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Primary ciliary dyskinesia: improving the diagnostic approach

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Abstract

Purpose of review—The diagnosis of primary ciliary dyskinesia (PCD) has relied on analysis of ciliary motility and ultrastructure; however, these tests are not readily available and have not been standardized. Consequently, the diagnosis of PCD may be delayed or missed or made incorrectly. This review outlines the potential utility of new diagnostic tests, including measurement of nasal nitric oxide (NO) production and systematic analysis for mutations in gene encoding ciliary proteins.

Recent findings—Clinical manifestations of PCD have been expanded to include neonatal respiratory distress and heterotaxy. Measurement of nasal NO has emerged as a useful screening test for PCD based on the very low levels in PCD (approximately 1/10 of normal values). Genetic testing is emerging for PCD and demonstrates extensive genetic heterogeneity. Some genes and gene mutations involved in PCD have been defined. Approximately one third of PCD cases have identifiable gene mutations in one of 6 different genes. An international effort is focused on defining PCD-causing defects in other genes.

Summary—The incorporation of nasal NO measurement as a screening test to define probable PCD cases and gene mutation analysis to make a definitive diagnosis of PCD should enhance diagnostic evaluation of PCD.

Keywords

Primary ciliary dyskinesia; ciliopathies; dynein; nasal nitric oxide

Introduction

Over the past 2 years, there has been increased interest in the biology of cilia and diseases associated with defects in cilia (ciliopathies) [1*, 2*, 3**], including primary ciliary dyskinesia (PCD). PCD is a rare, inherited, usually autosomal recessive, disorder with impaired ciliary function leading to progressive sino-pulmonary disease [4*]. Approximately half of PCD patients have situs inversus totalis, reflecting dysmotility of embryonic nodal cilia. Male infertility is common reflecting sperm tail dysmotility. Diagnosis of PCD has relied on identification of ciliary dysmotility and specific ciliary ultrastructural defects in outer dynein arms, inner dynein arms or central apparatus. Because these tests are not readily available or standardized, the diagnosis is often delayed or missed or made incorrectly.

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Clinical manifestations in PCD

Upper and lower respiratory tract manifestations are cardinal features of PCD [5, 6, 7, 8] and often are present in first month of life; however, the diagnosis is delayed because features overlap with other pediatric disorders [6]. Upper respiratory tract features include chronic year-round, nasal drainage that begins in the first weeks of life, chronic sinusitis that becomes apparent once the sinuses have developed and chronic otitis media that is most prevalent in the first years of life and often managed with tympanostomy tube placement [5, 6, 7, 8]. Lower respiratory features include neonatal respiratory distress, chronic productive cough, chronic bronchitis, recurrent pneumonia and bronchiectasis. Most patients have a history of neonatal respiratory distress with tachypnea, hypoxia and, occasionally, respiratory failure requiring mechanical ventilation that has been attributed to transient tachypnea of the newborn or neonatal pneumonia [7, 9,10]. Chronic, year-round productive cough [5, 7, 8, 9] often begins in the first weeks of life, but is attributed to recurrent viral infections, reflux and aspiration or cough-variant asthma. Chronic bronchitis and recurrent pneumonia with radiographic features of air-trapping and atelectasis are common in childhood and lead to bronchiectasis that typically involving the middle and lower lobes and may occur in childhood [11*, 12*, 13*] and even in the first years of life [14*].

Laterality defects occur in approximately half of PCD patients [5, 7]. Indeed, the first reported cases in the early 1900's had situs inversus totalis (mirror image orientation of thoraco-abdominal organs), chronic sinusitis and bronchiectasis, known as the Kartagener triad. A recent study showed that heterotaxy (situs ambiguous or laterality defect other than situs inversus totalis) occurs with a prevalence of at least 6% and can be associated with complex congenital heart disease in PCD [15**]. In addition, a mouse model study [16**] demonstrated that complex congenital heart disease was caused by mutations in one of the dynein genes (*DNAH5*) that accounts for over 20% of PCD cases (see PCD gene mutation analysis section below). These studies suggest that PCD-associated ciliary defects that affect embryonic nodal cilia can cause not only situs inversus totalis, but also heterotaxy and complex congenital heart disease [17*]; therefore, infants with congenital heart disease and respiratory symptoms should be evaluated for PCD.

A variety of other features may be seen in PCD. Almost all men with PCD have infertility from impaired sperm motility. Hydrocephalus occurs rarely in PCD, although a frequent feature in mouse models of PCD, suggesting that ependymal ciliary dysmotility has greater implications in mice. Retinitis pigmentosa, polycystic kidney disease, liver cysts and biliary atresia (all features of ciliopathies of sensory cilia) have been reported rarely in PCD [5] suggesting that there may be overlap of diseases associated with defects in motile and sensory cilia.

DIAGNOSTIC TESTS

The specialized techniques required for PCD diagnostic tests are not standardized or readily available; therefore, referral to research centers or tertiary diagnostic centers may be needed [18*].

Ciliary ultrastructure

The cornerstone diagnostic test for PCD has been examination of ciliary ultrastructure by transmission electron microscopy. Each normal cilium contains an array of longitudinal microtubules, consisting of nine doublets arranged in an outer circle around a central pair (9 plus 2 pattern). Dynein arms are large protein complexes (including 2-3 heavy chains, 2-4 intermediate chains, and at least 8 light chains) that are attached to the nine microtubule doublets as distinct inner and outer “arms” that are discernable on electron micrographs of

ciliary cross-sections [1] (see Figure 1). Dyneins generate the force for ciliary movement through microtubule sliding. The 9 plus 2 array of microtubules is maintained by inter-tubular linkages and accessory proteins (discernable on electron micrographs as radial spokes and nexin links) [1]. Several ciliary ultrastructural defects have been described, but the most frequent are absence or shortening of outer dynein arms or inner dynein arms, absence of radial spokes or loss of central pair of microtubules with transposition of a peripheral doublet to the center [5, 7]. A recent study demonstrated a genetic diagnosis involving one of the dynein proteins (*DNAH11*), but normal ciliary ultrastructure and a subtle alteration in ciliary beat detectable by high-speed videomicroscopy [19**], demonstrating that ultrastructural analysis alone will not identify all PCD cases. Absence of cilia, or acilia syndrome, has been described in a few families [20].

Ciliary motility

In the past, light microscopic examination of ciliary beat was used as a screening test for PCD. While this approach may identify immotile or markedly dyskinetic cilia, ciliary beat may appear normal in some cases of PCD. Digital high-speed videomicroscopy has been used to detect more subtle abnormalities in ciliary beat pattern and has demonstrated that certain ciliary beat patterns are associated with specific ultrastructural defects - immotile or limited flickering for outer dynein arm defects; low amplitude stiff beat for isolated inner dynein arm defect of radial spoke defect; circular, whip-like beat for central microtubular defects such as transposition [21]. This specialized technique has been incorporated into the PCD evaluation at some PCD diagnostic centers [18].

Nasal nitric oxide

Several studies have demonstrated that nasal NO is extremely low (10-15% of normal) in PCD patients suggesting that nasal NO measurement may be a useful screening test for PCD [7, 22, 23, 24]. Because low nasal NO levels have been reported in a limited number of other disorders with overlapping clinical features (e.g., cystic fibrosis [7, 23, 25], panbronchiolitis [26], and nasal polyposis [27]), confirmatory ciliary ultrastructure analysis and/or genetic mutation analysis are needed for a firm PCD diagnosis. At present, no FDA-approved devices for measurement of nasal NO are available. Nasal nitric measurement is used predominantly in research studies in the United States, but has become part of the diagnostic clinical testing at centers in Europe [19]. Nasal NO is measured by a non-invasive approach in which nasal air, aspirated through a catheter inserted at opening of one nostril, is directed to an NO analyzer that typically uses ozone-/NO_2-based chemiluminescence for direct on-line measurement of NO [28]. The nasal catheter is inserted through a foam sleeve or olive that is wedged at the opening of the nostril to limit dilution of nasal NO by ambient air. During the measurement, the subject is asked to perform maneuvers to close the soft palate to limit contamination with gases exhaled from the lung because exhaled NO from lower airways is typically much lower than nasal NO. These techniques have been used reproducibly in children over 5 years of age, but often are not possible in younger children who cannot cooperate with palate closure maneuvers. Measured NO concentration in parts per billion (PPB) varies with flow rate through the sampling line; however, nasal NO output (the product of transnasal flow rate and measured NO concentration) expressed in nL/min is constant over a wide range of transnasal flow rates and is the preferred nomenclature for reporting nasal NO measurements [28]. Cut-off values to delineate PCD from normal subjects range from 50-100 nl/min depending on the specific technique used [7, 22, 23, 24]. Recent studies have focused on optimizing and standardizing techniques for measuring nasal NO especially in children under 5 years of age who are unable to cooperate with maneuvers to close the soft palate [29*, 30*, 31*, 32*, 33*]. The biologic role of nasal NO has not been defined; however, its postulated function is local host defense through its antimicrobial actions and regulation of ciliary motility [34, 35].

PCD gene mutation analysis

Genetic diagnosis of PCD is challenging due to the extensive genetic heterogeneity and the large size of the disease-causing genes. To date, 6 genes have been linked with PCD (Figure 1). Two dynein genes, encoding ODA intermediate chain (*DNAI1*) and heavy chain (*DNAH5*) have been seen to be mutated in ~30-38% of the families evaluated [36, 37, 38, 39, 40, 41, 42]. Despite allelic heterogeneity, presence of founder mutations and mutation clusters led to the development of the clinical molecular genetic test for PCD, which aids in the diagnosis in a subset of PCD patients with the ODA defects. Mutations in other ODA genes (*TXNDC3* and *DNAI2*) have been noted in a small fraction (~2%) of all PCD patients [43, 44*], and have not been included in the clinical genetic panel yet. Recently, mutations have been described in *ktu* in ~12% of PCD patients with defects in both the ODA and IDA [45**]. The *ktu* encodes a cytoplasmic protein, Ktu/PF13, that is required for the dynein complex assembly. Although, allelic heterogeneity was present, given the relatively small size of this gene (3 exons), it is conceivable to incorporate this gene into the clinical genetic panel, especially for the subset of PCD families that have ultrastructural defects in both ODA and IDA. Diagnosis of PCD is very difficult in patients who present with the compatible clinical phenotype, but normal ultrastructure findings. Very recently, *DNAH11* was conclusively shown to be mutated in a PCD family [19]. At this juncture, studies to define large scale mutation profiling in a variety of PCD patients are needed to delineate the exact burden of *DNAH11* in the causation of PCD.

Genetic tests are very reliable because the presence of biallelic mutations in trans are diagnostic and the mutation identification techniques are more highly standardized and easier to perform, compared to ciliary ultrastructural analysis. Our knowledge about the PCD disease-causing genes is still emerging in parallel with the technology development to handle mutation scanning for multiple large genes. For most recent information on PCD genetic tests, refer to http://www.genetests.org/ which is updated as new mutations are identified.

Other diagnostic tests

Mucociliary clearance measurement (a non-invasive assessment of ciliary function in the lower airways) is available at a limited number of PCD diagnostic centers and has been proposed as an adjunctive diagnostic test for PCD [46*].

DIAGNOSTIC APPROACH

The criteria for the diagnosis of PCD include presence of characteristic phenotypic features and supporting laboratory studies. Only a few phenotypic features are apparent at birth (e.g., neonatal respiratory distress, laterality defects), but some phenotypic features become more obvious over the first years of life (e.g., chronic sinusitis, recurrent respiratory infections) and others may not be apparent until adulthood (e.g., male infertility). Therefore, the minimum number of phenotypic features varies with age from at least 3 in early childhood to typically 5 or more in late childhood and adulthood. The diagnostic approach to PCD (outlined in Table 1) is subject to modification with further development and refinement of diagnostic tests for PCD, as well as better definition of phenotypic features. The availability of genetic testing has enhanced our ability to make a definitive diagnosis of PCD, even in individuals with normal ciliary ultrastructure [19**]. Further studies are needed to provide more extensive genetic testing as well as to standardize other diagnostic testing. In the meantime, careful distinction between a definitive diagnosis of PCD versus a probable or possible PCD diagnosis is important for clinical decision-making as well as for research studies. Criteria for a definitive diagnosis of PCD are presence of at 3 (typically 5 or more) phenotypic features and either a genetic diagnosis (identification of 2 disease causing

mutations) or identification of ciliary ultrastructural defects that are specific for PCD (with no overlap with secondary ciliary defects that occur following airway infections or exposure to airway irritants). Individuals who have ultrastructural defects that may also be seen in secondary ciliary dyskinesia warrant repeat biopsy to determine if the defect resolves as expected after recovery from an airway insult; however, persistence of the defect does not exclude a secondary dyskinesia from an chronic airway insult.

As reviewed above, nasal NO measurement is a useful screening test for PCD. In an individual with at least 3 phenotypic features of PCD and a very low nasal NO level, PCD is highly probable, particularly if diagnostic tests for cystic fibrosis are negative. Only highly specialized research centers have expertise with the other adjunctive tests (high-speed videomicroscopy and mucociliary clearance measurement) to define criteria that distinguish “probable” versus “possible” PCD. With further research and standardization, these tests may become more useful as diagnostic tests.

CONCLUSIONS

The diagnosis of PCD is evolving with better definition of phenotypic features and expansion of diagnostic tests. Nasal nitric oxide measurement is likely to become a useful screening test for PCD once it is standardized and available in the clinical setting. Identification of genes involved in PCD is a very active area of research. Presently, available genetic testing for PCD can identify approximately one-third of individuals with PCD. The other adjunctive tests for PCD require specialized equipment and expertise and are likely to be restricted to PCD research centers.

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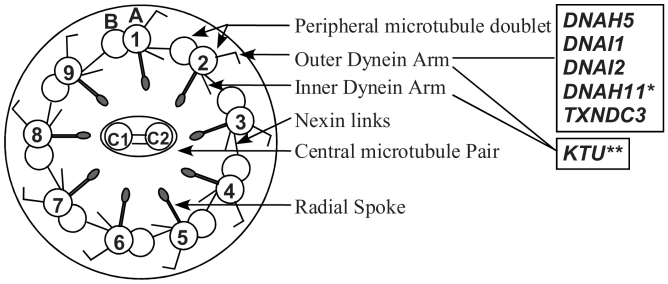

Figure 1.

Schematic showing 9+2 configuration in the cross-section of an axoneme: All of the axonemal components are labeled. Peripheral microtubules are arranged in 9 doublets (two microtubule components, A and B, are merged) with dynein arms arising from the A component. In the center is a pair of microtubules (C1 and C2). Genes mutated in human PCD are shown and linked with the corresponding axonemal structure that is involved.

* Mutations seen in patient with normal dynein arms

** Encodes cytoplasmic protein that is required for ODA assembly, and mutations seen in patients with defects involving both outer and inner dynein arms

Table 1

DIAGNOSIS OF PRIMARY CILIARY DYSKINESIA

Phenotypic clinical features (at least 3, typically 5 or more)
Neonatal respiratory distress in a term infant
Laterality defect (situs inversus totalis or heterotaxy)
Chronic, year-round, nasal congestion
Chronic, year-round, productive cough
Recurrent lower respiratory tract infections
Bronchiectasis
Chronic otitis media (middle ear effusion > 6 months duration)
Chronic pan-sinusitis
Male infertility due to impaired sperm motility
History of primary ciliary dyskinesia in the immediate family.

Laboratory evidence for definitive PCD diagnosis (at least 1)
Classic PCD ultrastructural ciliary defect
- absence or shortening of outer dynein arms
- absence or shortening of inner dynein arms
- absence of radial spokes
- absence of central pair of microtubules with transposition
Genetic diagnosis based on two disease-causing mutations in:
- DNAH5
- DNAI1
- Other genes pending definition of disease-causing mutations

Laboratory evidence supporting diagnosis of "Probable PCD"
(if accompanied by at least 3 phenotypic clinical features)
Nasal nitric oxide levels in very low range (<100 nL/min) *

Laboratory evidence supporting diagnosis of "Possible PCD"
(if accompanied by at least 3 phenotypic clinical features)
Ultrastructural ciliary defects that may overlap with secondary ciliary dyskinesia
- absence of central pair of microtubules (but no transposition)
- absence of cilia on multiple biopsies (ciliary aplasia)
- ciliary disorientation
PCD genetic testing identifying only one disease-causing mutation
Altered ciliary motility on high-speed videomicroscopy **
Altered mucociliary clearance **

* Availability limited to research sites in United States

** Specialized diagnostic centers are developing criteria to define specific characteristics that may be consistent with "Probable PCD".