

The Primary Ciliary Disorders: Underdiagnosed and Undertreated

Jane Braverman, PhD; Barbara Stewart, MD

"Primary ciliary dyskinesia is a prototypical example of a condition in which poorly functioning cilia contribute to the retaining of secretions and recurrent infections that, in turn, lead to bronchiectasis... Enhancing the removal of bronchial secretions in bronchiectasis has been shown to be useful... Traditional chest clapping or cupping has largely been replaced by the use of inflatable vests... applied to the chest."

Alan F Baker, Bronchiectasis. N Engl J Med 2002; 346 (18): 1383-1393

Medicine is replete with examples of diseases hidden in plain sight. A broad array of inherited abnormalities of ciliary structure and function fall into this category. The primary ciliary dyskinesias (PCD), disorders which were previously little-known and poorly understood, are rapidly gaining recognition as an important cause of chronic, refractory childhood ear, nose, throat and respiratory infections and of progressively deteriorating pulmonary health.^{1,44} Increasingly, unexplained bronchiectasis is now attributed to untreated PCD.^{2,31,32}

In order to make a correct diagnosis, physicians must be aware of the disorder, maintain a reasonable level of suspicion for its occurrence, recognize its symptoms and have access to appropriate diagnostic tools. An explosion of research in molecular genetics, macromolecular analysis and imaging have expanded knowledge of the structure, biochemistry and physiology of both healthy and abnormal cilia. In addition, there is a body of longitudinal data to demonstrate the health consequences of ciliary dysfunction.^{9,17,25,26,42} Awareness of the disorder has led alert physicians to consider PCD in the differential diagnosis of persistent, frequent sino-respiratory symptoms in infants and young children.^{5,10,14,15,17} Sophisticated diagnostic tools, most notably tracheal biopsies evaluated with transmission electron microscopy and genetic tests, have

permitted definitive diagnoses.^{19,25,28,37} A definitive diagnosis includes evidence of specific ultrastructural defects and a compatible genetic phenotype.^{13,43} Following the hugely successful "centers of excellence" model pioneered by cystic fibrosis (CF) physicians, PCD testing resource centers are growing in number.^{4,5} Their experience suggests that PCD prevalence figures, currently estimated at one case per 15,000 individuals, may represent only the tip of an iceberg. Some authorities suspect that as many as one person in 1,500 may be affected.⁵ Unsurprisingly, cases of PCD cluster around medical specialist centers that have the knowledge and facilities to diagnose the condition.

History

In 1901, a German physician, A Oeri, described the first case of advanced lung disease, or bronchiectasis, associated with the anatomical variation known as *sitis inversus*, in which the thoracic and abdominal organs are positioned in mirror image to the typical arrangement.^{1,42} Three years later, Dr A.K Siewert reported on a patient who also exhibited chronic sinusitis. In 1935, as more cases were seen, Dr. A. Kartagener described a series of four patients who presented with male infertility in addition to the previously described triad, *sitis inversus*, severe, refractory sinusitis and bronchiectasis. Subsequently, this clinical pattern was recognized as a distinct disease entity, eponymously called "Kartagener's Syndrome" (KS). Although *sitis inversus* appeared to be rare, Kartagener's description raised awareness of the condition, resulting in the recognition of quite a number of new cases. Currently, KS is classified as a subtype of a spectrum of inherited disorders characterized by dysmotility (primary ciliary dyskinesia, or PCD) or immotility of the cilia (immotile cilia syndrome, or ICS). Interestingly, only 50% of persons with *sitis inversus* also have dysmotile cilia.⁴

Etiology and clinical manifestations

PCD is the most common variant of a constellation of recessive heritable disorders characterized by defects in the structure and function of all ciliated cells throughout the body. The assortment and severity of clinical manifestations vary greatly depending upon the nature of the abnormality.^{4,6,20,25,28,37}

Jane Braverman is Director, Clinical Programs, RespirTech, St Paul, MN; Barbara Stewart is with the department of Pediatric Pulmonology, St Joseph's Children's Health, Phoenix, AZ.

Respiratory complications associated with inadequate secretion clearance in upper and lower airways are the major source of pathology in this population.^{23,25,37} Although other important mechanisms - alveolar clearance and cough - remain intact, stasis of airway secretions is manifested as chronic sinusitis, otitis media, nasal polyposis and recurrent respiratory infection. Over time, following a pattern similar to that seen in cystic fibrosis (CF), the accumulation of mucus in PCD lungs promotes bacterial colonization, setting in motion a vicious cycle of atelectasis, impaired gas exchange, increasingly antibiotic-resistant exacerbations, mucus plugging and ultimately irreversible lung damage.²⁶ Other clinical features may include male infertility, hearing loss, visual deficits, congenital heart disease, renal dysfunction and, less commonly, central nervous system involvement including hydrocephalus and joint pathology.^{4,7,18,37}

The consequences of untreated PCD are cumulative and devastating.^{29,31,32} Chronic illnesses, frequent hospitalizations, decreased quality of life, and progressive pulmonary decline are the norm. Individuals with PCD are frequently colonized with antibiotic-resistant organisms including those considered to be normal oral flora that have now colonized the airway because of inability to clear organisms from them effectively. Consequently, patients experience an array of febrile illnesses. A large proportion develops bronchiectasis. Increasingly, those with advanced disease are referred for lung transplantation.²⁵

Importance of early diagnosis

“Early recognition and treatment of respiratory infection, as well as chest physical therapy and postural drainage, have done more than anything else to reduce the morbidity and mortality of immotile cilia syndrome.”⁴²

Recent evidence has shown that neonatal respiratory distress is a common clinical presentation of PCD.^{5,10,14,15} Full-term neonates who develop respiratory distress or persistent hypoxemia or who have *sitis inversus* or an affected sibling should be screened for the condition.^{14,15} Increasingly, PCD is diagnosed retrospectively in older children whose histories show transient respiratory distress during the newborn period and have subsequently developed persistent cough or chronic otitis media.^{5,36,37} Numerous studies demonstrate a correlation between late diagnosis and poorer outcomes:

- In a longitudinal study of 24 PCD patients (12 adults and 12 children 7-18 years of age) with mild to moderate pulmonary impairment who adhered to standard protocol of twice daily physiotherapy and antibiotics as needed, lung function at baseline was significantly lower for those who started therapy as adults. (forced vital capacity FVC 70% vs 85% predicted; forced expiratory volume in one second (FEV₁) 59% vs 72% predicted). Bronchiectasis was found in 2/12 children and 6/12 adults. Most patients remained stable on the protocol. Results suggest that 1) lung damage begins early in life and will progress without treatment; 2) lung function can be maintained with aggressive physiotherapy and prompt treatment of infections and 3) early diagnosis and treatment have a strong impact on outcomes.⁹
- Several reports have shown extensive atelectasis and pneumonia in neonates diagnosed subsequently with PCD. Evidence suggests that ciliary dysfunction is critical for effective clearance of fetal lung fluid; infants with PCD fail to

rapidly and fully transition to air breathing. Undiagnosed infants are at high risk for progressive pulmonary disability and possible respiratory failure.^{4,10,14,15}

- In 47 children aged 1-15 with recurrent or chronic refractory respiratory infections undergoing nasal biopsies evaluated with transmission electron microscopy (TEM), 13 were diagnosed with PCD. Earlier diagnosis and treatment may have modified their lung damage.¹⁷

Mechanisms of disease

“Since patients with PCD are unable to clear secretions ... by mucociliary transport, they are totally dependent on ancillary clearance mechanisms ...”³⁵

The importance of normally beating cilia to maintain healthy airways is well-recognized in both CF and PCD.^{3,16,25,26} Although effective ciliary function is innately absent in PCD and is merely disabled by an excess burden of thick secretions in CF, both conditions result in serious chronic respiratory disease.^{26,31,33} While each condition has unique features, the pathogenesis of respiratory tract disease – prevalence of lung infection, contributing pathogens, longitudinal declines in pulmonary function and development of bronchiectasis- is similar. However, there are also considerable differences between PCD and CF. Persons with PCD are more likely to spike fevers and be more frequently diagnosed with pneumonia than those with CF. In contrast to infants and toddlers with CF, those with PCD have a higher prevalence of high spiking fevers and draining ears.^{5,43} Despite a delayed clinical course, PCD and CF patients have similar end-stage disease patterns and, as an alternative to death from respiratory failure, are faced with lung transplantation as a final option.^{25,26}

A number of factors may explain differences in the natural history of PCD versus CF:

Variable cough efficacy

Cough is the default mechanism for airway clearance in patients with impaired MCC.^{3,6,24}

- In PCD airway surface liquid content is assumed to be normal, thus permitting more effective cough clearance.
- In CF, owing to a defect in chloride ion transport, the volume of airway surface liquid is markedly reduced. Secretions are correspondingly denser, making cough clearance more difficult.

Variable patterns of particle deposition and clearance

Lung health depends upon effective defense mechanisms to clear inhaled debris from the airways.^{3,16,24} Larger particles are cleared from the upper airways by triggering coughing and sneezing. Smaller particles are entrapped in mucus lining the lower airways and are removed by the unidirectional “escalator” effect of the mucociliary clearance (MCC) system. Finally, alveolar macrophages and other scavenger cells ingest very small particles not captured by the MCC. The longer foreign substances including bacteria and viruses reside in the airways, the greater likelihood of inflammation and infection. Studies comparing particle clearance in CF and PCD versus healthy subjects shows that:

- Compared to healthy controls, both subjects with PCD and CF demonstrated significantly prolonged retention of radio-labeled particles but had different distribution patterns.³³
 - 1) CF subjects showed an increased retention in smaller airways at 24 hours - consistent with typical patterns of CF lung pathology
 - 2) PCD subjects showed increased retention in larger airways at 24 hours -consistent with typical patterns of PCD lung pathology
 - 3) CF subjects showed clearance rate delay in smaller lung regions
 - 4) PCD patients showed clearance rate delay in larger airways
 - 5) An inverse relationship emerged between lung function and regional deposition of particles in CF and PCD subjects versus normal controls
- Compared with healthy non-smoking subjects, PCD subjects showed significant delay in clearance of experimentally deposited microparticles.³⁰
 - 1) In healthy non-smoking subjects 49±9 % of particles were cleared with a mean half time of 3.0±1.6 hours.
 - 2) In PCD patients, particle clearance was retarded and prolonged; 42±12% of particles were cleared with a mean half time of 16.8±8.6 hours

Clinical Implications

MCC function and therefore particle clearance is impaired in both CF and PCD. Differences in regional particle deposition and clearance rates may explain differences in patterns of lung disease and progression.^{9,30,33,38,39} In CF patients, whose secretions are very thick and tenacious, alveolar and cough clearance mechanisms are considerably impeded in the small, lower lung airways; prolonged regional particle retention may contribute to the predominately lower lobe pathology characteristic in CF.^{24,26} In contrast, in PCD the physical qualities of airway secretions are normal, permitting alveolar and cough effects to move secretions from the tiniest passages even in the absence of ciliary movement.^{3,26} The prolonged retention of particles in the larger, upper airways in PCD result in prolonged regional exposure to bacteria and viruses and may account for the greater prevalence of upper respiratory illness in pre-bronchiectasis patients and the correspondingly slower rate of lung deterioration.^{30,33}

Treatment

“Unfortunately, no specific therapeutic modalities are available to correct the ciliary dysfunction [in PCD]... Consequently, treatment focuses on facilitating the clearance of retained mucus secretions from the respiratory tract.”¹⁰

PCD treatment is closely modeled on CF care paradigms.²⁶ The therapeutic goals are to control symptoms, maintain lung health and prevent or delay the onset of bronchiectasis. Accordingly, care plans include prompt intervention for acute exacerbations with administration of antibiotics to suppress microbial load, management of underlying conditions, reduction of excessive inflammatory response and, most importantly, promotion of

effective secretion clearance.^{4,12,26,34,43} Aggressive daily airway clearance therapy (ACT) is the “cornerstone of treatment” for both CF and PCD, but the higher prevalence of early morbidity in PCD demands an even more rigorous treatment plan.^{34,42,43} Because ACT benefits are diminished if treatment is deferred until the development of irreversible lung disease, therapy should be begun at the time of diagnosis.^{15,42}

High-frequency chest compression therapy: Standard of Care

“High frequency chest compression (HFCC) ...technology has proven to be the most effective way to remove mucus from the lungs of patients with CF and many other lung diseases.”⁴¹

High-frequency chest compression (HFCC) therapy is recognized as a *standard of care* ACT for patients with ineffective MCC. Its importance as a treatment modality is based upon a significant body of peer-reviewed research and more than a decade of clinical experience.⁸ Since its introduction in 1988, HFCC has gained rapid acceptance and widespread use. Currently, it is used by more than 70% of American CF patients.

HFCC is the most logical choice of therapy for patients with PCD and CF because it accelerates the rate of secretion clearance from both peripheral and central airways. By reducing exposure to excess mucus and to inhaled particulate matter, inflammation, infection and bacterial colonization are less likely to occur.

Several studies show increased rates of tracheal mucus clearance with HFCC:

- In 9 anesthetized dogs receiving HFCC at frequencies of 3 to 17 Hz, tracheal mucus clearance rate (TMCR) was determined by direct observation of the rate of displacement of a charcoal particle spot by means of a fiberoptic bronchoscope. Baseline TMCR during spontaneous breathing averaged 8.2 ±5.6 mm/min. The TMCR during 2 min of HFCC was increased at 5, 8, 11, 13, 15, and 17 Hz. The enhancement of clearance was most pronounced in the range of 11 to 15 Hz, reaching a peak value of 340% of control at 13 Hz.²¹
- A comparison of TMCR in anesthetized dogs during spontaneous breathing (SB) showed that high frequency chest compression (HFCC) enhances tracheal mucus clearance when compared with spontaneous breathing, *whereas high-frequency oscillation (HFO) at the mouth does not*. Rate of displacement of a charcoal marker in the lower trachea was observed by fiberoptic bronchoscope. Mean TMCR with HFCC was 240% of control (p = < 0.001) and 76% of control with HFO/AO (NS).²²
- To investigate whether increases in TMCR in dogs during high frequency chest wall compression (HFCC) is due, in part, to the expiratory bias in peak flow rate (VE/VI greater than 1) that occurs during HFCC, TMCR in 8 anesthetized, spontaneously breathing dogs was studied by comparing several randomized maneuvers designed to assess that effect. TMCR determined by direct bronchoscopic visualization of charcoal particle transport showed clearance rates during HFCC at 240% of rates obtained during spontaneous breathing (p = < 0.001), and that rates were influenced by expiratory flow-rate bias.²⁴

HFCC promotes secretion clearance in peripheral as well as central airways:

- To investigate the effect of high frequency chest compression (HFCC) on clearance of secretions from peripheral lung regions, 5 anesthetized, spontaneously breathing dogs received 30 minute treatments of HFCC at 13 Hz & cuff pressures at 50-60 cm H₂O. Correlations between peripheral mucus clearance indices (PMCI) and tracheal mucus clearance rates (TMCR) in two outer peripheral regions located under the cuff were statistically significant (13.0 ± 2.6 ; $p = < 0.05$); lower-middle outer peripheral region (9.1 ± 3.0 ; $p = < 0.05$). Overall, HFCC enhanced both central and peripheral mucus clearance.¹¹

Summary

The inherited dyskinetic ciliary disorders, including PCD, are an important cause of chronic respiratory illness and declining pulmonary health. In PCD, secretion retention is a direct cause of pulmonary deterioration. To prevent a growing burden of debilitating, costly respiratory illness, appropriate diagnostic screening and care plans are urgently needed. Consistent, effective removal of airway secretions is a critical component of every PCD treatment regimen. HFCC is an established "standard of care" therapy used widely for patients with absent or defective airway clearance mechanisms. It is the only ACT shown 1) to move secretions from smaller to progressively larger airways and; 2) to significantly increase tracheal mucus flow above rates achieved during spontaneous breathing. HFCC contributes to reduced morbidity, better survival and dramatically improved quality of life. PCD is a complex, multi-system disorder with serious complications arising from delayed clearance of particle-laden respiratory tract secretions. HFCC therapy provides a practical, effective, evidence-based intervention.

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