Rhinology Online
Notes, Techniques, and Cases

RESEARCH NOTE

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Defining and diagnosing primary ciliary dyskinesia*

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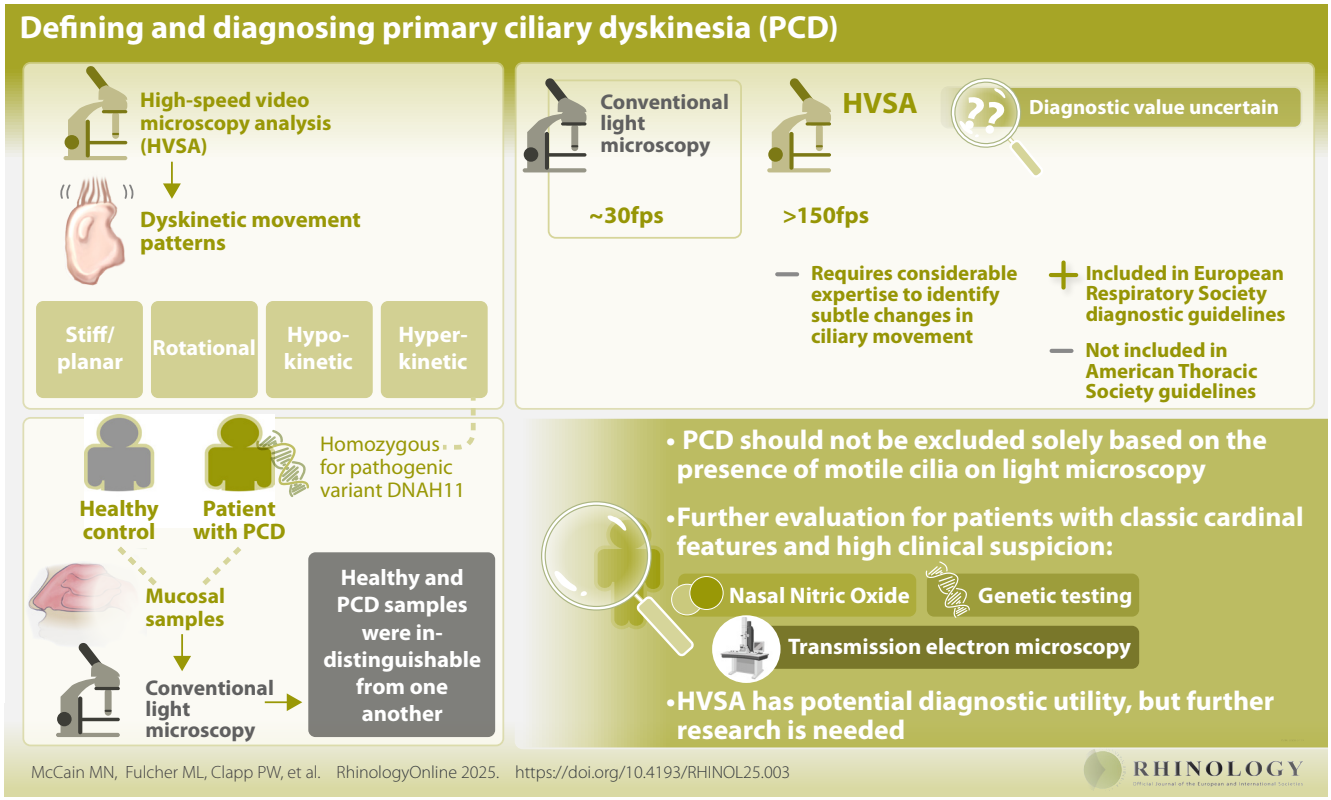

Abstract

Within primary ciliary dyskinesia, there are different ultrastructural and motility phenotypes. Inspection for cilia motility with conventional light microscopy should not be used to exclude diagnosis. Tools such as nitric oxide, genetics, electron microscopy, and clinical history should be used.

Key words: ciliary motility disorders, Kartagener syndrome, sinusitis, rhinosinusitis

Introduction

Primary ciliary dyskinesia (PCD) is a rare and genetically heterogeneous disorder characterized by impaired mucociliary clearance due to inherited defects in motile cilia (also known as secondary cilia). The term "primary" in PCD refers to the fact that the defect is intrinsic to the cilia themselves—primary in cause—rather than secondary to environmental damage or infection. This terminology can be confusing, as "primary cilia" are also a distinct type of cilia found on nearly all mammalian cells. Unlike motile cilia, primary cilia are non-motile, solitary organelles that serve as sensory hubs for cellular signaling and are not involved in mucociliary transport.

PCD was first described as Kartagener syndrome, characterized by the triad of bronchiectasis, sinusitis, and situs inversus [1]. The respiratory manifestations result from defective mucociliary transport [2], while left-right laterality defects, like situs inversus, occur in approximately 50% of cases due to dysfunctional embryonic nodal cilia, which normally direct viscera laterality.

The term "immotile cilia syndrome" was historically used, but "primary ciliary dyskinesia" is now preferred, as some variants exhibit ciliary movement that is dyskinetic rather than absent. High-speed video microscopy analysis (HVSA) has identified several dyskinetic movement patterns, including stiff/planar, rotational, hypokinetic, and hyperkinetic motion (Table 1) [3].

PCD diagnosis requires both clinical features and confirmatory testing, though no single test identifies all cases. Transmission electron microscopy (TEM) was once considered the diagnostic gold standard but only identifies definitive ultrastructural defects in ~70% of cases. Current North American guidelines recommend nasal nitric oxide (nNO) measurements, genetic testing, and TEM with an appropriate clinical history [4]. Notably, otitis media (OM) is not included in the clinical criteria given its high prevalence in the general pediatric population. However, the absence of OM would raise suspicion of an incorrect diagnosis [5].

Within otolaryngology literature, nasal brushings, biopsy, and conventional light microscopy have been explored as cost-effective screening tools for PCD [6]. We present a case of genetically confirmed PCD with light microscopy appearing to show normal, coordinated ciliary movement, highlighting the limitations of this approach.

Methods

Mucosal samples from a patient with PCD homozygous for pathogenic variant DNAH11 were collected during endoscopic sinus surgery. Healthy control mucosal samples were collected from a patient undergoing a transsphenoidal approach for pituitary adenoma. Institutional Review Board approval (UNC IRB

Table 1. Cilia beat pattern of specific PCD mutations.

Beat Pattern	Ultrastructure Defects, Protein Location	Specific Mutations
Immotile, flickering, stiff, minimal movement	Inner + Outer Dynein Arm	CFAP298/C21orf59/DNAAF16, CFAP300/C11orf70/DNAAF17, DNAAF1/LRRC50, DNAAF2/KTU, DNAAF3/C19orf51, DNAAF4/DYX1C1, DNAAF5/HEATR2, DNAAF6/PIH1D3, LRRC6/DNAAF11, SPAG1/DNAFF13, ZMYND10/DNAAF7
	Outer Dynein Arm	DNAH5, DNAI1, DNAI2, DNAL1, TXNDC3/NME8, CCDC103/DNAAF19, ODAD1/CCDC114, ODAD2/ARMC4, ODAD3/CCDC151, ODAD4/TTC25
	Normal, Ciliary Base	OFD1
	Inner Dynein Arm + Microtubular Disorganization	CCDC39, CCDC40
Rotational	Radial Spoke	STK36, DNAJB13, NME5, RSPH1, RSPH3, RSPH4A, RSPH9
	Normal, Central Pair	CFAP74, CFAP221, SPEF2, HYDIN
Reduced number of motile cilia	Normal, Cytoplasm	CCNO, MCDIAS, FOXJ1
Normal/Hyperkinetic	Normal, Outer Dynein Arm	DNAH11
	Normal, Nexin	DRC1/CCDC164, DRC2/CCDC65
	Normal, Ciliary Base	GAS2L2
Hypokinetic	Partial Outer Dynein Arm	DNAH9
	Normal, Ciliary Base	RPGR
	Normal, Intraflagellar Transport	LRRC56/DNAAF12

Adapted from Primary Ciliary Dyskinesia: A Clinical Review.3 Ultrastructural defects were identified via transmission electron microscopy (TEM). If ultrastructure was determined to be normal, the location of the mutated protein was listed following "normal." In the case of mutations with two commonly used names, both have been listed, separated by a forward slash (/).

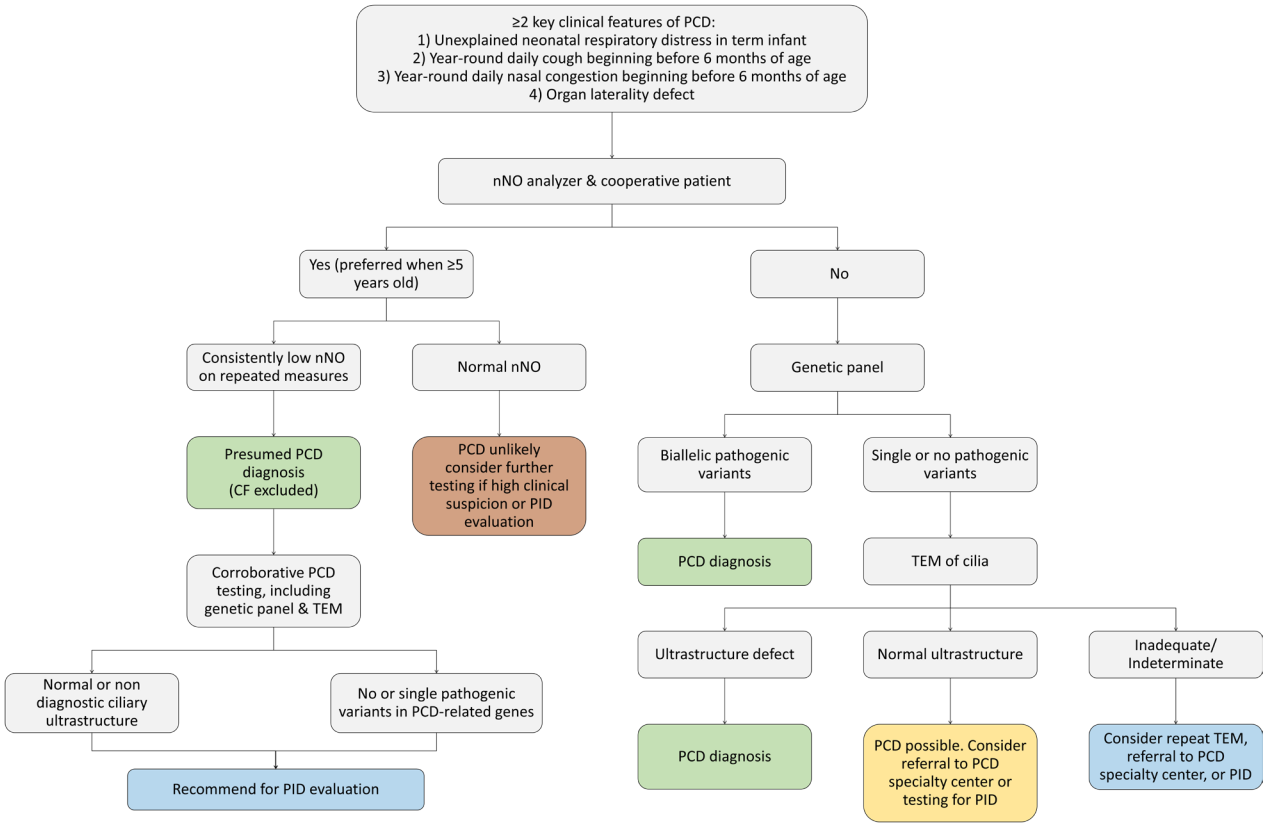

Figure 1. Recommended diagnostic algorithm for assessing patients with suspected PCD. Adapted from the revised American Thoracic Society Clinical Practice Guideline for Diagnosis of PCD [4]. No single test is 100% sensitive in diagnosing PCD. Thus, while PCD is unlikely if nNO is normal, it does not exclude PCD. We suggest further PCD testing (i.e., genetic panel, TEM) if there is high clinical suspicion. We also encourage clinicians to consider primary immunodeficiency testing if PCD and CF testing (nNO, TEM, genetic panels, sweat chloride test, etc.) have not explained the patient's symptoms. CF = cystic fibrosis, nNO = nasal nitric oxide, PCD = primary ciliary dyskinesia, TEM = transmission electron microscopy, PID = primary immunodeficiency.

03-1396) was obtained prior to procuring these excess surgical specimens.

Directly after surgical removal, airway epithelium was isolated from both samples and visualized with a light microscope at 10X magnification. Samples were prepared by washing in phosphate buffered saline and were viewed under a light microscope. Conventional light microscopy videos highlighting ciliary movement were captured at 30 frames per second (fps).

Results

Both the PCD and healthy samples demonstrated robust ciliary movement and were impossible to distinguish from each other (Supplemental Video 1).

Discussion

Nearly 60 genes are now associated with PCD (Table 1), and genotype-phenotype relationships have emerged. Our patient had homozygous pathogenic DNAH11 variants, characterized by hyperkinetic cilia that cannot effectively generate mucociliary clearance. Multiple other motile PCD variants exist, such as RSPH1, which classically has rotational motion due to a radial spoke defect. Interestingly, motile variants of PCD have not been associated with situs abnormalities. Similar to our case, these variants are difficult to distinguish from normal cilia using conventional light microscopy.

Adopted by many European centers, HSVA offers a potential solution by assessing ciliary beat frequency (CBF) and beat pattern (CBP) in freshly excised or cultured ciliated epithelia at >150 fps, often ranging from 250-600 fps [7,8]. In comparison, conventional video microscopy operates at ~30 fps. However, HSVA requires considerable expertise, as some forms of PCD are characterized by subtle changes in ciliary waveform.

Despite its utility, HVSA remain controversial [9–13]. The European Respiratory Society includes HSVA in its diagnostic guidelines, while the American Thoracic Society does not [4,14]. A large retrospective study from three English centers reported near-perfect sensitivity and specificity for HSVA [11], but its methodology has been criticized, raising concerns about inflated diagnostic ac-

curacy [10,12]. No large studies have since replicated these results, leaving the true diagnostic value of HSVA uncertain [10].

PCD diagnosis is difficult given its variability, with no single test reporting 100% sensitivity. Based on genetic epidemiological studies [15], many people with PCD go unrecognized, leading to underdiagnosis, with most presenting first to otolaryngologists because of their chronic sinonasal and middle ear disease. Often, these patients have recalcitrant disease. Awareness of motile PCD variants and advances in diagnostic tools is critical, as reflected in the revised diagnostic algorithm from the American Thoracic Society (Figure 1) [4].

Importantly, neither North American nor European guidelines support cilia inspection using conventional light microscopy alone to screen for PCD. While CBF measurements with conventional microscopy have been explored as a screening tool, this approach alone is insufficient and can miss cases of PCD, particularly those involving motile variants. Notably, 41% (24/58) of known pathogenic variants of PCD have motile, but dysfunctional cilia (3).

Conclusion

PCD should not be excluded solely based on the presence of motile cilia on light microscopy. In patients with classic cardinal features and high clinical suspicion, further evaluation with nNO, genetic testing, and TEM is warranted to avoid missed diagnoses. HVSA may also have diagnostic utility; however, further research is needed for its validation.

List of abbreviations

CBF = cilia beat frequency, CBP = cilia beat pattern, CF = cystic fibrosis, fps = frames per second, HSVA = high-speed video microscopy analysis, IRB = Institutional Review Board, nNO = nasal nitric oxide, OM = otitis media, PCD = primary ciliary dyskinesia, PID = primary immunodeficiency, TEM = transmission electron microscopy

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Authorship contribution

MNM: data collection, manuscript preparation; MLF: technical preparation, manuscript revision; PWC: manuscript revision; BDT: specimen procurement, manuscript revision; BAS: manuscript revision; SDD: manuscript revision; TWF: manuscript preparation and revision; SHR: technical preparation, manuscript revision; AJK: study formulation, specimen procurement, manuscript preparation and revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the University of North Carolina Institutional Review Board (03-1396).

Consent for publication

Written informed consent for publication of their clinical was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and material

Not applicable.

Conflict of interest

The authors have no conflicts of interest to declare.

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Supplemental Video 1. Comparison of Normal and PCD Tissue Samples Under Light Microscopy. Both the PCD and healthy samples demonstrated robust ciliary movement and were impossible to distinguish from each other with this method. Note: The small white cells shown within the normal sample are red blood cells due to sample being particularly bloody.