Primary Ciliary Dyskinesia

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Abstract

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder of cilia structure, function, and biogenesis leading to chronic infections of the respiratory tract, fertility problems, and disorders of organ laterality. The diagnosis can be challenging, using traditional tools such as characteristic clinical features, ciliary function, and ultrastructural defects and newer screening tools such as nasal nitric oxide levels and genetic testing add to the diagnostic algorithm. There are 32 known PCD-causing genes, and in the future, comprehensive genetic testing may screen young infants before developing symptoms, thus improving survival. Therapies include surveillance of pulmonary function and microbiology, in addition to airway clearance, antibiotics, and early referral to bronchiectasis centers. As with cystic fibrosis (CF), standardized care at specialized centers using a multidisciplinary approach likely improves outcomes. In conjunction with the CF foundation, the PCD foundation, with experienced investigators and clinicians, is developing a network of PCD clinical centers to coordinate the effort in North America and Europe. As the network grows, clinical care and knowledge will improve.

Keywords
- bronchiectasis
- cilia
- ciliary dyskinesia
- sinusitis
- otitis
- dynein arms
- situs inversus
- *Pseudomonas aeruginosa*

Primary ciliary dyskinesia (PCD) is a rare, autosomal recessive disorder of motile cilia that leads to oto-sino-pulmonary disease.[1] PCD was first described by Kartagener et al in 1936 as a syndrome based on the triad of chronic sinusitis, bronchiectasis, and situs inversus. Forty years later, Afzelius expanded on this by observing that these patients had "immotile" cilia and defective ciliary ultrastructure, specifically noting a deficiency of dynein arms, decreased mucociliary clearance, and a lack of ciliary motion.[2,3] Later on, the syndrome was renamed "primary ciliary dyskinesia" when it was observed that functional ciliary impairment without ultrastructural deformities, as well as motile cilia with obvious abnormal movement patterns, could result in clinical disease.[4–6] The prevalence of PCD is difficult to determine due to (hitherto) inadequate diagnostic methods and often an under-recognition of the syndrome; it is estimated to be approximately 1 in 15,000 to 20,000 individuals.[7] Focused clinical and research efforts in recent years have led to an increased understanding of the phenotype, as well as the discovery of PCD-causing genetic mutations. Indeed, the use of genetic testing has greatly aided the diagnosis of PCD and further helped the understanding of PCD. Nonetheless, even with improvements in diagnostic and screening tests at specialized centers, up to 30% of patients may be missed. Secondary ciliary dyskinesia may be seen in diseases associated with acute and chronic airway inflammation and infection.

This review focuses primarily on PCD, the genetically transmitted form of the disease, with a brief review of the structure and function of normal and dysfunctional cilia, the clinical manifestations of PCD, including diagnosis, genetic mutations, therapies, and a glimpse into future.

Normal Cilia Structure and Function

Respiratory cilia are an important part of airway host defense, protecting the airways from inhaled pathogens, allergens, and other inhaled noxious particles via the mucociliary escalator. In the airways, they are surrounded by a thin, watery, periciliary fluid layer overlaid by a more viscous mucus layer. The efficiency of the mucociliary escalator in defense of the airway depends on the viscosity and

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composition of the periciliary fluid and mucus layer, the integrity of the airway epithelium, and the synchrony and beat frequency of the cilia. The density of cilia decreases from the upper to the lower respiratory tract with an absence of cilia in the alveoli and air sacs.[8] Cilia are hair-like attachments found on the epithelial cell surfaces (~200 per cell) of various organs. The cilia basal body attaches to the apical cytoplasm on the cell surface and extends into the extracellular space. They are composed of α- and β-tubulin monomers organized into longitudinal microtubules. The axonemal structure consists of a circular arrangement of nine microtubule doublets surrounding a central pair of microtubules (9 + 2) or with an arrangement where the central pair is absent (9 + 0).[9] Cilia are categorized into 9 + 2 motile cilia with dynein arms, 9 + 0 motile cilia (nodal cilia) with dynein arms, and 9 + 0 nonmotile cilia lacking dynein arms.[10]

"9 + 2" motile cilia are found on the apical surfaces of the upper and lower respiratory tract, on the ependymal cells lining the ventricles of the central nervous system, in the oviducts, and in the flagellum of sperm.[10] Outer dynein arms (ODAs) and inner dynein arms (IDAs) traverse along the length of the peripheral microtubules forming a doublet (►**Fig. 1**) and are organized into nine microtubule pair doublets, surrounding a central pair. This organizational structure creates this distinctive 9 + 2 arrangement. The central pair is linked to the surrounding pair doublet through radial spoke proteins, and the surrounding pair doublets are linked to one another via nexin-linked proteins (►**Fig. 1**). The microtubules slide by one another to produce ciliary motion via an ATP-containing dynein arm on the peripheral microtubule. The protein links between the microtubules limit the degree of sliding, causing them to bend. Through coordinated and synchronized bending, wave-like movements occur at approximately 6 to 12 Hz, which function to propel mucus and adherent particles/bacteria on the surface of the airway—hence the term "mucociliary escalator." The ability of numerous adjacent cilia on airway epithelial cells to beat at such a high frequency in part reflects the very low friction among the cilia, which results from negatively charged glycoproteins that coat the ciliary shaft. Thus, given such an efficient, if complex, system of defense, it can readily be visualized that clinical disease may result from disruptions in the various components of the system. For example, cystic fibrosis (CF) results from abnormalities in the CF transmembrane conductance regulator, a critical airway surface epithelial protein. Similarly, mutations in genes encoding for axonemal structures of the functional components of motile cilia, or proteins involved in the biogenesis of cilia, including cytoplasmic proteins, can result in clinical disease (PCD).[11–14]

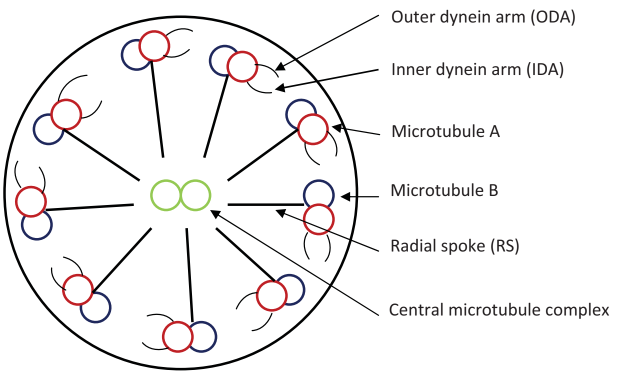

Fig. 1 Diagrammatic representation of a normal ciliary cross section illustrating major ultrastructural components.

Although dysfunctional motile cilia lead to the main clinical manifestations of PCD, abnormal nodal motile cilia can also lead to interesting phenotypic features. Nodal cilia occur during embryonic development and have a 9 + 0 configuration rather than the classic 9 + 2 configuration and are found on the epithelial cell surface of the kidneys, the bile ducts, and the endocrine pancreas and on nonepithelial cells such as chondrocytes, fibroblasts, smooth muscle cells, and neurons. In contrast to the waveform sliding motion of 9 + 2 cilia, nodal motile 9 + 0 cilia beat with a vertical/rotational motion resulting in a leftward flow of extracellular fluid which is important for cell signaling during the development of normal human left–right asymmetry. Mutations in the genes that encode the outer doublets result in laterality defects (e.g., situs inversus), while mutations in the genes that encode the nondirectional central apparatus (central complex, radial spoke) do not.[15] This represents a predictable genotype–phenotype relationship (see section "Genetic Testing").

Phenotypic Features

Overview

Cells lining the nasopharynx, middle ear, paranasal sinuses, the lower respiratory tract, and the reproductive tract contain cilia; these cilia are abnormal in structure and function in PCD, leading to clinical expression of disease. The clinical manifestations of PCD are thus predictable, with an age-dependent and organ system spectrum of presentation (►**Table 1**). Symptoms of PCD can occur at birth, or within the first several months of life. Normal ciliary function is critical in the clearance of amniotic fluid from the fetal lung; more than 80% of full-term neonates with PCD have a syndrome of respiratory distress. Unexplained respiratory distress, radiographic abnormalities, atelectasis in particular, and hypoxia in a full-term infant should raise the suspicion for PCD.[16,17] Almost all children with PCD have a daily productive cough, a logical symptom, as cough can partially compensate for the dysfunctional mucociliary clearance. However, recurrent bacterial infections of the lower airways ultimately lead to bronchiectasis, which is seen in virtually all older adults with PCD.[16–18] Despite aggressive medical care, PCD is generally a progressive disease and some patients develop severe disease, respiratory failure, and/or require lung transplant (►**Fig. 2**).[1]

Airway Microbiology

Regular surveillance of the respiratory flora is important, as a variety of organisms may colonize or infect the lung, which may require targeted therapy because of resistance, or lead to specific infectious problems (e.g., nontuberculous mycobacteria [NTM]). Monitoring protocols developed for

Table 1 Clinical signs and symptoms of primary ciliary dyskinesia

By system affected	By age of presentation
Middle ear • Chronic otitis media with tube placement • Conductive hearing loss Nose and paranasal sinuses • Neonatal rhinitis • Chronic rhinosinusitis • Chronic pansinusitis • Nasal polyposis Lung • Neonatal respiratory distress • Chronic cough • Recurrent pneumonia • Bronchiectasis Genitourinary tract • Male/female fertility problem or history of in vitro fertilization Laterality defects • Situs inversus totalis • Heterotaxy (+/− congenital cardiovascular abnormalities) Central nervous system • Hydrocephalus Eye • Retinitis pigmentosa	Family history • Communities or ethnicities with consanguinity • Close (usually first degree) relatives with clinical symptoms Antenatal • Heterotaxy on prenatal ultrasound Newborn period • Continuous rhinorrhea • Respiratory distress or neonatal pneumonia Childhood • Chronic productive cough • Atypical asthma unresponsive to therapy • Idiopathic bronchiectasis • Chronic rhinosinusitis • Recurrent otitis media with effusion Adolescence and adult life • Same as for childhood • Subfertility and ectopic pregnancies in females • Infertility in males with immotile sperm • Sputum colonization with nontuberculosis mycobacterium or smooth/mucoid pseudomonas

CF and PCD patients vary, but most centers obtain airway cultures every 3 to 6 months. The respiratory microbiology in PCD generally mirrors that of CF; however, in PCD colonization with *Pseudomonas aeruginosa*, it generally occurs later, and the incidence of *Streptococcus pneumoniae* is much higher.[1] Children with PCD have airway colonization with *Haemophilus influenza*, *Staphylococcus aureus*, and *S. pneumoniae* and recently, there has been an upsurge of *P. aeruginosa* in infants/preschoolers. *P. aeruginosa* (smooth and mucoid varieties) normally occurs in teenagers and young adults and is often the dominant organism in adults with PCD. NTM are seen in approximately 15% of adults with PCD.[1]

Lung Function

Patients with PCD, as with other patients with non-CF bronchiectasis, usually develop progressive airway obstruction as the disease advances. The disease progression is usually slower than that seen in CF; however, it is just as important to follow lung function serially to establish a baseline, to help guide therapy, and to determine prognosis.[18–20]

Radiology

High-resolution chest computed tomography scan (HRCT scan) is the most sensitive imaging modality to diagnosis bronchiectasis. While HRCT cannot confidently distinguish between the different etiologies for bronchiectasis (PCD vs. idiopathic vs. postinfectious disease), there are disease distributions that may support specific diseases. For example, PCD may be associated with more bronchiectasis in the middle and lower lobes, as compared with CF which usually shows more disease in upper lobes.[21] Subtle lung disease may start early in life, as HRCT scans of infants and children with PCD show subsegmental atelectasis, peribronchial thickening, mucus plugging, evidence of air trapping, and ground glass opacities. HRCT may show bronchiectasis even in infancy, and its frequency increases with age. The absence of bronchiectasis on a HRCT scan of an adult virtually excludes PCD from the differential.[21,22]

Nonpulmonary Manifestations

Situs abnormalities result in early diagnosis; thus, it is found in approximately 60% of newly diagnosed pediatric patients and approximately 50% of newly diagnosed adults. The defect is in the 9 + 0 nodal motile cilium during embryogenesis whose unidirectional rotational beat determines normal thoracoabdominal orientation. Without this, thoracoabdominal orientation develops at random, resulting in a 50% incidence in adults.[15] Recently, this phenotypic expression of situs abnormalities has expanded to include other clinical manifestations, including that of cardiac abnormalities; approximately 6% of patients with PCD have congenital heart disease.[23] Spermatozoa depend on cilia for motility; thus, infertility is seen in almost all males with PCD. However, a small number of men with PCD have appeared to conceive naturally. Females have abnormal cilia in their fallopian tubes with longer ovum transit time, and there appears to be an increased incidence of infertility and ectopic pregnancies.[24] Less clear phenotypic associations include pectus excavatum (10%), scoliosis (5–10%), retinitis pigmentosa, and hydrocephalus.[25]

Diagnostic Approaches

A precise diagnosis of PCD may be difficult, especially in nonclassic clinical situations (e.g., without situs abnormalities). Often, only specialized centers have the resources to make a definitive diagnosis (see later). Obviously, the presence

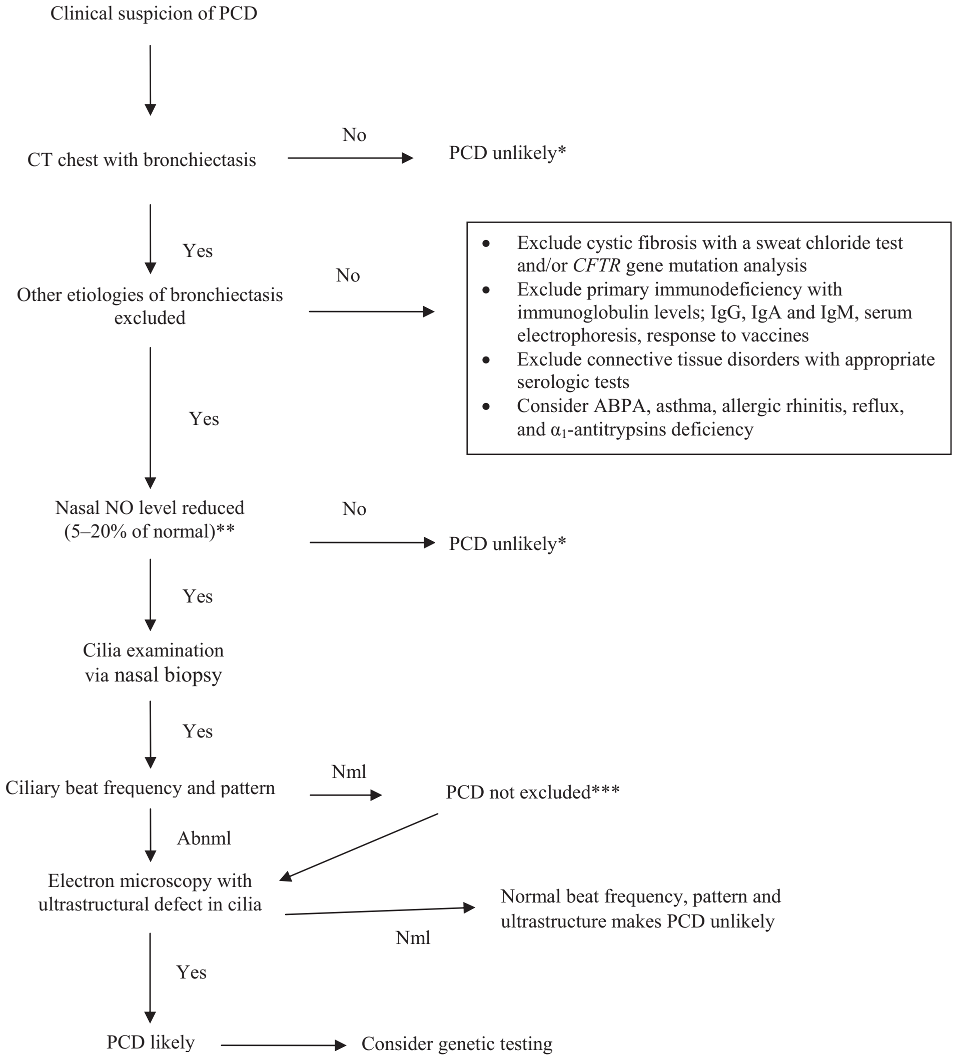

Fig. 2 Diagnostic algorithm for PCD. *If clinical suspicion is still high for PCD, may go to other, more specific tests. **A nasal NO level less than 77 nL/min has a sensitivity and specificity of 0.98 and >0.99, respectively. ***Normal ciliary beat frequency and pattern does not exclude PCD. Abnml, abnormal; Nml, normal; NO, nitric oxide; PCD, primary ciliary dyskinesia.

of any laterality abnormalities, or congenital heart disease, in the presence of chronic respiratory disease should prompt the notion of PCD as a potential unifying cause. A history of unexplained neonatal respiratory distress, early onset and persistent nasal-pulmonary symptoms, unexplained bronchiectasis, a family history of PCD, and immotile sperm/infertility should trigger an evaluation. There is overlap with other chronic respiratory diseases, particularly CF, although immunologic deficiencies, allergic bronchopulmonary aspergillosis (ABPA), and recurrent aspiration may also be in the differential. Early referral to a specialized center is recommended for both diagnosis and management, given the complex nature of the disease, and the rapid nature with which new information is emerging in relation to diagnosis and management.

Indirect Assessment of Ciliary Function

Saccharin test—The saccharin test was a traditional, simple, indirect way to test ciliary function, and was used as a screening tool for PCD at many centers. A 1- to 2-mm particle of saccharin is placed on the inferior nasal turbinate and the time it takes the patient to taste the saccharin is a rough estimate of nasal mucociliary clearance. However, at best it is crude, limited by technical errors (inadequate placement of saccharin), patient compliance (unable to sit still for test, especially children), and false positives (poor sense of taste, rhinosinusitis). Thus, it is rarely used currently, and has been superseded by the more accurate tests below.

Nasal nitric oxide (NO) levels—The fortuitous observation several years ago that levels of NO produced in the upper airway are reduced in PCD led to the concept that nasal NO levels could be used as screening test in PCD.[26] NO is produced by the paranasal sinus epithelium via NO–synthase and low levels are seen in PCD, CF, acute/chronic sinusitis, and nasal polyposis. In patients with PCD, however, levels of exhaled NO are extremely low (~10% of normal value) when compared with other diseases. Interestingly, carriers of PCD have been shown to have intermediate levels of exhaled NO.[1,27,28] Using a standardized protocol, nasal NO measurements can accurately identify patients with PCD 98.6% of the time.[29]

Direct Assessment of Ciliary Function

Microscopic analysis—Function can be classed as qualitatively normal, dyskinetic, or immotile with direct visualization of ciliary beat pattern and frequency with microscopic analysis of transnasal brushings or nasal scrapes of the inferior turbinate. However, this test is technically difficult outside of research centers, and is neither sensitive nor specific.[30]

High-speed digital video imaging—Transnasal brushing or nasal scrape ciliated epithelial samples can be analyzed with high-speed digital video imaging to get quantitative measurements of the ciliary beat frequency (CBF) to help differentiate between abnormally beating cilia and normal beat patterns.[9,31] The cilium can be viewed in slow motion, with 40 to 50 frames per ciliary beat cycle. Normal cilia beat back and forth within the same frame with no sideways recovery sweep. CBF and beat pattern abnormalities are associated with specific ultrastructural defects including transposition and defects in isolated outer arms, isolated inner arms, and radial arms.[32] Active sinusitis can cause secondary ciliary dysfunction resulting in false positives, and thus samples should be obtained when the patient is relatively stable clinically. A normal CBF and beat pattern is sensitive enough to exclude classic PCD, but any abnormality should provoke further testing.[27] Thus, this test (like other studies of cilia, often available at only research centers) should be used along with structural and genetic analysis to confirm the diagnosis.

Assessment of Ciliary Ultrastructure

Transmission electron microscopy [33]—Once the suspicion for PCD is high, the axonemal structure of the respiratory cilia may be studied using transmission electron microscopy, the traditional way of diagnosing PCD since Afzelius' first report in the mid-1970s.[2] Various ciliary ultrastructural defects have been described, including the absence of, or alteration in, IDAs or ODAs, absence of the central pair, or defect of radial spokes.[34] The most common ultrastructural defect in PCD is either the absence or shortening of an ODA (55% prevalence) or a combined of absence/shortening of both the IDA and the ODA (15% prevalence). Other abnormalities include defects in the IDA alone or in combination with defects in radial spokes, central microtubule pairs (transposition), or central microtubular agenesis. Thus, until recently, the identification of ultrastructural defects on TEM was the "gold standard" for the diagnosis; however, with advances in our molecular understanding in PCD, it is known that approximately 30% of patients with genetically proven PCD have normal ciliary ultrastructure and in some cases, a ciliary or oligoplasia, hence inadequate for the TEM analysis. In addition, the technique is limited by false-positive conditions (those associated with active mucosal epithelium inflammation, viral or bacterial), inadequate samples, poorly processed samples, and reader error.[35–38] Studies have shown a 3 to 10% prevalence of defective cilia in the airways of healthy individuals, and normal ultrastructure in up to 15% of PCD patients.[39] Dependence on TEM alone therefore is an unreliable way of solely diagnosing PCD.

Fluorescence-labeled antibodies—Immunofluorescent analysis using antibodies directed against the main axonemal components has been used to identify structural abnormalities of cilia. For example, PCD patients with ODA defects have absence of DNAH5 staining from the entire axoneme and accumulation of DNAH5 at the microtubule organizing center. Antibody-based techniques can diagnose defects in both the ODAs and the IDAs caused by the KTU mutation in PCD. Currently, a panel of antibodies directed toward multiple ciliary proteins is being developed that may add to the diagnostic armamentarium in screening for PCD; however, like many sophisticated techniques, it is restricted to a few centers that have this technology.[40]

Genetic Testing

PCD is a recessive disorder, and exhibits locus and allelic heterogeneity. That is, multiple genes are involved in the disease, and different mutations in the same gene may also cause PCD. Mutations in 11 different PCD-causing genes have been described between 1999 and 2010 with linkage mapping and/or candidate gene testing. An additional 23 genes have been discovered since 2011 owing to the availability of whole-exome sequencing (►**Table 2**). Some of these genes (e.g., DNAH8 and NME8) have only been seen in few patients; thus, replication studies are necessary. About 80% of the mutations are loss-of-function variants (nonsense, frame shift, or defective splice mutations), while the others are conservative missense mutations or in-frame deletions. Most mutations occur in only one patient/family ("private" mutations); a few of the mutations have been seen to recur in two or more unrelated patients. Collaborative efforts in recent years have allowed the collection of large amounts of data from many clinical centers in the United States and Canada and thus facilitated large-scale genetic studies and identification of many causative genes, which had previously been very difficult to do in this rare disease.[41] Approximately 65% of the 200 PCD patients in the rare disease consortium (Genetic Disorders of Mucociliary Clearance [GDMCC]) have biallelic mutations (mutations in both copies of the same gene). At this point, with the use of next generation sequencing, approximately 66% of patients with PCD can be identified, thus facilitating early diagnosis and treatment.[40,42–45] This is especially helpful in the cases where ciliary ultrastructural analysis is equivocal or inadequate.

As the basic structure of the cilia is highly conserved across species, nonhuman models have helped in the discovery of PCD genes and the effects of the mutations on the cilia. Multiple publications have documented the effects of specific mutations on the cilia structure and function. Some of the genes code for proteins in the ODA, IDA, or radial spoke causing specific dysfunction or dysmotility, while others are expressed by proteins in the cytoplasm used for the preassembly of the cilia causing loss of both the ODA and the IDA leading to cilia immotility.[43,46–48] Recently, two proteins (CCNO and MCIDAS) have been shown to affect cilia biogenesis.[49,50] Specific classes of mutations are associated with specific phenotypes. Mutations in genes that lead to loss of function of the cilia also lead to low

Table 2 Primary ciliary dyskinesia–associated genes in humans showing extensive locus heterogeneity

Human gene	Chromosomal location	Axonemal component	Ultrastructure defect	[a]Phenotype, gene OMIM no.	PCD locus
DNAH5	5p15.2	ODA dynein HC	ODA defect	608644, 603335	CILD3
DNAI1	9p21-p13	ODA dynein IC	ODA defect	244400, 604366	CILD1
DNAI2	17q25	ODA dynein IC	ODA defect	612444, 605483	CILD9
DNAL1	14q24.3	ODA dynein LC	ODA defect	610062, 614017	CILD16
TXNDC3 (*NME8*)	7p14-p13	ODA dynein IC/LC	Partial ODA defect (66% cilia defective)	610852, 607421	CILD6
CCDC114	19q13.32	ODA DC	ODA defect	615067, 615038	CILD20
CCDC151	19q13.32	ODA DC	ODA defect	616037, 615956	CILD30
ARMC4	10p12.1-p11.23	ODA transport component	ODA defect	615451, 615408	CILD23
DNAAF1 (*LRRC50*)	16q24.1	Cytoplasmic DA preassembly factor	ODA + IDA defect	613193, 613190	CILD13
DNAAF2 (*KTU*)	14q21.3	Cytoplasmic DA preassembly factor	ODA + IDA defect	612518, 612517	CILD10
DNAAF3 (*C19ORF51*)	19q13.42	Cytoplasmic DA preassembly factor	ODA + IDA defect	606763, 614566	CILD2
CCDC103	17q21.31	Cytoplasmic DA attachment factor	ODA + IDA defect	614679, 614677	CILD17
C21orf59	21q22.1	Cytoplasmic DA assembly or adaptor for transport	ODA + IDA defect	615500, 615494	CILD26
DYX1C1	15q21.3	Cytoplasmic DA preassembly factor	ODA + IDA defect	615482, 608706,	CILD25
LRRC6	8q24	Cytoplasmic DA preassembly and/or transport	ODA + IDA defect	614935, 614930	CILD19
HEATR2	7p22.3	Cytoplasmic DA preassembly or transport	ODA + IDA defect	614874, 614864	CILD18
SPAG1	8q22	Cytoplasmic DA preassembly or transport	ODA + IDA defect	615505, 603395	CILD28
ZMYND10	3p21.31	Cytoplasmic DA assembly	ODA + IDA defect	615444, 607070	CILD22
CCDC39	3q26.33	N-DRC	IDA defect + microtubular disorganization	613807, 613798	CILD14
CCDC40	17q25.3	N-DRC	IDA defect + microtubular disorganization	613808, 613799	CILD15
CCDC65 (*DRC2*)	12q13.12	N-DRC	Mostly normal, CA defects in small proportion of cilia	615504, 611088	CILD27
CCDC164 (*DRC1*)	2p23.3	N-DRC	Nexin (N-DRC) link missing; axonemal disorganization in small proportion of cilia	615294, 615288	CILD21
RSPH1	21q22.3	RS component	Mostly normal, CA defects in small proportion of cilia	615481, 609314	CILD24
RSPH4A	6q22.1	RS component	Mostly normal, CA defects in small proportion of cilia	612647, 612649	CILD11
RSPH9	6p21.1	RS component	Mostly normal, CA defects in small proportion of cilia	612650, 612648	CILD12
HYDIN	16q22.2	CA component	Normal, very occasionally CA defects	608647, 610812	CILD5
DNAH11	7p21	ODA dynein HC	Normal	611884, 603339	CILD7
CCNO	5q11.2	Required for cilia biogenesis	Ciliary a/oligoplasia	615872, 607752	CILD29

Table 2 (*Continued*)

Human gene	Chromosomal location	Axonemal component	Ultrastructure defect	[a]Phenotype, gene OMIM no.	PCD locus
MCIDAS	5q11.2	Required for cilia biogenesis	Ciliary a/oligoplasia	NA, 614086	NA
DNAH8[b]	6p21.1	ODA dynein HC	NA	603337, NA	NA
RPGR[c]	Xp21.1	outer segment of Rod & Con photoreceptors	Mixed	300455, 312610	NA
OFD1[d]	Xq22	Centriole component, required for cilia biogenesis	NA	300209, 300170	NA

Abbreviations: CA, central apparatus; DA, dynein arm; DC, docking complex; HC, heavy chain; IC, intermediate chain; IDA, inner dynein arm; LC, light chain; N-DRC, nexin-dynein regulatory complex; NA, not available; ODA, outer dynein arm; RS, radial spokes.

[a] Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/.

[b] Ciliary ultrastructure not available[50]; however, *DNAH8* is paralogous to *DNAH5*.

[c] Cosegregation of X-linked PCD with X-linked retinitis pigmentosa.

[d] Cosegregation of X-linked PCD with X-linked mental retardation.

nasal NO levels (<77 nL/min). Mutations that affect the dynein arm's ultrastructure lead to situs abnormalities, while mutations that affect the central apparatus do not. Mutations in patients with normal TEM can have cilia with normal beat frequencies and waveforms.

Overall, the more that is learnt about the molecular basis of PCD, the more is learnt about the spectrum of phenotypes, ranging from "classic" to mild, that is associated with late presentation or normal cilia structure, analogous to the experience with CF—classic, early presentation disease versus nonclassic disease often presenting later in life, or even well into adulthood.

Therapies

As there are currently no therapies available that can reverse the underlying ciliary abnormalities, the goals of therapy are to prevent exacerbations and slow down the progression of the disease. As with other forms of CF and non-CF bronchiectasis, patient education is a critical part of the care plan, including imparting an understanding of the underlying cause of the disease, its prognosis, and the various therapies available to try to control the symptoms, especially airway clearance. Currently, there are no data from randomized clinical trials to support any particular forms of therapy; thus, most management strategies (including those discussed later) are extrapolated from CF and non-CF bronchiectasis. As with any chronic disease, usual good health practices such as refraining from smoking and administration of recommended immunizations including influenza and pneumococcal vaccines are recommended.

Surveillance

To guide the management plan, regular (twice yearly to quarterly) lung function testing, together with microbiologic assessments of airway flora (using either expectorated sputum or induced samples using 3–7% hypertonic saline), is recommended to establish clinical trends and detect exacerbations, thus allowing targeted antimicrobial therapy. A baseline CT scan is useful to assess the nature and extent of disease (as noted earlier, bronchiectasis may be evident even in young patients), followed by periodic chest imaging to track disease progress or to assess the significance of new pathogens such as multidrug-resistant gram-negative organisms or NTM.

Airway Clearance

Physiotherapy—There are no data to support any particular form of airway clearance in PCD, but clinical experience supports its use in a form acceptable to the patient. Daily airway clearance with cardiovascular exercise, use of percussion vests, manual chest physical therapy, and valve/positive pressure expiratory devices help mobilize and aid expectoration of bronchopulmonary secretions, improve efficiency of ventilation, maintain/improve exercise tolerance, and reduce breathlessness.

Osmotic agents—"Hydration" therapy of the airway is an attractive concept to augment clearance of secretions in a disease such as PCD, in this case "cough clearance" given the dysfunctional cilia.[51] Nebulized hypertonic saline (3–7% hypertonic saline) modulates the liquid content of the periciliary fluid layer via increased hydration, thinning thick secretions and triggering cough in the CF population. It has been shown to improve lung function, quality of life, and reduce antibiotic needs in the non-CF bronchiectasis population.[51,52] Recently, another agent which works via the osmotic approach is inhaled mannitol, again studied in non-CF bronchiectasis rather than specifically PCD.[53] Although the inhaled drug (400 mg BID) did not achieve its primary outcome of reducing exacerbations, it did perform better than placebo (low-dose mannitol) in slowing down the time to first exacerbation and improving the quality of life measures.

Deoxyribonuclease (Dornase-α)—Dornase-α is an enzyme that hydrolyses eukaryotic DNA released from decaying neutrophils to reduce mucus viscosity and aid airway clearance in the CF population.[54] It is, however, not beneficial in the non-CF bronchiectasis population, as studies show that the drug is associated with pulmonary exacerbations and a decline in lung function.[55]

Antibiotics

Given the propensity for chronic infection, as with other forms of bronchiectasis, antibiotics are the cornerstone of treatment for PCD exacerbations (usually associated with an increase in cough, dyspnea, wheeze, with a change in sputum volume or character, or purulence, or hemoptysis), as they generally improve symptoms and hasten recovery.[56,57] Antibiotic therapy should be based on previous respiratory culture data and previous therapeutic responses. Susceptibility patterns and clinical responses may guide physicians between oral, inhaled, and intravenous routes of administration. There are no randomized data to support any particular drug, or route of administration, and clinical judgment is required; however, milder exacerbations often respond to oral or oral–inhaled combinations, while more significant exacerbations usually require systemic antibiotics (in combination, if gram-negative organisms are cultured). There is a good deal of interest in the development of inhaled antibiotics in recent years in non-CF bronchiectasis, and over the next 5 to 10 years it is likely that there will be more approved drugs with better evidence of efficacy available (a reduction in exacerbation frequency, bacterial burden), for example, inhaled aminoglycosides and quinolones.[58–60] Early attempts to eradicate newly acquired bacteria, especially *P. aeruginosa*, are recommended; however, this has not been shown to preserve lung function. Chronic or cycling oral or inhaled antibiotics may be used in patients with frequent exacerbation to try to improve quality of life, reduce exacerbations, and (hopefully) stabilize lung function.[56,58,61,62]

Anti-Inflammatories

A variety of anti-inflammatory agents including oral prednisone, inhaled corticosteroids, and macrolides have been used in airways disease associated with bronchiectasis. Prednisone is generally not efficacious in the CF population outside of coexistent asthma and ABPA, and there are no studies in the PCD population. Inhaled corticosteroids have not been shown to be beneficial in non-CF bronchiectasis.

The best data for “preventive” therapy come from recent studies using oral macrolides, which have shown promising outcomes in non-CF bronchiectasis, with reductions in exacerbation frequency, delayed time to first exacerbation, and reduced hospitalizations. It is unclear if this benefit is from an anti-inflammatory or antimicrobial effect. Before initiating therapy with a macrolide, patients should be tested for NTM, in case macrolides should form part of a multidrug regimen, and to avoid the emergence of resistance from chronic single-agent macrolide use.[63–65]

Miscellaneous Approaches

Lung resection—Surgery may be considered in areas of localized lung disease if it is causing severe systemic symptoms, frequent exacerbations, or recurrent/life-threatening hemoptysis despite aggressive medical therapy. Patients in such situations have undergone successful resection, but long-term data are lacking.[66] Often the diffuse nature of disease elsewhere in the lung mitigates against the likelihood of success in resecting more diseased parts of the lung.

Lung transplant—PCD patients undergoing double-lung transplant generally have good survival outcomes. The usual concerns pertain to candidacy for the procedure, and also specifically include multiple drug-resistant organisms, and poor nutritional status. Interestingly, patients with *situs inversus* do not pose any additional risk to posttransplant outcomes; the anatomic disorientation is challenging but not a contraindication.[67]

Extra-pulmonary Disease Management

Otitis media—Management may be controversial, especially in the pediatric community. The long-term sequelae of chronic disease in the upper airway include conductive hearing loss, delayed speech and language development, and cholesteatoma formation. Standard medical therapy is recommended for acute episodes. There are no enough data on surgical tympanostomy to make a definitive statement regarding its utility; experts argue against the utility of this approach.[27] Regular audiology assessments are encouraged.[68,69]

Chronic sinusitis—As with CF, the sinuses are usually involved. Management includes nasal steroids, nasal lavage and intermittent antibiotic lavages, and systemic antibiotics. Otolaryngology evaluation for surgery and polypectomy to promote sinus drainage is helpful for patients' refractory to medical therapy.[70]

Infertility—Male infertility is secondary to sperm immotility and assisted fertilization techniques such as intracytoplasmic sperm injections are promising. Female infertility is secondary to sluggish fallopian tube transit time, and direct ovum harvesting with in vitro fertilization leads to successful pregnancy.

Prognosis

As compared with CF, the disease severity and deterioration in lung function is less marked, especially with appropriate medical therapy. A study by Ellerman and Bisgaard reported that adults had worse lung function at the time of diagnosis as compared with adolescents; however, once diagnosed and therapy started, no further lung deterioration was noted.[71] However, other studies have shown progression to severe lung disease before adulthood. These discrepancies in severity and survival may relate at least in part to the genetic and phenotypic heterogeneity of PCD, as well as the usual aspects of access to care, socioeconomic backgrounds of patients, and accompanying comorbidities. Overall, the majority of patients with PCD appear to have a near-normal life expectancy when compliant with recommended therapies. A minority of patients develop progressive severe bronchiectasis, end-stage lung disease, and early death, unless they undergo lung transplant.[71]

Summary and into the Future

In the past two decades, much has been learned about PCD. Accurate and earlier diagnosis is possible, and access to specialized centers has become easier. Standardized care at specialized centers using a multidisciplinary approach is expected to improve outcomes. The recent creation of the PCD foundation has facilitated the creation of a network of PCD clinical centers to help achieve this goal. As the network grows, and clinicians and research scientists accumulate more data from growing numbers of PCD patients, clinical care and knowledge will undoubtedly improve. In parallel, genetic correlates with larger clinical datasets have shown that PCD is a genetically heterogenous disease with different mutations in several genes resulting in a phenotype spectrum, across many races and ethnic groups. The severity of disease ranges from mild to severe. Delays in recognition may result in the development and progression of irreversible lung disease. In CF, early identification and diagnosis leads to early treatment and frequent monitoring to decrease morbidity and mortality, and one assumes the same principles apply to PCD, despite differences in pathogenesis. Still, it must be remembered that PCD is not the same as CF, and management is not identical. Without large numbers of patients with PCD, there has hitherto been little incentive for industry to pursue drug development; thus, currently we rely on studies in non-CF bronchiectasis (mucoactive agents, macrolides, inhaled antibiotics). However, as noted earlier, with the creation of clinical and research networks, with improved identification, and more accurate diagnosis of PCD, we can expect larger cohorts of PCD patients available to participate in longitudinal studies of the natural history of the disease, as well as studies of novel therapies, with the goal of improving clinical care and outcomes in this rare disease.

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