children with PCD. No specific therapies are available to correct ciliary dysfunction in PCD. Treatment is not evidence based, and recommendations are largely extrapolated from cystic fibrosis and other conditions with impaired mucociliary clearance. There is a pressing need to develop and validate outcome measures, including patient-reported outcomes, that could be used to evaluate potential therapies in PCD. This review concludes with recommendations for clinical endpoints and outcome measures and a prioritized list of treatments to study in PCD clinical trials.

Keywords: primary ciliary dyskinesia; lung disease; outcome measure; patient-reported outcome; clinical trial

Primary ciliary dyskinesia (PCD) is a rare genetic disease characterized by abnormal ciliary structure and function. The symptoms of PCD are directly related to organs where ciliary motility is an important component of normal function. The respiratory tract, which has cilia present from the middle ear to the conducting bronchioles, is the defining organ system involved. Upper and lower respiratory tract manifestations are cardinal features of PCD and often present shortly after birth.

In this session, "Update of Respiratory Tract Disease in PCD," Dr. Scott Sagel from Children's Hospital Colorado and University of Colorado Denver School of Medicine began by summarizing our current knowledge about lung function and structure as well as chronic airway infection and inflammation in individuals with PCD. Dr. Stephanie Davis from the University of North Carolina followed with a presentation about the challenges of detecting and treating early lung disease in very young children with PCD. Dr. Paolo Campisi from the Hospital for Sick Children and the University of Toronto then provided an overview of the otolaryngologic manifestations of PCD. Dr. Sharon Dell, also from the Hospital for Sick Children and the University of Toronto, concluded the session by discussing the current approach to care and the need for evidence-based management strategies for patients with PCD. This article summarizes the presentations and highlights gaps in knowledge and areas in need of further investigation.

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OVERVIEW OF PCD-RELATED LUNG DISEASE: WHAT HAPPENS WHEN LUNG DEFENSES FAIL?

The onset of lung disease in PCD occurs early in childhood. The progression and severity of lung disease varies considerably among individuals with the condition. Although it is not clear how the basic defect in PCD leads to lung damage and respiratory failure, many would generally agree with the cascade of events depicted in Figure 1. We now recognize that mutations in cilia genes are the basis for defective ciliary function. This results in impaired mucociliary clearance, chronic airway infection and inflammation, and bronchiectasis.

Lower respiratory tract manifestations are cardinal features of PCD and often present in the first month of life (1, 2). The majority of patients with PCD present in the neonatal period with respiratory distress characterized by congestion, coughing, tachypnea, hypoxia, and infrequently respiratory failure that is generally attributed to "wet lungs," neonatal pneumonia, or transient tachypnea of the newborn (3, 4). Some of these children require hospitalization in a neonatal intensive care unit and oxygen therapy for a prolonged period (5). This suggests cilia play a critical role in clearing fetal lung fluid after birth. If a chest radiograph obtained in the newborn period reveals dextrocardia, situs inversus, or another laterality defect, PCD should be in the differential diagnosis to explain these findings and respiratory symptoms. Although most individuals with laterality abnormalities do not have cardiac defects, PCD is associated with an increase in the prevalence of heterotaxy with and without congenital heart disease (6). Chronic daily productive cough and nasal congestion are almost universal features of PCD. In comparison to cystic fibrosis (CF), individuals with PCD are frequently able to expectorate sputum at a younger age, presumably related to better preserved cough clearance in PCD (7). Children with PCD also present with a history of chronic bronchitis, recurrent pneumonia, and bronchiectasis.

Lung function may be normal during early childhood, but many children have varying degrees of airflow obstruction (2, 8, 9). Limited longitudinal data in PCD reveal that lung function remains relatively stable in a significant percentage of individuals but can decline over time (8, 10, 11). We need to better characterize changes in lung function in children and adults with PCD and identify risk factors associated with physiologic decline.

Radiographic abnormalities of PCD include peribronchial thickening, atelectasis, and airtrapping; these abnormalities lead to bronchiectasis (9, 12, 13). These findings typically occur in the middle and lower lobes, which can be a distinguishing feature from CF, where lung abnormalities more commonly occur in the upper lobes. Lobar or segmental atelectasis with associated bronchiectasis in the middle lobe seems to be a common occurrence in childhood (5).

Chronic airway infection begins in early childhood and is believed to be a leading cause of morbidity and mortality in PCD. The most common bacteria isolated in respiratory cultures from children and adolescents with PCD are oropharyn-

Figure 1. Proposed pathogenesis of primary ciliary dyskinesia lung disease.

geal flora, nontypeable *Haemophilus influenza*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. Older patients with more advanced lung disease are more commonly infected with *Pseudomonas aeruginosa* and nontuberculous mycobacteria (2). *P. aeruginosa* is infrequently isolated from respiratory cultures in childhood. Although there are no controlled trials examining the effects of antibiotic treatment in PCD, anecdotal evidence supports the use of antibiotics.

There are scant data available on lower airway inflammation in PCD. Examination of sputum collected from children with PCD reveals a predominantly neutrophilic inflammation (14, 15). Two studies demonstrate a remarkably similar degree of airway inflammation in small cohorts of PCD and subjects with CF (15, 16), despite the generally milder pulmonary phenotype observed in PCD. There is a need to investigate local and systemic inflammation in larger cohorts of children and adults with PCD and to carefully examine the relationships between airway infection, inflammation, structural lung injury, and functional impairment.

There are many unanswered questions related to the pathogenesis and manifestations of lung disease in PCD. It is unclear how different types of mutations (e.g., frameshift, missense, etc.) or mutations in different genes differentially affect the pulmonary phenotype and lung disease severity. We need to better understand the relationships between airway infection (individual pathogens and lung microbiome) and inflammation and disease progression in PCD. Virtually nothing is known about the nature and frequency of acute pulmonary exacerbations in PCD and how they relate to lung function decline or disease progression. Because nasal nitric oxide (NO) is decreased in PCD, there is rationale to determine whether strategies to augment airway NO levels could be of value in treating PCD lung disease.

In summary, lung disease is universal in PCD, whereas progression is variable. For the majority of individuals with PCD, the rate of lung function decline appears slower than in

CF (10, 11). Although some individuals die prematurely from respiratory failure as a result of PCD, many can live a near normal life span. Large cohort studies, preferably multicenter and international, are required to provide a better understanding of the natural history of PCD, including lung function changes over time, the prevalence of airway infection by age, and the influence of treatment on symptoms and indicators of disease severity.

DETECTING EARLY LUNG DISEASE IN YOUNG CHILDREN WITH PCD

Detecting early lung disease in PCD could lead to more aggressive management and improved prognosis. The challenges in evaluating these patients are diagnosing the disease, the lack of standardization in performing nasal NO measurements as well as determining abnormal values in this age group for normal subjects and those with non-PCD respiratory tract disease, obtaining quality lung function data, and acquiring and quantifying high-quality imaging data. There are scant published data in the youngest patients with PCD; therefore, more research is needed to better understand the early natural history of this disease.

Diagnosing the Disease and Nasal NO Measures

Diagnosing the disease proves challenging due to the difficulty in using clinical history as a criterion as well as the relative inability to use nasal NO in the youngest child. Patients with PCD have a classic history of recurrent otitis media, sinusitis, and respiratory infections. These symptoms are not uncommon in otherwise healthy young children, especially the infant or toddler who attends daycare. Unlike the school-age child, nasal NO values have been reported to be low in healthy infants, making it especially difficult to use this tool as a screen for diagnosing PCD (17). Early studies suggest that nasal NO measurements can be done during tidal breathing; however, this has not been standardized and further study is needed, as discussed by Leigh and colleagues in this symposium summary (18).

Lung Function Data

Due to the inability to cooperate, performing lung function tests in infants and preschoolers has unique challenges. Infant lung function testing requires sedation, specialized equipment, and an experienced team; therefore, these types of studies are only performed in a few medical centers (19, 20). Preschoolers are not sedated for testing but should be tested in a child-friendly setting with experienced technicians (21). Previous studies demonstrate that approximately 65 to 80% of children in this age group are able to perform acceptable spirometry (22, 23). Data in children less than 5 years of age with PCD have demonstrated diminished flows and volumes (24). In children 6 years of age and older, abnormal FEV₁ and FVC values are present early (11); these data highlight the importance of obtaining lung function data at a young age. However, based on the published data in CF, quality control and expert training in the performance of infant and preschool lung function testing may be required for specialized centers caring for the youngest population (20).

Imaging Data

Adequate CT images are needed to identify early structural changes, such as atelectasis/opacities, bronchial wall thickening, air trapping, and bronchiectasis. In the young child, unique challenges are present. Motion artifact may occur due to the infant's increased respiratory rate, leading to images that are

harder to interpret. To overcome this issue, controlled breathing must be instituted during the scanning (25); therefore, a specialized team performs the procedure, and the child is sedated. Radiation dosage must be considered, and recent protocols demonstrate that adequate images are possible with lower dosing specific for the special needs of pediatric patients (26). Due to recent evidence of early bronchiectasis that is not easily identified on chest radiographs (Figure 2), performing these scans on a routine basis may be indicated for more aggressive management.

In conclusion, the young child with PCD presents special challenges that should be considered when diagnosing and managing the disease. Irreversible disease begins early; therefore, identification is important to improve the overall prognosis.

OTOLARYNGOLOGIC MANIFESTATIONS OF PCD

The pseudostratified, ciliated columnar epithelium lining the middle ear, Eustachian tube, nasal cavity, and paranasal sinuses is susceptible to the same PCD-induced ciliary dysfunction observed in the lower airways. The clinical manifestations of PCD in the upper airways include otitis media with effusion, chronic rhinitis, and sinusitis. Although these clinical entities are common in the general population, the prevalence, persistence, and severity of symptoms is greater in patients with PCD.

Otitis media with effusion, the presence of middle ear fluid in the absence of acute inflammation, is considered the most common otolaryngologic manifestation of PCD, affecting up to 85% of children with PCD (15–40% prevalence in children without PCD) (27). The potential long-term implications of chronic otitis media with effusion include conductive hearing loss, delayed speech and language development, atelectasis of the tympanic membrane, and cholesteatoma formation. Among the general population, the management of prolonged otitis media with effusion is widely accepted as surgical and involves the insertion of ventilation tubes. In the setting of PCD, the management of otitis media with effusion with ventilation tubes is a source of considerable controversy. The European Respiratory Society Consensus Statement purports that “the use of ventilation tubes (grommets) should be avoided where possible” because ventilation tubes often result in prolonged and offensive otorrhea (27). The Consensus statement indicates

that the strength of this recommendation is “strong” yet the level of evidence is “low.” The evidence surrounding this issue has been thoroughly and critically reviewed by Campbell and colleagues (28). However, the evidence does not strongly endorse the recommendation against ventilation tube insertion.

The arguments for and against the use of ventilation tubes extend beyond the discussion of offensive otorrhea and include issues such as hearing outcomes and tympanic membrane health. According to Majithia and colleagues, spontaneous resolution of otitis media with effusion was expected in most children by the age of 12 years (29). However, it may not be appropriate to withhold ventilation tubes in children with mild to moderate levels of hearing loss for the first decade of life given the potential detrimental effect on speech and language development. Hadfield and colleagues reported the hearing outcomes in 30 children aged 1 month to 9 years (30). In this study, detailed audiometric (pure tone average) data were available for 12 children. Regardless of the management strategy (“watch and wait or hearing aid” versus “ventilation tubes”), the pure tone average was equal and in the expected normal range at 9 years. However, 8 of the 12 children were managed with ventilation tubes, and these 8 children had significantly more severe pretreatment hearing loss. In other words, the children treated with ventilation tubes had the best improvement in hearing at the end of the study. The available data on hearing outcomes in children with PCD suggest that ventilation tubes may be appropriate in children with severe pretreatment hearing loss.

Chronic rhinitis and sinusitis are other otolaryngologic manifestations of PCD that significantly affect quality of life. Patients report abundant nasal secretions and congestion (31). Nasal polyps are found in around 15% of patients with PCD (32). The European Respiratory Society Consensus Statement does not provide definitive recommendations for the management of rhinitis and sinusitis but suggests a role for saline nasal douches, prolonged antibiotic treatment, anticholinergics, and endoscopic sinus surgery (27). There is a paucity of literature concerning the surgical management of chronic sinusitis related to PCD. In fact, there is only one study that recommends conservative endoscopic sinus surgery that should be limited to the maxillary and ethmoid sinuses and osteomeatal complex (33). Any surgical intervention should be followed by saline rinses and topical nasal steroid sprays.

It is apparent from a review of the literature that further study is required to determine the appropriate management of conditions such as otitis media with effusion, chronic rhinitis, and sinusitis. Given the rarity of PCD, randomized prospective trials will only be possible with multicenter and possibly international collaboration.

THE CLINICAL APPROACH TO LUNG DISEASE IN PCD: IS THERE EVIDENCE?

There are no therapies that have been adequately studied to definitively prove their efficacy in the treatment of PCD. A number of high-quality, randomized, controlled trials of therapy have been published to help establish an evidence-based approach to care of the patient with CF (34). It is not surprising that treatments used for patients with PCD in clinical practice tend to be extrapolated from CF care.

CF medical management practices, which have some biological rationale for extrapolation to PCD, include the practice of daily airway clearance and drug therapies that address airway infection, inflammation, and impaired mucociliary clearance (34). In patients with PCD, antibiotics are used acutely with disease exacerbation and are directed toward treating bacteria

Figure 2. High-resolution chest CT image from a 3-year-old child demonstrating mild bronchiectasis (bronchial dilatation, signet ring sign) in bilateral lower lobes (arrows). Reprinted by permission from Reference 24.

grown in recent sputum cultures. Chronic suppressive use of antibiotics would be considered if a patient is repeatedly growing *P. aeruginosa* in the sputum. There are no data to recommend for or against agents that improve mucociliary clearance or reduce inflammation (such as inhaled corticosteroids or macrolide therapy) in PCD. The clinical utility of bronchodilators has not been demonstrated in PCD. Monitoring for progression of lung disease is also an important part of the regular clinic visit. This includes routine lung function testing and respiratory cultures and periodic lung imaging. Consideration should be given to obtaining a chest CT, instead of a chest radiograph, at the time of diagnosis because chest CT is the gold standard for diagnosing bronchiectasis (35). Chest CT has been used to monitor the progression of bronchiectasis in CF (36). There are no data supporting the clinical use of periodic chest CT scans in PCD. In clinical practice, the risk of increased radiation from a CT scan must be weighed along with the potential added structural information to decide whether or not to pursue follow-up CT scans.

Surgical options for PCD lung disease include segmentectomy, lobectomy, and lung transplantation. Lobectomy is generally not recommended for diffuse lung disease processes such as PCD or CF; however, the procedure has been shown to improve symptoms and to have low perioperative mortality in case series of selected patients with PCD (37) and idiopathic bronchiectasis (38, 39). One case series reviewing surgical treatment of bronchiectasis in children cautions that complete cardiologic evaluation should be conducted in patients with PCD because cardiac arrest and death occurred in three patients with PCD (40). Consideration for lobectomy should be limited to selected patients with severe localized bronchiectasis who fail medical management and should only be performed in centers with appropriate expertise (37). Lung transplantation is an option for severe end-stage lung disease (41). There are no published evidence-based clinical criteria for when to refer patients with PCD for lung transplantation. However, many transplant centers have developed their own referral criteria for end-stage lung disease, which include bilateral disease with disabling symptoms, severe functional impairment, oxygen dependency, and failure to respond to further medical or surgical management.

EVIDENCE FOR CENTER-BASED CARE FOR PATIENTS WITH PCD

Center-based care occurs when all patients with a particular chronic disease within a specified geographic region are cohorted together at a single center for disease management. A multidisciplinary “disease management” approach to chronic disease (CF, diabetes, asthma, and many others) is now well recognized to be the most successful strategy for improving patient outcomes (42). Centers need to be able to provide the five basic components of disease management: diagnosis, assessment, treatment, education, and follow-up (42). Other key elements for advancing disease management include research, performance measurement (measuring clinical and other outcomes), and quality improvement (audits of practice) (43). Dramatic improvements in survival (from age 7 to 37 years) and quality of life for patients with CF over the last 30 years can be largely attributed to the better treatment developed at major CF centers (44). When one considers that PCD is a chronic airways disease with many similarities to CF, including a similar (albeit slower) progression of lung function deterioration with age (2), the notion of a need for specialty “PCD Centers” seems worthy of consideration. In addition to improved clinical outcomes, disease-specific centers are generally regarded favorably

by patients and have numerous psychosocial benefits, including opportunities to meet other families and patients with the same rare disease and share experiences (45). Finally, major CF centers provide a natural infrastructure for the conduct of clinical research to further improve outcomes.

There is limited evidence from observational data that early diagnosis and management of patients with PCD in a specialized PCD clinic may improve long-term lung function outcomes (10). The PCD disease management approach reported in this study followed an algorithm very similar to the CF disease management approach (10). Therefore, it is reasonable to speculate that medical management in a specialized PCD diagnostic and treatment center will provide the PCD patient with the best chance for preservation of lung function over time.

MOVING FORWARD: DEVELOPING EVIDENCE-BASED MANAGEMENT STRATEGIES FOR PATIENTS WITH PCD

To study new therapies or management strategies for any disease, clinically meaningful, valid, and responsive outcome measures must be developed for the disease of interest. We have a paucity of information about clinically relevant outcomes in patients with PCD. There is a need to understand the measurement properties (e.g., average values, variation between and within patients, reliability, validity, and responsiveness) of existing respiratory outcome measures (e.g., pulmonary function measurements), identify the gaps in existing outcome measures, and develop new outcome measures that address these gaps. This will include more sensitive patient-reported outcomes (PROs) such as Health-Related Quality of Life (HRQL), early surrogate markers of lung disease such as the lung clearance index, and biomarkers of lung disease such as sputum inflammatory biomarkers. What we do know about PCD is that traditional outcome measures of lung health used in clinical trials, such as survival and lung function decline, are too insensitive to be used in short-term trials of therapy for patients with PCD. Recently, the Food and Drug Administration (FDA) released a Guidance on PROs, which advocates the use of psychometrically sound PROs in chronic disease conditions (46).

HRQL measures the impact of disease and treatments on patient’s daily functioning and adds unique information to standard clinical measures such as lung function. If we look to CF research networks, we can appreciate that the development and validation of a sensitive and responsive HRQL outcome measure has made the testing and approval of new therapies much more efficient (47). The CF Questionnaire Revised (CFQ-R) is a newly developed HRQL instrument for individuals with CF. Developmentally appropriate versions for children aged 6 to 13 years (CFQ-R child), parents of children aged 6 to 13 years (CFQ-R parent), and adolescents and adults 14 years and older (CFQ-R teen/adult) have been developed and validated (48, 49). Aztreonam is the first respiratory drug approved by the FDA based on “improvement in respiratory symptoms” as measured by the CFQ-R Respiratory Symptoms Scale (50). The CFQ-R has been tested for measurement properties within the PCD population and shows similar, if not worse, burden of disease compared with patients with CF (51). Efforts are underway by the Genetic Diseases of Mucociliary Clearance Consortium to rigorously develop a similar but PCD-specific HRQL measure that would be acceptable to regulatory bodies such as the FDA and Health Canada.

Well designed and executed clinical trials will eventually better inform our PCD management strategies. There are several necessary steps we must keep in mind that are inherent to the design of clinical trials. These include establishing accurate

diagnostic and phenotypic characterization of patients; developing sensitive, valid, and responsive outcome measures within the PCD population; developing multicenter collaborations for recruitment of patients with a rare disease; establishing patient advocacy groups; identifying “out of the box” funding strategies; and developing new therapeutic strategies. Many of these steps are being addressed in parallel through national and international research and stakeholder collaborations.

FUTURE DIRECTIONS

In a breakout session entitled “Optimizing clinical care of PCD patients and developing clinical research networks to test therapies through clinical trials,” a working group discussed the following topics: (1) defining standards of care in PCD, (2) prioritizing treatments for clinical trials in PCD, (3) defining clinical endpoints and outcome measures to include in PCD clinical trials, and (4) identifying barriers that need to be addressed before embarking on PCD clinical trials.

For the first topic, defining standards of care, we did not formulate specific treatment recommendations. For the most part, we agree with the European Respiratory Society consensus statement on the lower airway management of children with PCD, which recommends routine airway clearance, antibiotic treatment for acute respiratory infections or worsening respiratory symptoms, consideration of suppressive inhaled antipseudomonas antibiotics for patients chronically infected with *P. aeruginosa*, and consideration of inhaled mucolytic therapies (27). Our working group concluded that individuals with PCD should be evaluated at least twice annually at centers specializing in PCD diagnosis and treatment, akin to the CF Care Center model. In terms of prioritizing therapies to consider for initial clinical trials in PCD, we identified the following treatments to study (in order) (1) inhaled antibiotics (tobramycin, aztreonam) in patients with PCD with new or chronic *P. aeruginosa* infection, (2) prophylactic oral “immunomodulatory” antibiotics (azithromycin, trimethoprim-sulfamethoxazole) in children with PCD, and (3) inhaled “mucoactive” therapy (hypertonic saline, rhDNase, mannitol) in children and adults with PCD. Our group acknowledged the paramount importance of identifying endpoints and outcome measures that could be used to demonstrate the efficacy (or lack thereof) of potential therapeutic agents in PCD. To this end, we compiled a list of potential clinical endpoints and outcome measures to consider for PCD clinical trials (Table 1). Regarding the last topic, we identified several barriers that need to be addressed as we move forward with performing clinical trials in PCD. These barriers include the need for a PCD patient registry, the need to cultivate international collaborations and possibly establish an international clinical trials network to enhance patient recruit-

ment and enrollment into clinical trials, and the critical importance of identifying funding mechanisms (NIH, industry) to support clinical trials in a rare disease like PCD.

CONCLUSIONS

Chronic upper and lower respiratory tract manifestations that begin early in childhood are cardinal features of PCD. Evidence is lacking as to how best to treat and manage children and adults affected with PCD. There is a pressing need to perform clinical trials to determine which therapies can reduce respiratory symptoms, restore or maintain lung function, and improve quality of life in individuals with PCD.

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TABLE 1. POTENTIAL CLINICAL ENDPOINTS AND OUTCOME MEASURES TO INCLUDE IN PRIMARY CILIARY DYSKINESIA CLINICAL TRIALS

Lung physiology: spirometry, lung volumes, mucociliary clearance, lung clearance index
Physical capacity: 6-min walk test
Patient-reported respiratory symptoms: health-related quality of life surveys, cough scores
Clinical course: pulmonary exacerbations, frequency of antibiotics
Microbiology: presence and emergence of pathogens (culture-based detection, microbiome assessment), bacterial density
Inflammation: local (sputum, exhaled breath, exhaled nitric oxide) and systemic biomarkers of inflammation
Radiology: chest CT scans (qualitative and quantitative assessments)
Otolaryngologic: symptom scores of rhinosinusitis (e.g., sinonasal outcome test)

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