Primary Ciliary Dyskinesia

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KEYWORDS

• Primary ciliary dyskinesia • Kartagener syndrome • Nasal nitric oxide • Genetic testing

KEY POINTS

- Primary ciliary dyskinesia (PCD) is a recessive genetically heterogeneous disorder of motile cilia with chronic otosinopulmonary 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 measurement of nasal nitric oxide and genetic testing has allowed rigorous diagnoses and determination of a robust 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.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous recessive disorder of motile cilia associated with respiratory distress in term neonates, chronic otosinopulmonary 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[6] later recognized that these patients had immotile cilia and defective ciliary ultrastructure. Over time, it was recognized that most patients had stiff, uncoordinated, and/or ineffective ciliary beat, and the term PCD 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 to 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 because of suboptimal diagnostic approaches.[9] Further, many physicians do not appreciate and recognize the key clinical features, particularly in infants and children;

Disclosures: None relevant to this publication.
Grant Support: National Institutes of Health (NIH), number U54HL096458, 5R01HL071798; the Genetic Disorders of Mucociliary Clearance (U54HL096458) is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR). NCATS funded through a collaboration between NCATS and NHLBI; CTSA NIH/NCATS UNC ULTR000083; CTSA NIH/NCATS Colorado UL1TR000154; Intramural Research Program of NIH/NIAID.
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Clin Chest Med 37 (2016) 449–461
http://dx.doi.org/10.1016/j.ccm.2016.04.008

however, recent advances in defining the clinical phenotype are likely to increase the level of awareness for PCD.[10,11] Moreover, better 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, it is now recognized that ~30% of patients with PCD have normal ciliary electron micrographs, which precludes diagnosis by ciliary EM. Genetic testing is also becoming feasible, because 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 composed of alpha and beta monomers of tubulin (**Fig. 1**).[17] Outer dynein arms (ODAs) and inner dynein arms (IDAs) 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 (eg, 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 slightly higher into the mucus layer than the recovery stroke.[23] Ciliary beating is regulated by multiple signaling molecules, including cyclic AMP, cyclic GMP, 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 years and 5.0 years, respectively).[1] Because most institutions do not have adequate resources for a rigorous diagnostic evaluation for PCD, referral to specialized centers may be beneficial. This recommendation includes patients with situs inversus with any respiratory disease, or unexplained neonatal respiratory distress, as well as bronchiectasis without a defined cause, and/or a family history of PCD. For adults, all men 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, compared with other diseases.[11,15] Neonatal respiratory distress is a common feature (>80%) and a useful marker of PCD (**Box 1**), particularly for infants or children who have not developed bronchiectasis, and represents a special challenge for diagnosis.[11,15,25,26] Laterality defects are fairly specific