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A Heterogeneous Genetic Disorder: Primary Ciliary Dyskinesia

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Primary ciliary dyskinesia (PCD) is a genetic disorder that affects approximately 1 in 15,000–30,000 people, with the majority of patients inheriting the disorder via autosomal recessive inheritance. PCD is characterized by abnormal ciliary ultrastructure and/or function, which results in impaired mucociliary clearance and recurrent respiratory infections. Despite the presence of symptoms from birth, many patients with PCD remain undiagnosed until adulthood. Many advances in the diagnosis of PCD have occurred in recent years, including nasal nitric oxide assays, ciliary motility tests, and genetic sequencing. Early diagnosis and symptom management may reduce morbidity and mortality from PCD improving the patient's quality of life.

Key words: Primary ciliary dyskinesia, Genetic disorder, Diagnosis

REVIEW ARTICLE

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INTRODUCTION

Primary ciliary dyskinesia (PCD, MIM 244400) is a rare heterogeneous genetic disorder characterized by abnormal ciliary function or ultrastructure [1]. PCD Inheritance is mostly autosomal recessive, with an estimated prevalence of 1:15,000–30,000 [2]. PCD can be caused by mutations in genes that code for the axonemal structure or functional components of motile cilia [3]. PCD is a respiratory ciliopathy characterized by decreased mucociliary clearance of the airway [3]. There is no single gold standard diagnostic test for PCD [4]. Early PCD diagnosis is important for proper clinical management and better prognosis of patients with PCD.

CLINICAL FEATURES

The clinical manifestations of PCD typically begin in childhood. They may differ by the sites of dysfunctional cilia [5]. Mucociliary clearance is affected by ciliary dysfunction, resulting in chronic airway infections and inflammation. The primary manifestations are a situs inversus and unexplained neonatal respiratory distress in the neonatal period (82%), chronic otitis media (92%), pansinusitis (100%), and/or bronchiectasis in the infancy to preschool period, and infertility in the adult period [5]. Laterality defect is present in approximately half of PCD cases and is caused by the dysfunction of embryonic nodal cilia [6]. The prevalence of infertility and subfertility in PCD is still unknown. According to a systematic review, 58% of women and 100% of men are infertile [5].

PATHOGENESIS

Cilia are classified into three types: primary cilia, nodal cilia, and motile cilia.

Motile cilia are long, thin protrusions that extend up to 20 μm from the cell surface and move fluids along surfaces of respiratory epithelium such as the nasal and sinus cavities, eustachian tubes in-ear, lungs, brain ependyma, and fallopian tubes [7]. Sperm tails have an ultrastructure that is similar to cilia. The axoneme of motile cilia is made up of nine peripheral doublet microtubules with attached inner and outer dynein arms and radial spokes that surround a central complex made up of two central microtubules surrounded by a central sheath (9+2 axonems) [8]. Cilia play an important role in mucociliary clearance. Therefore, the ultrastructure of cilia is critical for improving the clearance of the lower respiratory tracts.

The nodal cilia are important in establishing left-right body orientation during embryogenesis. The nodal cilia are found in embryonic nodal plate cells and have a "9+0" microtubule arrangement [8]. Abnormalities in the nodal cilia can result in laterality defects, which may be associated with congenital heart defects [9].

PCD has various ciliary ultrastructural defects. In patients with PCD, cilia are stiff, ineffective, or absent, resulting in a build-up of mucus in the nose, sinuses, ears, and lungs, as well as a fertility problem.

DIAGNOSIS

There is no gold standard test for PCD. Several tests for PCD diagnosis have been developed, including cilia structural and functional assessments, a nasal nitric oxide (nNO) assay, and genetic testing [10]. The European Respiratory Society (ERS) guidelines, recently published, provide evidence-based recommendations on the diagnosis of PCD and offer an algorithm for diagnostic testing, which should be based on clinical symptoms, nNO assessment, high-speed video microscopy analysis (HSVMA), transmission electron microscopy (TEM) and genetic testing [10]. A definitive positive diagnosis of ERS comes with a non-ambiguous bi-allelic mutation or hallmark ciliary ultrastructural defect, according to PCD classification guidelines [10]. A highly likely diagnosis is given with compatible history, very low nNO, and either highly abnormal ciliary beat pattern on HSVMA or highly abnormal ciliary beat pattern on HSVMA following cell culture [10]. Modest or non-suggestive history and normal or high nNO renders the diagnosis of PCD extremely unlikely [10].

Traditional diagnostic tests of PCD have incorporated TEM to identify ciliary ultrastructural defects and HSVMA from airway epithelium biopsies to assess the ciliary beat frequency and motility [11]. However, chronic respiratory infection and inflammation often result in additional secondary ciliary damage, which modifies the primary ciliary abnormality. Diagnostic tests for cilia ultrastructure or function are not widely available or standardized. Furthermore, approximately 30% of patients with PCD have normal ciliary ultrastructure and/or subtle functional deficits [12,13]. Therefore, readily available diagnostic tests for PCD, such as the nNO assay and genetic testing, have benefited diagnosis.

The nNO assay has proven to be a useful PCD test. nNO is measured using a chemiluminescent nitric oxide analyzer accordance with international guidelines [14]. nNO levels are low in patients with PCD (10%–20% of normal values). However, low nNO levels have been found in some patients with cystic fibrosis, and on acute viral infections, acute bronchiolitis, and acute sinusitis [15]. Furthermore, a recent meta-analysis found high levels of heterogeneity among studies, and there is no agreement on appropriate thresholds, particularly for children under the age of 6 [16].

A genetic test should be considered as one of the diagnostic tests. PCD is a genetically heterogeneous autosomal recessive disorder. Previous studies reported over 40 pathogenic genes causing PCD [17]. Based on homozygosity and candidate gene testing, PCD-causing mutations were identified in 11 genes from 1999 to 2010 [18,19]. Exome sequencing has revealed PCD-causing mutations in 10 additional genes since 2011 [3]. There are several other newly discovered novel genes with PCD mutations [3].

Most of these genes code proteins in the axonemal structure or functional components of motile cilia. Mutations in PCD-causing genes affect the outer dynein arm (ODA), inner dynein arm (IDA), cytoplasmic proteins, microtubular disorganization, nexin link, central pair microtubules, and radial spoke proteins (Table 1) [10,20]. The majority of PCD mutations are loss-of-function variants, such as nonsense, frameshift, or splice mutations, with missense mutations occurring in a minority of cases [3].

Genetic testing is useful for diagnosing PCD in patients who have limitations with the nNO assay and electron microscopy assessment. Several studies have identified the causative genes up to 65% of cases [21,22]. Candidate gene analysis remains the primary tool for gene identification, though next-generation sequencing technologies may offer a greater advance. To establish the genetic diagnosis, non-ambiguous bi-allelic mutations in autosomal recessive and hemizygous mutations in X-linked PCD should be identified. Furthermore, to confirm

Table 1. Overview of primary ciliary dyskinesia causing genes

Sites of Defect	Gene	Locus
ODA	*DNAI1*	9p21-p13
	DNAI2	17q25.1
	DNAH5	5p15
	DNAL1	14q24.3
	CCDC103	17q12
	NME8/TXNDC3	7p14.1
	CCDC114	19q13.33
	CCDC151	19p13.2
	ARMC4	10p21
	TTC25	17q21.2
	DNAH8	6p21.2
ODA+IDA	*LRRC50/DNAAF1*	16q24
	KTU/DNAAF2	14q21.3
	C19orf51/DNAAF3	19q13
	LRRC6	8q24
	HEATR2/DNAAF5	7p22.3
	DYX1C1/DNAAF4	15q21
	ZMYND10	3p21.3
	SPAG1	8q22
	C21orf59	21q22.1
	PIH1D3	Xq22.3
MT disorganization+IDA	*CCDC39*	3q26
	CCDC40	17q25
Normal/subtle: N-DRC links missing with occasional MT disorganization	*CCDC164/DRC1*	2p23
	CCDC65/DRC2	12q13.12
Normal/subtle: increased frequency of transposition defects	*HYDIN*	16q22
Normal/Central pair defects	*RSPH9*	6p21
	RSPH4A	6q22
	RSPH1	21q22.3
	DNAH6	2p11.2
	DNAJB13	11q13.4
	STK36	2q35
	RSPH3	6q25.3
Normal/subtly abnormal: increased frequency of MT misalignment	*GAS8/DRC4*	16q24.3
Reduction of cilia number	*CCNO*	5q11.2
	MCIDAS	5q11.2
Variable	*RPGR*	Xp21.1
Unknown	*OFD1*	Xp22
Normal	*DNAH11*	7p15-21

ODA, outer dynein arm; IDA, inner dynein arm; MT, microtubular; N-DRC, nexin-dynein regulatory complex.

the genetic cause of PCD, the genetic variants should be correlated with the ultrastructural defects.

MANAGEMENT

The management of patients with PCD is not standardized and the evidence-based treatment for patients with PCD is lacking. Therefore, management strategy is based on expert consensus and the clinician's experience [4].

According to European guidelines, patients should be checked every three months for respiratory assessment [4,23]. Because patients with PCD have impaired mucociliary clearance, routine airway clearance management, elimination of inflammatory triggers, and use of antibiotics when patients with PCD have infectious diseases are required. High-resolution computed tomography can detect bronchiectasis in its early stages, before changes in lung function or plain chest radiography [24].

The treatment of otitis media aims to improve hearing levels while also preventing delays in speech and language development [25]. PCD patients frequently have chronic otitis media and/or effusion, which causes conductive hearing loss. Therefore, episodes of otitis media should be treated using standard methods, but data on surgical intervention are lacking. Hearing needs to be evaluated on a regular basis.

Sinusitis is a major issue for PCD patients. Nasal irrigation, nasal steroids, and intermittent courses of systemic antibiotics are used to treat the condition [26]. Clearing the nose allows patients to breathe more easily, improves their senses of smell and taste, and improves their sleep quality. Sinus irrigation is a safe, simple, inexpensive, and generally well-tolerated treatment option, but more studies are needed to determine its effectiveness in PCD [4].

An in vitro study with aminoglycosides demonstrated the efficacy of premature termination codon read-through stimulation in PCD-causing mutations. Because this precision medicine for PCD was a preclinical cell-line study, more study is required to validate its efficacy [27].

In the future, therapies that can potentially correct the basic disease defect or the resulting defective proteins will be required in genetic disorders such as PCD [28].

CONCLUSION

Despite the fact that symptoms are present from birth, PCD remains underdiagnosed. Significant advances in PCD diagnosis have been made in the last decade. Early diagnosis and treatment may reduce morbidity and mortality, delay irreversible lung damage, and improve quality of life.

CONFLICTS OF INTERESTS

No potential conflict of interest relevant to this article was reported.

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