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Primary Ciliary Dyskinesia

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INTRODUCTION

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous recessive disorder of motile cilia associated with respiratory distress in term neonates, chronic oto-sino-pulmonary disease, male infertility, and organ laterality defects in ~50% of cases (1-4). This syndrome was initially recognized based on the triad of chronic sinusitis, bronchiectasis, and situs inversus (Kartagener syndrome) (5) and Afzelius later recognized that these patients had “immotile” cilia and defective ciliary ultrastructure (6). Over time, it was recognized that most patients had stiff, uncoordinated, and/or ineffective ciliary beat, and “primary ciliary dyskinesia” was used to distinguish this ciliary genetic disorder from secondary or acquired ciliary defects.

Even though PCD has an estimated incidence of 1 per 10,000–20,000 births, based on population surveys of situs inversus and bronchiectasis (7, 8), it is difficult to determine the prevalence of PCD in the United States, largely due to sub-optimal diagnostic approaches (9). Further, many physicians do not appreciate and recognize the key clinical features, particularly in infants and children; however, recent advances in defining the clinical phenotype are likely to increase the level of awareness for PCD (10, 11). Moreover, better

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definition of genotype/phenotype will also facilitate recognition of the early onset and severity of clinical disease in children with PCD (2, 4, 11, 12).

Laboratory diagnostic capabilities have recently benefited from the development of nasal nitric oxide (nNO) as a new test for PCD (13). Analysis of ciliary ultrastructure is improving; however, we now recognize that ~30% of PCD patients have normal ciliary electron micrographs (EMs), which precludes diagnosis by ciliary EMs. Genetic testing is also becoming feasible, as there are now 35 genes with PCD-causing genetic mutations (14, 15), which likely accounts for ~70% of PCD.

There are no validated PCD-specific therapies, and the treatment of PCD has not been standardized; however, recently published PCD Foundation consensus recommendations on diagnosis, monitoring, and treatment of PCD provide guidelines for clinical care (15).

This article provides an overview of the rapidly evolving state-of-the-art for PCD, including a focus on the diagnosis and treatment of PCD, and a summary of the progress that promises to revolutionize the identification and treatment of patients with PCD (1-4, 11-15).

STRUCTURE AND FUNCTION OF MOTILE CILIA

Cilia are evolutionarily conserved organelles and motile respiratory cilia have a complex (9 + 2) axonemal structure to generate functional ciliary motility (16, 17). Motile cilia have microtubules comprised of α- and β-monomers of tubulin (17) (Figure 1). Outer and inner dynein arms are present along the length of the peripheral microtubules (doublets), and contain enzymes for ATP hydrolysis (16, 17). Nexin–dynein regulatory complexes (“nexin links”) connect the doublets, and radial spokes connect the doublets to the central pair for structural support during cilia bending (18). Mutations in genes necessary for the biogenesis of cilia, or genes encoding the axonemal structure and/or functional components of motile cilia, can result in PCD.

During early development, each cell in the embryonic ventral node contains a single motile cilium. This specialized cilium has 9 peripheral doublets and dynein arms, but lacks the central pair of microtubules (9 + 0 axonemal structure) (17). Functionally, this cilium has a rotary motion, which drives a vectorial movement and laterality of organ lateralization during embryogenesis (19). When nodal ciliary function is absent, organ lateralization is random. Mutations in genes that encode for components of the central apparatus (central pair, radial spokes) do not cause laterality defects (1, 14, 15).

In addition to motile cilia, most cells of the body have a single nonmotile (sensory or primary) cilium that has specialized receptors to sense the local environment, and that play a key role in planar cell polarity (20). Mutations in genes encoding proteins for sensory cilia cause disorders involving multiple organs (e.g., Bardet- Biedl syndrome, nephronophthisis, retinitis pigmentosa, and Joubert syndrome) (20).

The function of normal motile cilia is to clear mucus as well as bacteria and toxic substances from the conducting airways (21, 22). ATP hydrolysis in dynein arms induces sliding of adjacent axonemal structures, and generates the complex ciliary waveform in human airways

(16-18, 23). Several hundred cilia per cell beat in a coordinated fashion, which generates coordinated vectorial flow from planar orientation (24). The cilia beat in-plane, and the forward (power) stroke is more rapid and extends a bit higher into the mucus layer than the recovery stroke (23). Ciliary beating is regulated by multiple signaling molecules, including cAMP, cGMP, and NO (16).

ULTRASTRUCTURAL AND FUNCTIONAL DIAGNOSTIC TESTS

The diagnosis of PCD is delayed in both European and North American children (median age of diagnosis, 5.5 yrs. and 5.0 yrs., respectively) (1). Since most institutions do not have adequate resources for a rigorous diagnostic evaluation for PCD, referral to specialized centers may be beneficial. This certainly includes patients with situs inversus with any respiratory disease, or unexplained neonatal respiratory distress, as well as bronchiectasis without a defined etiology, and/or a family history of PCD. For adults, all males with abnormal spermatozoal movement should be evaluated for PCD, if they have respiratory symptoms. Several medical disorders and phenotypes may coexist with PCD, including complex congenital heart disease, laterality defects, retinitis pigmentosa, hydrocephalus, pectus excavatum, and scoliosis (1-4).

In the evaluation of patients with chronic respiratory disease, it is critical to identify phenotypic features that characterize PCD, as compared with other diseases (11, 15). Neonatal respiratory distress is a common feature (> 80%) and a useful marker of PCD (Table 1), particularly for infants or children who have not developed bronchiectasis, and represent special challenge for diagnosis (11, 15, 25, 26). Laterality defects are relatively specific for distinguishing children with PCD from other children with chronic respiratory symptoms. The early onset and persistence of respiratory symptoms may help distinguish PCD from disorders with more episodic respiratory symptoms (11, 12, 15). In PCD, the chronic nasal congestion and wet cough occur on a daily basis throughout the year. Chronic otitis media often appears in the first months of life, and is persistent, despite antibiotics and/or use of tympanostomy tubes (11, 12). If bronchiectasis is identified in a young child, and CF has been ruled out, PCD is highly likely (25-27). In summary, the typical clinical phenotype in PCD includes (1) neonatal respiratory distress, and/or (2) chronic, persistent lower respiratory symptoms (early onset and persistent wet cough), and/or (3) chronic, persistent upper respiratory symptoms (nasal congestion and otitis media), and/or (4) a laterality defect (situs inversus or ambiguus) (Table 1). Indeed, the presence of any two of these four hallmark clinical features provides a strong clinical phenotype for PCD, assuming that CF has been excluded (11, 15).

Electron microscopy (EM) to identify ciliary ultrastructural defects historically has been the test used to confirm a diagnosis of PCD, but this approach is no longer the sole “gold standard” for diagnosis, since at least 30% of PCD patients have normal ultrastructure (1-4, 14, 15). For PCD patients with ultrastructural defects, the majority involve the absence or shortening of outer dynein arms (ODAs; 38.5%), or an ODA defect in conjunction with an inner dynein arm (IDA) defect (10.5%) (Figure 1). Isolated IDA defects occur in only a small fraction of confirmed PCD (< 1%), and false-positive EM diagnoses are common with IDA defects (9, 28). Before an isolated IDA defect can be used to validate a diagnosis of

PCD, a ciliary biopsy for EM must be repeated when the nasal epithelium is healthy (28). Most validated IDA defects have associated central apparatus abnormalities (~14% of PCD), and these abnormalities occur in only 5–20% of cilia (Figure 1). Central apparatus defects associated with IDA defects include microtubular disorganization and transposition of outer doublets into the center of cilia cross-sections, and frequently reflect mutations in *CCDC39* or *CCDC40* (29, 30). Ciliary "disorientation" (misalignment of the central pair) is a secondary change, and is no longer used as a diagnostic ultrastructural feature (31). A few patients have absent, or only a few, cilia on multiple biopsies (oligocilia), and recent studies show that some of these cases reflect mutations in *CCNO* or *MCIDAS* (32, 33). A recent report suggested that ultrastructure of respiratory epithelia with "inclusions" of basal bodies, and microvilli and cilia, is a variant form of PCD (34), but follow-up studies in several of those patients demonstrate that these EM findings are not specific for PCD (personal communication, M. Leigh and S. Sagel). The limitations of EM testing of cilia was highlighted by the experience in our North American Rare Disease Consortium, where as many as 15–20% of the patients referred with a "confirmed" diagnosis of PCD (based on ciliary ultrastructure) had a false-positive diagnosis of PCD (35, 36). To optimize the use of ciliary EM for diagnosis, many EM cross-sections (multiple sections containing high quality images of at least 20 unique cilia), should be examined by experienced readers, using a quantitative approach to interpretation (9). EM analysis is more successful in biopsies from adults versus children, likely due to limitations in obtaining adequate "scrape" biopsies from narrow airways (35, 37). Acquired (secondary) ciliary defects result from airway damage, from recurrent infections, and can sometimes be difficult to differentiate from PCD. Finally, at least 30% of patients with a strong PCD clinical phenotype and low nNO have normal ciliary Ems. For example, a recent study demonstrated that 22% of 61 such patients have PCD-causing mutations in *DNAH11* (38). Thus, normal ciliary ultrastructure cannot rule out PCD.

Evaluations of ciliary motility from fresh biopsies of respiratory epithelium has been used to confirm a diagnosis of PCD, particularly in Europe. However, substantial limitations preclude reliance on this as the sole diagnostic approach. In this regard, "secondary" effects on ciliary function create problems and recognition of more subtle motility defects requires experienced investigators (18, 39). It is also now clear that standard light microscopic analysis is not sufficient, since many patients with PCD have ciliary movement (40). Even with high speed video microscopy (HSVM), there is overlap of ciliary beat frequency between PCD and disease control and normal subjects, and there is no standardized protocol for interpretation of HSVM (41, 42). There have been multiple approaches to try and improve accuracy of HSVM, but these modifications do not eliminate all of the limitations (43-45). A recent publication touted the use of "automated" identification of abnormal ciliary motion (46), but this approach has not been independently validated, and should not be used to diagnose PCD. It is also now clear through genetic testing that many forms of PCD have no, or only subtle, abnormalities of ciliary ultrastructure and/or beat frequency and waveform. Therefore, these biological assays of ciliary function are not sensitive to detecting the growing range of ciliary phenotypes in PCD.

Nasal nitric oxide (nNO) levels in patients with PCD are quite low (<77 nl/min), relative to normal values (range 125 to 867 nl/min; mean, 287 nl/min); thus, nNO can be a useful test

for PCD if performed correctly (1, 9, 13, 47). Nasal NO is measured by aspirating nasal air through a catheter placed at the opening of one nostril and analyzed by an NO analyzer (48). Exhaled air from the lower airways has a much lower concentration of NO than the nose; thus, maneuvers must be instituted to close the soft palate to limit contamination of nasal air by air from the lower airways (48). This approach has been validated in adults and children over 5 years of age (13, 49), but is less feasible in younger children. For infants and young children, one study measured nNO during tidal breathing (50); however, it should be noted that nNO values during tidal breathing are ~40% lower in healthy subjects than values obtained at plateau during palate closure. It is critical to recognize that low nNO levels are seen in some patients with CF (9, 13, 47). Therefore, CF needs to be ruled out by sweat testing or *CFTR* genetic studies if nNO is low. Because nNO values can be low during acute viral infections, acute sinusitis, and panbronchiolitis, measurements should be performed when respiratory status is stable, and confirmed on a separate day (1, 13, 15). Although nNO has previously been used in a limited number of specialized PCD centers, there is a growing number of these specialized Centers in North America (see PCD Foundation website, www.pcdfoundation.org). With standardization, and definition of appropriate cut-off values (13), nNO measurement is becoming more widely used as a diagnostic test for PCD (Table 1) (15).

Fluorescence-labeled antibodies have been used to demonstrate absence of cilia axonemal and cytoplasmic preassembly proteins, but only a few laboratories are using this approach (51, 52). Measurement of mucociliary clearance in the lung has been used in some cases, but is not reliable, because it is confounded by involuntary cough and bronchiectasis from other etiologies (53). There is no role for the nasal saccharine clearance test as a diagnostic method, because of multiple limitations in performance and interpretation of the test.

GENETIC TESTING FOR DIAGNOSIS

PCD is a Mendelian recessive and genetically heterogeneous disorder. Between 1999 and 2012, PCD-causing mutations were described in 14 genes (1, 2, 4, 14, 15). Since early 2012, there has been an explosion of genetic discovery, through exome sequencing, whereby PCD-causing mutations in 21 additional genes have been published (1, 2, 4, 14, 15) (Table 2). The vast majority (81%) of the mutations are loss-of-function changes (nonsense, frameshift, or defective splice-sites), and ~19% are conservative missense changes or in-frame del-dup. Based on studies of genetic mutations in PCD patients in our North American rare disease consortium, and a review of the published literature, it is estimated that ~75% of the mutations are private occurring in only one family/patient, but ~25% are seen in multiple unrelated families/patients (founder, or recurrent mutations). Mutations in 5 genes (*DNAH5*; *DNAH11*; *DNAI1*; *CCDC39*; *CCDC40*) are the most prevalent in PCD, and ~26% of these mutations are recurrent (14). There are also > 20 mutations that are associated with specific ethnic groups or geographical locations (4, 14). It is estimated that ~65-70% of patients with PCD can be identified as having two mutations in one of these 35 published PCD genes (14). The feasibility of testing a multi-gene panel of PCD genes at a reasonable cost is becoming a reality, as several CLIA approved labs and companies have recently begun to offer such services (see PCD Foundation website, www.pcdfoundation.org) (15). This type of genetic

testing will revolutionize the diagnostic approach in PCD, and lead to early identification and initiation of clinical monitoring and treatment.

The role of PCD-associated genes in normal ciliary biogenesis and function, and the effect of mutations on cilia structure and function, are detailed in several reviews (1, 2, 4, 14), and key points are summarized, here. There is strong correlation between mutations in specific genes and effect on ciliary ultrastructure (Table 2). Although most PCD-associated genes code for proteins in the ciliary axonemes, there are 10 PCD-associated genes that have a functional role in the cytoplasm in "preassembly" of the cilia components, and mutations in these genes lead to loss of both ODA and IDA (see Table 2). There is strong correlation between mutations in genes that lead to ultrastructural dynein arm defects and the development of situs abnormalities, but mutations in genes that code for central apparatus, radial spoke, or nexin link proteins are not associated with organ laterality defects. Genetic discovery has also provided opportunity to examine ciliary EMs from multiple patients with mutations in the same PCD-causing gene, which has allowed recognition of unusual changes, such as: 1) radial spoke genes, where as many as 80% of ciliary EM cross-sections are normal; and 2) IDA defects associated with microtubular disorganization, which may affect only 10% of ciliary cross-sections, and reflect mutations in *CCDC39* and *CCDC40* (29, 30). Except for *RSPH1* (54) (see below) biallelic loss-of-function mutations routinely lead to low nNO (<77 nl/min) (13). Pathogenic mutations in DNAH11 in patients with PCD with normal ciliary ultrastructure provides confirmation that PCD can occur in the absence of ciliary EM defects (38). Finally, the ciliary beat frequency in patients with mutations in some genes (e.g., *DNAH11*, *RSPH4A*, *RSPH9*, *RSPH1*) with mostly normal EMs can be normal (or higher than normal), and the waveforms can appear normal, or have only subtle defects (14).

Identification of genetic etiologies of PCD has uncovered unique genotype/phenotype relationships. PCD patients with mutations in *RSPH1* have milder disease with less neonatal respiratory distress (NRD; 50% versus usual 80%), later onset of clinical symptoms, subtle EM defects and changes in ciliary waveform, better FEV_1 (% Pred.) versus age-and gender-matched PCD patients with axonemal defects, and borderline (or normal) nasal NO levels (54, 55). The milder disease is thought to reflect some residual ciliary function associated with a partially intact radial spoke system (55). In contrast, PCD patients with mutations in *CCDC39* or *CCDC40* have more severe disease with a higher prevalence of neonatal respiratory distress, earlier onset and severity of clinical symptoms, lower BMI and worse FEV_1 than other PCD patients, as well as a greater extent of bronchiectasis (56). The mechanism of worse disease with mutations in *CCDC39* and *CCDC40* is not known, although we speculate that these genes may play some role in lung host defense that extends beyond ciliary function.

EARLY FEATURES OF CLINICAL DISEASE

The clinical features of PCD reflect defective function of motile cilia in the conducting airways, paranasal sinuses, middle ear (eustachian tube), and the reproductive tract, as well as specialized motile cilia in the ventral node during embryogenesis (1-4) (Table 1). Manifestations of PCD occur early in life, and the clinical phenotype gives strong insight

about the likelihood of PCD, based on systematic analysis of patients in our rare disease consortium (11).

The earliest manifestations of PCD occur in the neonatal period, as > 80% of full-term PCD neonates have respiratory distress. Signs include tachypnea and increased work of breathing, and affected individuals typically require supplemental oxygen for a few hours to weeks (12, 57). These infants are often diagnosed with transient tachypnea of the newborn or neonatal pneumonia, but the clinical presentation in PCD is quite different with: 1) later onset of respiratory distress (12 hours of age); 2) longer duration of required oxygen therapy; and 3) higher frequency of atelectasis and/or lobar collapse (57). This neonatal presentation of respiratory distress indicates that normal ciliary function plays a critical role in the clearance of fetal lung fluid at birth, although the mechanism is unknown. Unexplained respiratory distress and radiographic abnormalities, along with supplemental oxygen requirements in a full-term infant, should raise suspicion for PCD, particularly in neonates with situs inversus.

Infants and children with PCD typically have year-round wet cough and daily nasal congestion (rhinitis) starting soon after birth (1-4, 11). Chronic otitis media that causes temporary or permanent hearing loss and recurrent sinusitis are common. Sinusitis is sometimes not recognized in young children because radiographic imaging is not performed. Bronchiectasis occurs in some infants and preschoolers (12, 25-27). Chest computed tomography (CT) scans show various abnormalities, including atelectasis, mucus plugging, air trapping, and thickened airway walls (26, 27, 58). These respiratory manifestations overlap with other common early childhood diseases; thus, the diagnosis of PCD is frequently missed, despite the presence of typical clinical features, even when situs inversus is present. This lack of recognition of cardinal clinical features in PCD highlights the importance of education for many pertinent subspecialties, including neonatology, pulmonology, otolaryngology, and cardiology, as well as primary care.

LUNG DISEASE

Nearly all infants and children with PCD have a year-round daily wet cough, which compensates, in part, for defective mucociliary clearances. Despite the daily cough, infections occur in the lower airways, and there is age-dependent development of bronchiectasis, which is universal in adults with PCD (1, 12, 25, 47, 58).

Respiratory bacteriology of children with PCD is dominated by Haemophilus influenza, Staphylococcus aureus, and Streptococcus pneumonia (12). Unlike CF, children with PCD, including infants/preschoolers, also intermittently culture Pseudomonas aeruginosa, which evolves into chronic airway infection in teenagers and young adults with PCD (12, 47, 59). Many patients culture more than one type of bacteria in the same sample. Nontuberculous mycobacteria (NTM) are present in 15% of adults with PCD, but there is a lower prevalence in children (1, 15, 47).

In contrast to the perceptions of many clinicians, the severity of lung disease in children with PCD is substantial. Abnormal lung function develops early in life, as many infants and young children demonstrate abnormal airflow mechanics (60-63). The range of FEV1 in

PCD is quite heterogeneous at age 6–8 years, as some young PCD patients have obstructive airways disease that is worse than patients with CF at the same age. PCD patients have evidence of airflow obstruction in “small airways” (i.e., decreased maximum midexpiratory flow) and ventilation inhomogeneity, as measured through multiple breath washout (60-64). Cross-sectional and longitudinal data show that airflow obstruction worsens with increasing age (61-63). However, airways disease does not progress as rapidly in late childhood and early adulthood compared with CF, which may relate to preservation of cough clearance. One longitudinal study demonstrated that lung function remains stable in PCD patients who received regular monitoring and treatment (62).

Radiographic studies utilizing high-resolution chest CT show that lung disease in PCD begins in infancy or early childhood. Findings include subsegmental atelectasis, mucus plugging, air trapping, ground-glass opacity, and peribronchial thickening. Bronchiectasis can occur during infancy, and ~50–75% of older pediatric patients and nearly all adults with PCD have bronchiectasis with worse disease in the middle lobe and lingula, as well as basilar regions (25-27, 49, 58). Chest CT is more sensitive for detecting early lung disease in PCD, compared to lung function testing by spirometry (60). Magnetic resonance imaging of the chest may be as effective as chest CT in defining the extent and severity of lung disease in PCD, which is an intriguing option for longitudinal evaluation and research (65).

NONPULMONARY MANIFESTATIONS

Situs abnormalities are present in > 50% of pediatric patients, which may aid earlier recognition of PCD. Laterality defects reflect abnormal function of the specialized (9 + 0) motile cilium during embryogenesis (19). At least 12% of PCD patients have situs ambiguous, and these patients have a 200-fold increased probability of having structural congenital heart disease compared with the general population with heterotaxy (66-68). Indeed, some patients with situs ambiguous have heterotaxia syndromes, which include polysplenia (left isomerism) and asplenia (right isomerism). Taken together, these clinical characteristics demonstrate a strong association between defective cilia and congenital heart disease. Patients with heterotaxy and congenital heart disease have increased respiratory complications after cardiac surgery, which suggests that some of these patients may have PCD (69, 70). Studies in mice with mutations in motile cilia confirm that cilia are required for normal heart development (71).

Almost all men with PCD are infertile, secondary to dysmotility of spermatozoa, or rarely, azoospermia. A few men with PCD have adequate sperm motility and have fathered children (72). Females with PCD have impaired ciliary function in the fallopian tubes, which may lead to reduced fecundity and/or a history of ectopic pregnancies (73).

Pectus excavatum occurs in as many as 10% of patients with PCD, versus 0.3% in the general population (58). We and others have also reported a high prevalence of scoliosis (5–10%) in PCD (1); thus, PCD should be considered in patients with pectus excavatum and/or scoliosis and unexplained sinopulmonary disease.

MANAGEMENT OF LUNG DISEASE

Respiratory symptoms and lung disease in PCD begin early in life, and reflect defective mucociliary clearance, which is the key innate pulmonary defense mechanism (21). No validated PCD-specific therapies are available; therefore, therapies for PCD are extrapolated from other disease, such as cystic fibrosis and non-CF bronchiectasis, particularly as relates to antibiotic therapy and macrolides as anti-inflammatory agents (15, 74-78). A recent state-of-the-art publication provides consensus recommendations from the PCD Foundation for monitoring and management of lung disease in PCD (15). Clinic visits at least twice per year are recommended for monitoring lung function and respiratory microbiology, including NTM. Chest imaging studies are also indicated to periodically monitor the extent of disease. Preventive measures include infection control training and routine immunizations, as well as pneumococcal and influenza vaccines.

Multiple studies demonstrate that systemic antibiotics are effective at treating worsening respiratory symptoms (“exacerbations”) in CF and non-CF bronchiectasis, including some patients with PCD (76). Antibiotics should be chosen based on respiratory cultures. Unexpectedly, preliminary studies of inhaled antibiotics in non-CF bronchiectasis did not show benefit with respect to lung function, although there was a reduction of neutrophil elastase activity in sputum in some studies (78, 79). One controlled study (12-months long) of inhaled gentamicin in non-CF bronchiectasis demonstrated striking reduction in frequency of exacerbations, as well as reductions in the burden of bacteria and markers of pulmonary and systemic inflammation (80). It is noteworthy that one study in patients with non-CF bronchiectasis demonstrated high rates of eradication for patients who develop airway infection with P. aeruginosa (75).

Stimulation of chloride (and liquid) secretion by an inhaled P2Y2 receptor agonist has been reported to improve cough clearance of radiolabeled particles in a small study of adults with PCD (81). More recently, nebulized 7% hypertonic saline improved lung function and quality of life, and reduced antibiotic use in non-CF bronchiectasis in a three month study (82). The therapeutic concept is that stimulation of cough and increased hydration of airway secretions with hypertonic saline (or other osmotic agents) can benefit cough clearance. By analogy, hydrating airway secretions may benefit cough clearance in PCD, even though defective mucociliary clearance persists. Dornase alfa has not been shown to improve pulmonary status in non-CF bronchiectasis, even though it is beneficial in CF. Indeed, adults with non-CF bronchiectasis taking dornase alfa for 24 weeks experienced more pulmonary exacerbations and a greater decline in FEV1 compared with the placebo group (83).

Oral macrolides are clearly effective in CF through anti-inflammatory mechanisms, resulting in improvement in lung function and reduction in exacerbations. In non-CF bronchiectasis, similar data are emerging in small studies in regards to reducing exacerbations (74, 77). In contrast to CF, most patients with non-CF bronchiectasis have bacterial infections other than P. aeruginosa; therefore, the mechanism of action for macrolides in non-CF bronchiectasis could relate, in part, to antibiotic effect. PCD patients should not receive chronic oral macrolides unless they have been tested and shown to not harbor NTM (74, 77). The

widespread use of inhaled or systemic corticosteroids in non-CF bronchiectasis has not been validated by standardized clinical studies.

Resection of severely affected lung in PCD is occasionally useful, but should be undertaken only after careful consideration and consultation with PCD experts, because PCD affects all regions of the lung. The selection of patients for resection should focus on those with severe localized bronchiectasis and recurrent febrile relapses or severe hemoptysis, despite aggressive medical management (84). Patients with end-stage PCD lung disease are candidates for lung transplantation, and a modest number of transplants have been successfully performed.

Some key goals for the PCD community to develop the requisite capabilities for performing therapeutic clinical trials have recently been achieved. Specifically, there is now expanded capability to perform genetic testing for the diagnosis of PCD at a reasonable cost, which will expand the pool of patients with a confirmed diagnosis of PCD. There is also an increasing number of PCD clinical sites to perform those clinical trials. Further, there is a published quality-of-life (QOL) instrument as an outcome measure in PCD adults (85) and another QOL instrument for pediatric patients is close to being finalized. Therefore, the PCD community is poised to do therapeutic studies for lung disease in PCD (see “Future Directions” below, and PCD Foundation website, www.pcdfoundation.org).

MANAGEMENT OF OTOLARYNGOLOGIC MANIFESTATIONS

Otitis media with effusion affects almost all children with PCD, but there is no consensus for management, even though this disorder has implications for conductive hearing loss, delayed speech and language development, and cholesteatoma formation (12, 15, 86). Those who support the use of tympanostomy tubes suggest that hearing may be improved long term in some patients, and otorrhea can be controlled (86). In contrast, the European Respiratory Society Consensus Statement recommends against placement of tubes for chronic otitis media in PCD, because resultant otorrhea is problematic, and spontaneous resolution of chronic otitis media may occur in the teenage years (87, 88). Acute episodes of otitis media should be treated by standard approaches, but the question of surgical intervention remains. It should be recognized that chronic otitis media may persist into adulthood, and conductive hearing loss (“glue ear”) occurs in some patients. Therefore, audiology assessments, hearing aids, and communication assistance should be employed.

Sinus disease is a major problem in PCD. Initial management may include nasal steroids, nasal lavage, and intermittent courses of systemic antibiotics. Polyps may require surgery, and functional endoscopic sinus surgery is helpful in many patients who are refractory to medical therapy, particularly if there is good postsurgical treatment to maintain adequate drainage (89, 90).

FUTURE DIRECTIONS

Although treatment of patients with PCD has not been standardized, the recent PCD Foundation consensus statement on diagnosis and management offers specific guidance for clinicians. It is hoped that this will improve clinical care, including regular surveillance of

clinical status, lung function, and respiratory microbiology, and allow antibiotic treatment targeted to specific pathogens. A multidisciplinary approach to management of chronic disease is well recognized to benefit long-term outcomes, particularly for rare diseases, such as CF. The PCD Foundation is developing a national registry, and an ever-growing network of certified PCD clinical centers, which should alleviate some of the inconsistency in care. This network will also facilitate discovery of additional PCD genes, and allow more extensive studies of genotype/phenotype in PCD. Further, this network will also facilitate the identification of patients with PCD for participation in prospective clinical trials, and provide geographically dispersed sites for these therapeutic trials (see PCD Foundation website for further information, www.pcdfoundation.org). In summary, there has been striking progress in our understanding of PCD over the past 15 years, and this is being rapidly translated into more available and effective clinical care.

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Key points

- Primary ciliary dyskinesia (PCD) is a recessive genetically heterogeneous disorder of motile cilia with chronic oto-sino-pulmonary disease and organ laterality defects in ~50 of cases.
- The prevalence of PCD is difficult to determine, because there has historically been no readily available and standardized diagnostic approach.
- Recent diagnostic advances through nasal nitric oxide (nNO) and genetic testing has allowed rigorous diagnoses, and determination of a strong clinical phenotype, which includes neonatal respiratory distress, daily nasal congestion and wet cough starting early in life, along with organ laterality defects.
- There is early onset of lung disease in PCD with abnormal airflow mechanics and radiographic abnormalities detected in infancy and early childhood.
- The treatment of PCD is not fully standardized, but PCD Foundation Consensus recommendations on diagnosis, monitoring, and treatment of PCD have recently been published.

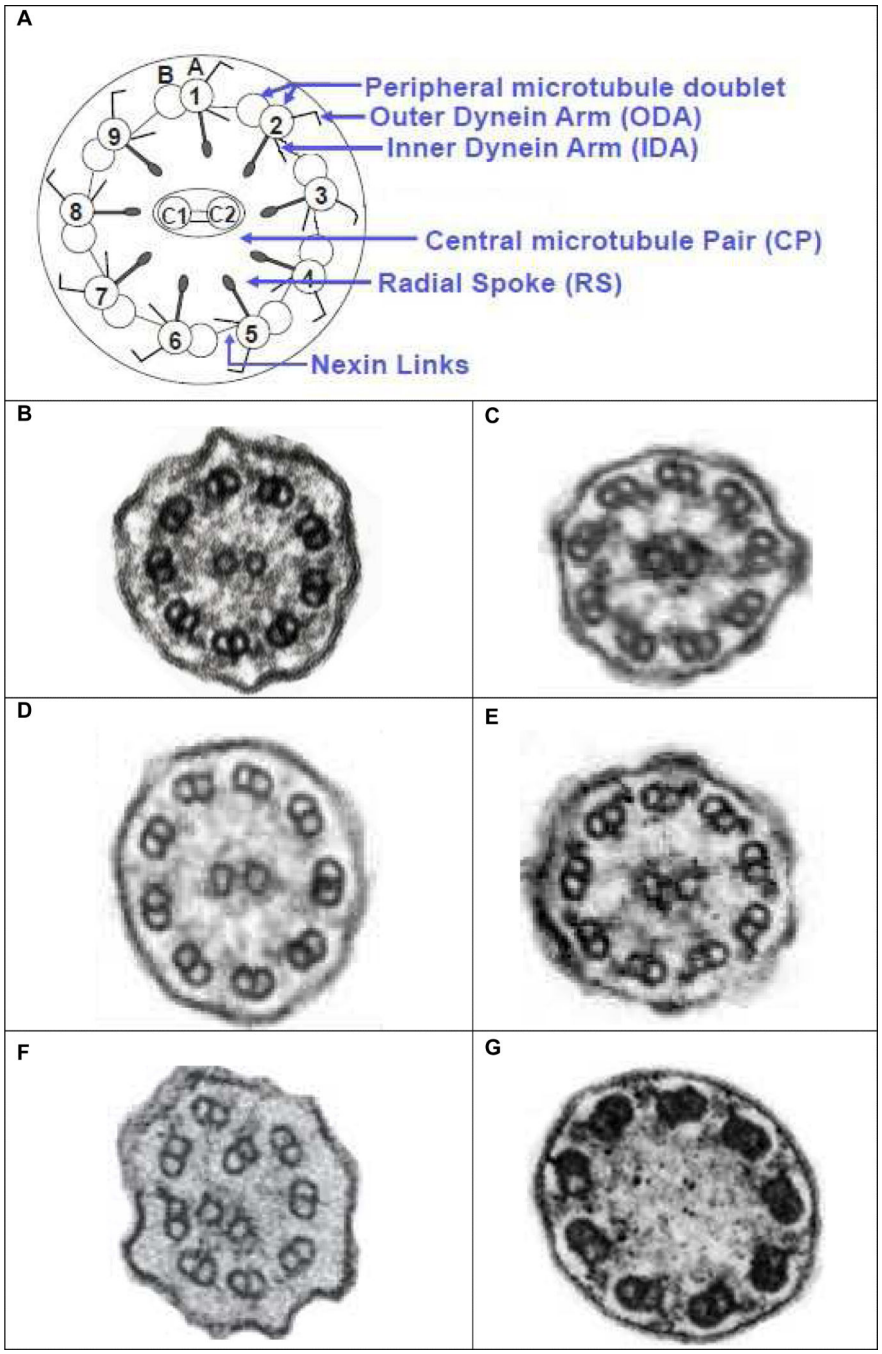

Figure 1.

Ciliary ultrastructure. (A) Schematic of cross-section of cilium with 9 + 2 configuration. Ciliary ultrastructure by electron micrographs (EMs) from (B) normal subject and (C-G) patients with primary ciliary dyskinesia (PCD). (A) The 9 + 2 structure is shown with individual components of the axonemal structure. (B) Normal EM. (C) ODA defect, as seen in DNAH5 mutations. (D) ODA + IDA defect, as seen in DNAAF1 mutations. (E-F) IDA

defect alone, and IDA defect with microtubular disorganization, as seen in CCDC39 mutations. (G) Missing central pair, as seen in ~12% of cilia with RSPH1 mutations.

Table 1

Consensus-based PCD Diagnostic Criteria by Age[*].

Newborns (0 to 1 month of age)
Situs inversus totalis and unexplained NRD[**] at term birth, **plus** at least one of the following:
Diagnostic ciliary ultrastructure electron micrographs **or** two mutations in PCD-associated gene
Children (1 month to 5 years)
Two or more major PCD clinical criteria (NRD[**]; wet cough; nasal congestion; laterality defect), **plus** at least one of the following (nasal nitric oxide not included in this age group, since it is not yet sufficiently tested):
Diagnostic ciliary ultrastructure on electron micrographs
Two mutations in one PCD-associated gene
Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
Children (5-18 years of age) and adults
Two or more PCD clinical criteria (NRD[**]; wet cough; nasal congestion; laterality defect), **plus** at least one of the following:
Nasal nitric oxide during plateau < 77 nL/min on 2 occasions, > 2 months apart (with cystic fibrosis excluded)
Diagnostic ciliary ultrastructure on electron micrographs
Two mutations in one PCD-associated gene
Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions

[*] Pediatric Pulmonology, (15)

[**] NRD, Neonatal Respiratory Distress (in term neonates)

Table 2

Mutations in genes that cause PCD; associations with ciliary ultrastructure and organ laterality defects.

Ciliary EM	Genes	Laterality Defects
ODA defect	*DNAH5, DNAI1, DNAI2, DNAL1, NME8, CCDC114, CCDC151, ARMC4*	Yes
ODA+IDA defect	*DNAAF1, DNAAF2, DNAAF3, LRRC6, C21orf59, DNAAF5 (HEATR2), ZMYND10, DYX1C1 (DNAAF4), SPAG1, CCDC103*	Yes
IDA defect+MTD	*CCDC39, CCDC40*	Yes
RS/CP defect	*RSPH1, RSPH3, RSPH4A, RSPH9, HYDIN*	No
Nexin Link defect	*CCDC164 (DRC1), CCDC65 (DRC2), GAS8 (DRC4)*	No
Normal EM	*DNAH11*	Yes
EM not available	*DNAH1, DNAH8*	Yes *(DNAH1)* Unknown *(DNAH8)*
Oligocilia	*CCNO, MCIDAS*	No
PCD+XLMR	*OFD1*	Yes***
PCD+XLRP	*RPGR*	No

*difficult to discern EM defect (appear normal); RS/CP, radial spoke/central pair; PCD with x-linked syndromes.

**unpublished data from Genetic Disorders of Mucociliary Clearance Consortium