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REVIEW ARTICLE

Primary ciliary dyskinesia

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a rare genetic respiratory disease caused by a dysfunction of motile respiratory cilia and is characterized by laterality defects, neonatal respiratory distress, recurrent upper and lower airway tract infections, and infertility or subfertility. Diagnosis requires a combination of different tests, such as nasal nitric oxide measurement, high-speed video microscopy analysis, immunofluorescence, transmission electron microscopy for ultrastructural analysis, and genetic testing. It is an underdiagnosed disease, and prompt diagnosis improves its prognosis. The purpose of this article is to review the current knowledge regarding the clinical aspects, management, diagnosis, and treatment of PCD. The diagnosis of PCD is complex, but early diagnosis is important to improve the prognosis. In the near future, patients may benefit from specific treatments.

Keywords: Primary ciliary dyskinesia. Kartagener syndrome. Cilia. Bronchiectasis.

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INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare respiratory disease characterized by impaired mucociliary clearance due to a structural defect in the cilia, which affects their function.

It is primarily an autosomal recessive disease, although X-linked and autosomal dominant genes have been described.

Its estimated prevalence is close to 1/7,500 individuals[1]. It is an underdiagnosed disease with an important diagnostic delay, even though symptoms appear at very early ages. In Europe, the mean age at diagnosis is 5.3 years, which is reduced to 3.5 years in patients with situs inversus. Kuehni *et al.*, in 2010, found a correlation between early diagnosis and greater government investment in health systems: While the mean age at diagnosis in the British Isles is 4.8 years, in Western and Northern Europe and in Eastern and Southern Europe, it is 5 and 5.5 and 6.8 and 6.5 years, respectively[2].

The main symptoms are recurrent upper and lower airway tract infections starting from birth or the 1st months of life, neonatal distress of unknown cause, laterality defects in up to 50% of cases, and infertility or subfertility[3]. Respiratory problems are the primary factors impacting prognosis and quality of life.

CILIARY STRUCTURE AND FUNCTION

Cilia are classified according to their axoneme structure and movement capacity (motile and immotile). They are longitudinally divided into the following subcomponents (from proximal to distal): Basal body, transition zone, axoneme, and ciliary tip (Fig. 1A). The ciliary axoneme is composed of nine peripheral microtubule doublets (A-tubule and B-tubule) and a central pair based on two single microtubules (C1 and C2) (Fig. 1B)[4].

An important number of multiprotein complexes are distributed along the microtubule core of the ciliary axoneme: The dynein arms, the nexin links, the central sheath, and the radial spokes (Fig. 1B). More than 650 proteins comprise these structures and gene variants encoding those proteins are associated with motile ciliopathies[5].

The function of the outer dynein arms (ODAs), located more peripherally, is to generate the majority of the beating force and control the speed of the ciliary beat, whereas the inner dynein arms (IDAs) seem to regulate the beat amplitude or waveform. The nexin-dynein regulatory complex connects the peripheral microtubules. Moreover, *CCDC39* and *CCDC40* are components of the axoneme ruler and create a structure that repeats every 96 nm. The radial spokes provide the structural cilia interface for transmitting regulatory signals to the arms. The microtubules are anchored to the basal body, thus connecting them to the cell. It is composed of three microtubule triplets A, B, and C. In the transition zone, these microtubule triplets are converted from the basal body to the 9 + 2 doublet structure of the axoneme. The most distal part of the cilium is formed by microtubule A and the central pair, with microtubule B disappearing[5].

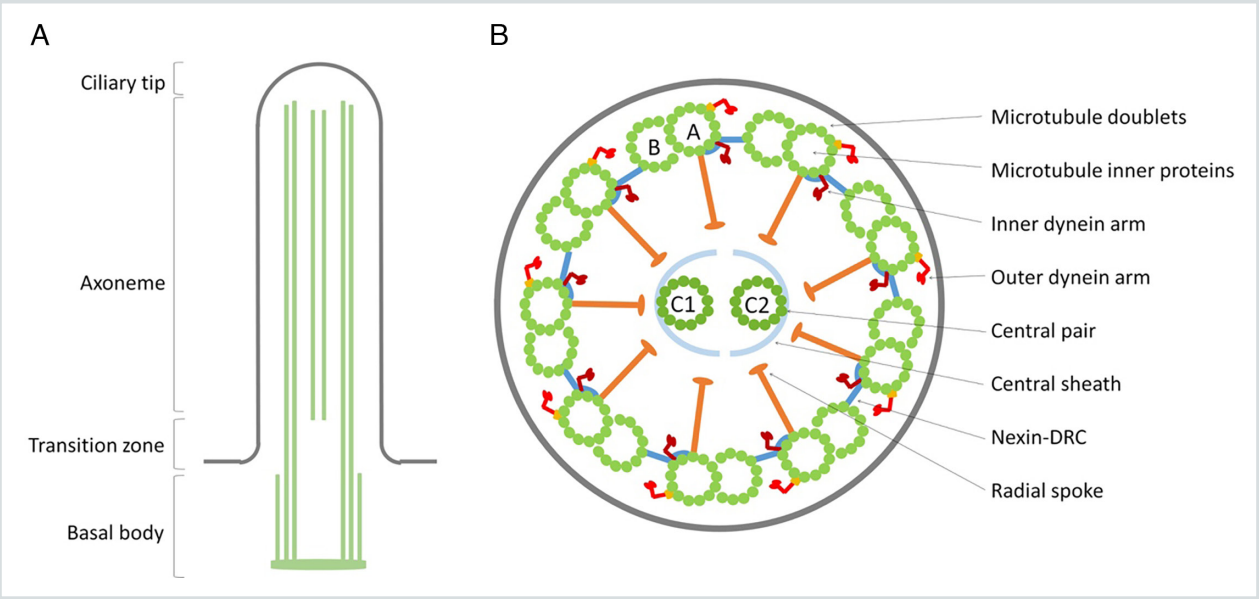

FIGURE 1. Diagram of cilia structure. **A:** longitudinal section of motile cilium with microtubule structure (*green*) and its parts. **B:** diagram of the ultrastructure of a 9 + 2 cilium in transverse section, with nine peripheral microtubule doublets (A and B) and a central pair (C1 and C2). Labels indicate the ultrastructure parts. DRC: dynein regulatory complex.

The function of the cilia in the respiratory tract is to perform a coordinated beating with a correct frequency and pattern to clear secretions and remove detritus from the airway.

CLINICAL MANIFESTATIONS

Clinical manifestations by age of presentation

The cilia motility disorder compromises mucociliary clearance, one of the airway defense mechanisms. This explains the increased pre-disposition of these patients to develop chronic respiratory infections from birth.

The clinical presentation of PCD shows considerable variability at different stages of life (Table 1).

PCD should be considered in term newborns without risk factors, such as pneumonia, situs inversus, and persistent and recurrent atelectasis[6]. Respiratory distress starting later than 12-24 h after birth and/or the need for oxygen therapy beyond the first 2 days of life has a sensitivity of 87% and a specificity of 96% for PCD diagnosis. Unexplained persistent tachypnea and neonatal rhinitis are other characteristic findings at this stage. The cause of these findings remains unclear, but some authors postulate a greater pre-disposition to air trapping and hyperinflation in the lower lobes leading to atelectasis and compression

Table 1. Clinical presentation of primary ciliary dyskinesia according to the different life stages

Presentation	Symptoms
Antenatal	*Situs inversus*, heterotaxy with/without heart defect Mild fetal cerebral ventriculomegaly
Neonatal	Persistent rhinorrhea Neonatal respiratory distress or unknown pneumonia *Situs inversus*, heterotaxy with/without heart defect Family history
Childhood	Chronic wet cough Chronic rhinosinusitis Chronic otitis media with effusion, hearing loss Asthma-like Idiopathic bronchiectasis
Adolescents and adults	Male infertility Female subfertility, ectopic pregnancy Chronic lung disease Bronchiectasis, nasal polyposis
Possible associations	Polycystic renal and hepatic disease Congenital heart defect Hydrocephaly Retinitis pigmentosa

in the upper lobes or also due to neonates spending most of the time in the supine position, compromising mucociliary clearance in the middle and upper lobes as opposed to the middle and lower lobes in children and adults[7].

Other manifestations include situs inversus (present in almost 50% of patients with PCD) or heterotaxia (6–12%) associated or not with congenital heart disease. Congenital heart disease is present in only about 5% of PCD cases and is usually accompanied by laterality defects.

Hydrocephalus due to cerebral ventriculomegaly has also been described, and it is presumed to be due to dysfunction of the motile ependymal cilia found in the cerebral ventricles and aqueducts of the brain, which are responsible for the flow of cerebrospinal fluid. Although not all cases of cerebral ventriculomegaly are caused by ciliary dysfunction, this finding, together with any organ situs abnormality, should prompt consideration of the possibility of PCD (6). It is associated with genes, such as *CCNO*, *MCIDAS* (both autosomal recessive inheritance), and *FOXJ1* (autosomal dominant inheritance)[8–10].

During infancy, symptoms of chronic wet cough, asthma-like with poor response to treatment, bronchiectasis of unclear cause, chronic rhinosinusitis (daily and year-round) associated or not with nasal polyposis and prolonged suppurative otitis media are frequent. Bronchiectasis is found in 33% of preschool children, 56-71% of school children, and 100% of adults[11]. Persistent nasal symptoms, such as rhinorrhea and nasal obstruction are frequently reported (89%). Repeated ear infections are common in many preschool children and serous otitis media (usually bilateral) is the most common otoscopic finding (80%), with tympanic membrane retraction and sclerosis also found in adults. The persistence of ear symptoms, tympanic membrane perforations, and conductive hearing loss associated with chronic middle ear effusions result in significant morbidity in terms of speech acquisition, developmental progress, and in the possibility of structural damage to the middle ear, tympanic membrane, mastoid bone, and surrounding structures[12].

Although motile and immotile ciliopathies are not usually present in the same patient and are only reported as case reports, the true

Table 2. PICADAR score

PICADAR		
Does the patient have a daily wet cough that started in early childhood?		**Yes** - Complete PICADAR
		No - Stop. PICADAR is not designed for patients without a wet cough
1. Was the patient born pre-term or full-term?	Term	2
2. Did the patient experience chest symptoms in the neonatal period (e.g. tachypnea, cough, and pneumonia)?	Yes	2
3. Was the patient admitted to a neonatal unit?	Yes	2
4. Does the patient have a situs abnormality (situs inversus or heterotaxy)?	Yes	4
5. Does the patient have a congenital heart defect?	Yes	2
6. Does the patient have persistent perennial rhinitis?	Yes	1
7. Does the patient experience chronic ear or hearing symptoms (e.g. glue ear, serous otitis media, hearing loss, and ear perforation)?	Yes	1
		Total score:

PICADAR: primary ciliary dyskinesia rule. *Adapted from Behan, et al.*[17].

overlap between the two entities is unknown. However, increased rates of motile ciliary dysfunction have been described in several retinopathies, rare syndromes such as Bardet-Biedl syndrome, and adults with polycystic kidney disease. Therefore, all patients with non-motile ciliopathies should be screened for chronic respiratory symptoms and referred to rule out PCD if respiratory ciliary dysfunction is suspected[13].

Adults present the same symptomatology as children, although chronic otitis media is less common. Thirty percent of adults report anosmia or hyposmia, and polyps are found in 15%[14]. Nasal symptoms significantly correlate with a worse quality of life scale score[15]. In patients diagnosed in adulthood, bronchiectasis is usually present in most cases. Progression of lung disease and development of bronchiectasis may eventually lead to chronic respiratory failure. In a recent multicenter study, 78% of men with PCD were infertile and 61% of women were infertile and had an increased risk of ectopic pregnancy in 7.6% of cases[16].

Primary ciliary dyskinesia rule (PICADAR) score

Since diagnostic techniques for PCD are not available in all centers and are expensive, it is important to properly select patients most likely to have a positive result. Therefore, although it has limitations, a diagnostic tool based on clinical data, called the PICADAR score, has been validated in which a score above 5 offers a sensitivity of 86% and a specificity of 73% for the final diagnosis of PCD (Table 2)[17]. Since this score includes several clinical aspects that refer to the neonatal period and are difficult to recall when the patient is an adult, a modified PICADAR score was designed where a score of 2 or more offered a sensitivity of 100% and a specificity of 89%[18].

Pulmonary function

Pulmonary function tests may be normal early in life but most often show an obstructive pattern of mild-moderate severity during development, especially in adulthood. A recent meta-analysis found heterogeneity in the results of forced expiratory volume in the first second (FEV_1), attributed to the methodological variability of the different studies but also to the possible differences that may exist according to genotypes, with a mean FEV_1 of 63% (95% confidence interval [CI]: 57-69%) in adults and 81% (95% CI: 78-83%) in children[19]. Patients with *CCDC39*, *CCDC40,* and *CCNO* variants have lower FEV_1, while *DNAH11* and *ODAD1* genotypes have less lung function impairment[20].

The lung clearance index has proven useful as an early marker of lung disease in cystic fibrosis (CF). In PCD it is also affected earlier than FEV_1 or forced expiratory flows ($FEF_{25-75\%}$) and correlates with changes found on chest computed tomography (CT) better than forced vital capacity, FEV_1, and $FEF_{25-75\%}$ [21].

It has been related to worse pulmonary function in patients colonized by *Pseudomonas aeruginosa* and those with poorer treatment adherence[22,23].

Radiographic findings

The most frequent radiographic findings are dextrocardia (in about 50% of cases), hyperinflation, peribronchial thickening, laminar atelectasis, and bronchiectasis. Chest CT is the most sensitive technique for detecting early lesions. Bronchiectasis predominantly affects the middle lobe, lingula, and inferior lobes[24]. The severity of the findings is related to the genotype of the patients, with more significant mucous plugs in patients with defects of the internal arm of dynein and microtubular disorganization with respect to patients with defects of the dynein external arm[25]. Recently, scoring scales for chest CT findings specific to PCD have been designed to assess the efficacy of PCD therapies or to identify adult patients with bronchiectasis who may have PCD[26,27].

Most patients with PCD present with sinusitis on paranasal sinuses CT, and sinus hypoplasia or aplasia is frequently found in at least 60% of adults[28].

Microbiology

Haemophilus influenzae is the most frequently isolated pathogen in patients with PCD, followed by *Streptococcus pneumoniae*, *Moraxella catarrhalis,* and *Staphylococcus aureus*. Other bacteria such as *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, *Enterobacteriaceae*, other Gram-positive bacteria, and non-tuberculous mycobacteria are less frequent. The isolation of *P. aeruginosa* varies between studies, ranging from 5 to 39%, and its incidence increases with age and in some genotypes (for example, patients with genotypes *CCDC39* and *CCDC40* have a higher prevalence than the combined group *DNAH5* and *DNAH11*)[23,29].

DIAGNOSIS

Introduction

Symptoms related to PCD may also occur in other diseases, allergic diseases, immunodeficiencies or CF should be excluded,

especially in patients with bronchiectasis of unknown cause.

The diagnosis of PCD is complex, and patients should be referred to a specialized center. Present diagnostic methods include nasal nitric oxide (nNO) as a screening test, ciliary beat frequency and pattern studies measured by high-speed video microscopy (HSVM) study, electron microscopy (EM), immunofluorescence (IF), cell culture, and genetic studies.

Both the European Respiratory Society (ERS) and the American Thoracic Society have developed guidelines and diagnostic recommendations[30,31]. The decision to conclude whether a patient has PCD or not is not always clear and easy. Both guidelines propose a combination of several tests to approximate the diagnosis. The European algorithm begins with the measurement of nNO and HSMV. If the results are abnormal or questionable, or if the patient has typical symptoms, then EM or genetic testing is conducted. In contrast, the American algorithm starts with nNO and genetic testing, and EM or HSMV is performed in questionable cases. In many cases, it is not possible to exclude or confirm the diagnosis with certainty, even if the clinical symptoms are highly suggestive, despite the test results.

The ERS diagnostic guideline recommends, based on moderate evidence, that patients should be referred for diagnostic workup of PCD when they have several of the following symptoms: chronic productive cough, persistent rhinitis, chronic ear disease with hearing loss, neonatal history of respiratory symptoms in a term newborn often requiring intensive care, laterality abnormalities, or congenital heart disease.

nNO and other screening tests

Saccharin test

The saccharin test consists of placing a saccharin particle at the level of the inferior nasal turbinate and then monitoring the time it takes for the patient to perceive its taste. It requires excellent patient collaboration, and the result is very subjective. It does not allow for distinguishing between primary and secondary ciliary dyskinesia due to other factors such as infections, allergic processes, or airway inflammation[32].

Mucociliary clearance test with radioaerosol

The pulmonary radioaerosol mucociliary clearance consists of the nebulizing technetium 99-m-labeled albumin colloid and subsequent measurements over up to 120 min to calculate the mucociliary clearance. It is a very sensitive (100%) but not a very specific test (85.7%) test. Limitations include patient radiation and the fact that coughing can invalidate the results[33].

nNO

nNO and exhaled nitric oxide are decreased in PCD for reasons not yet fully elucidated. Possible causes are reduced nitric oxide biosynthesis due to decreased nitric oxide synthase activity, increased shunting of nitric oxide to its metabolites, or retention of nitric

oxide in the sinuses[34]. nNO is more discriminative than exhaled and is a good screening test, although it is difficult to perform in children under 5 years old. The guidelines recommend using a stationary chemiluminescence analyzer and the soft palate closing maneuver. However, in recent years, it has been published that tidal breathing maneuvers may be helpful as an approximation in non-cooperative patients. Still, they are less discriminative and require establishing reference values[35].

Ideally, the patient should not have an exacerbation as the results could be falsely lower. Recent studies warn that a low nNO value may be found in the case of respiratory infections and in patients with adenoid hypertrophy, with numbers similar to those found in patients with PCD, so they recommend repeating the measurement at an asymptomatic moment[36]. At least two repeatable measurements should be performed in each nostril, and the highest result should be taken and expressed as flow (nL/min). The cut-off point established as normal when the maneuver is performed by exhalation against resistance is 77 nL/min.

In non-cooperative children, nNO is measured by holding the breath or at tidal volume, the cut-off points for the latter maneuver being somewhat lower (30 nL/min in 1-2 years old and 40-44 nL/min in children > 2 years old)[35].

Until recently, the determination of high nNO-levels was considered to rule out PCD, but this is not always true if symptoms are highly suggestive of the disease since some publications have reported cases of patients with normal nNO levels that may differ according to the genotype (Table 3)[37].

HSVM

The frequency and pattern of the ciliary beat are analyzed in a sample of ciliated respiratory epithelium obtained by brushing the nasal mucosa at the level of the inferior nasal turbinate or the septum with a small diameter brush. Upper respiratory tract infection can cause damage to the airway epithelium (secondary ciliary dyskinesia). For this reason, the test should be postponed for 4-6 weeks after an acute episode.

The movement of the cilia is recorded with a high-speed digital camera (connected to an optical microscope) at 120-500 images/s and then reproduced at a slower speed to analyze the beating frequency and pattern in different planes, such as lateral, toward the observer and viewed from above (Fig. 2A). It is as important to analyze the ciliary beat frequency as its pattern because 10% of patients with PCD have a normal frequency and an impaired motility pattern[30]. The reference range for ciliary beat frequency differs from study to study (between 8.7 and 18.8 Hz), so each center should have its reference values. The normal value for the ciliary dyskinesia rate is not clearly established but ranges from 2.8 to 25.2%. European guidelines are needed to improve sample processing and to have validated normal values[38].

Specific beating patterns have been related to specific ultrastructural alterations and genetic defects (Table 3).

A recent study shows that video microscopy has a high sensitivity (0.96-1) and specificity (0.96-0.91) for the diagnosis of PCD[39].

Table 3. Correlation between the different genes described, the level of nasal nitric oxide and the findings in the motility study and electron microscopy

Ciliary defect	GENE	nNO	Motility	Electron microscopy
Outer dynein arms	*DNAH5*	Low	Immotile or stiff	Outer dynein arm defect
	DNAH9	Normal or low	Reduced distal bend	Partial outer dynein arm defect
	DNAH11	Low	Stiff, hyperkinetic, or immotile	Normal
	DNAI1	Low	Residual movement	Outer dynein arm defect
	DNAI2	Low	Residual movement	Outer dynein arm defect
	DNAL1	Low	Residual movement or immotile	Outer dynein arm defect
	NME8 (TXNDC3)	Not reported	Residual movement in some areas, normal in other areas	Partial outer dynein arm defect
	CCDC103	Normal or low	Residual movement or normal	Outer dynein arm defect ± inner or normal
	LRRC56 (DNAAF12)	Normal or low	Reduced distal bend/Variable	Normal
Outer dynein arm docking complex	*ODAD1 (CCDC114)*	Low	Immotile or flickering	Outer dynein arm defect
	ODAD2 (ARMC4)	Low	Immotile or flickering	Outer dynein arm defect
	ODAD3 (CCDC151)	Low	Residual movement or immotile	Outer dynein arm defect
	ODAD4 (TTC25)	Low	Immotile or flickering	Outer dynein arm defect
	ODAD5 (CLXN/EFCAB1)	Not reported	Not reported	Outer dynein arm defect
Inner dynein arm subset assembly/ targeting	*CFAP57 (WDR65)*	Low	Reduced bending angle	Normal
	TTC12	Normal or low	Variable	Outer dynein arm defect ± microtubular disorganization
	DNAH1	Not reported	Not reported	Normal
Cytoplasmatic dynein arms assembly	*DNAAF11 (LRRC6)*	Low	Immotile	Outer and inner dynein arm defect
	DNAAF1 (LRRC50)	Not reported	Immotile	Outer and inner dynein arm defect
	DNAAF2 (KTU)	Low	Immotile	Outer and inner dynein arm defect
	DNAAF3 (C19orf51)	Low	Immotile	Outer and inner dynein arm defect
	DNAAF4 (DYX1C1)	Low	Immotile	Outer and inner dynein arm defect
	DNAAF5 (HEATR2)	Low	Immotile or residual movement	Outer and inner dynein arm defect
	DNAAF6 (PIH1D3)	Low	Immotile	Outer and inner dynein arm defect
	DNAAF13 (SPAG1)	Low	Immotile	Outer and inner dynein arm defect
	ZMYND10 (DNAAF7)	Low	Immotile	Outer and inner dynein arm defect
	CFAP298 (DNAAF16/ C21orf59)	Low	Immotile	Outer and inner dynein arm defect
	CFAP300 (DNAAF17/ C11orf70)	Low	Immotile	Outer and inner dynein arm defect
96-nm axonemal ruler	*CCDC39*	Low	Stiff with reduced bending angle	Microtubular disorganization and inner dynein arm defect
	CCDC40	Low	Stiff with reduced bending angle	Microtubular disorganization and inner dynein arm defect
Radial spoke	*RSPH1*	Normal or low	Stiff and some areas rotational pattern	Central pair complex defect/Intermittent transposition
	RSPH3	Low	Stiff or immotile	Intermittent central pair defect/absence of radial spoke

(Continues)

Table 3. Correlation between the different genes described, the level of nasal nitric oxide and the findings in the motility study and electron microscopy (*continued*)

Ciliary defect	GENE	nNO	Motility	Electron microscopy
	RSPH4A	Normal or low	Rotational pattern	Central pair complex defect/intermittent transposition
	RSPH9	Normal or low	Rotational pattern	Central pair complex defect/intermittent transposition
	RSPH23 (NME5)	Not reported	Not reported	Central pair complex defect
Central pair complex	*HYDIN*	Normal or low	Normal, immotile, and some areas rotational pattern	Normal/transposition
	STK36	Normal	Stiff and some areas rotational pattern	Normal/transposition
	SPEF2	Normal or low	Stiff and some areas rotational pattern	Normal/transposition
	CFAP74	Normal	Rotational pattern or stiff	Normal
	CFAP221 (PCDP1)	Normal	Rotational pattern	Normal
	DNAJB13	Low	Reduced bending angle	Normal/transposition
Nexin-dynein regulatory complex	*DRC1 (CCDC164)*	Low	Reduced bending angle/ hyperkinetic	Normal/intermittent microtubular disorganization
	CCDC65 (DRC2)	Low	Dyskinetic/hyperkinetic	Normal/intermittent microtubular disorganization
	GAS8 (DRC4)	Normal or low	Reduced bending angle	Normal/intermittent microtubular disorganization
Multiciliogenesis	*MCIDAS*	Low	Inadequate for analysis (oligocilia)	Normal/oligocilia
	CCNO	Normal or low	Inadequate for analysis (oligocilia)	Normal/oligocilia
	FOXJ1	Normal	Normal or stiff	Normal/oligocilia
	NEK10	Normal	Normal	Normal/short cilia
	TP73	Not reported	Not reported	Normal/oligocilia/short cilia
	TUBB4B	Not reported	Not reported	Oligocilia/short bulbous tips
	IFT74	Low	Not reported	Short cilia/microtubular disorganization
Basal body, distal appendage assembly, and basal axoneme	*RPGR*	Normal or low	Variable	Normal/outer and inner dynein arm defect
	OFD1	Normal or low	Variable	Normal
	GAS2L2	Normal or low	Mild dyskinesia/hyperkinetic	Normal/disoriented cilia
Inner microtubular proteins	*MNS1*	Not reported	Reduced bend angle	Partial outer dynein arm defect
	CFAP106 (ENKUR)	Normal	Normal	Normal
	CFAP53 (CCDC11)	Normal	Normal	Normal
	CFAF45 (CCDC19)	Normal	Normal or mild hyperkinetic	Normal
	CFAP52 (WDR16)	Normal	Not reported	Normal

nNO: nasal nitric oxide. *Adapted from references* [3,46-48].

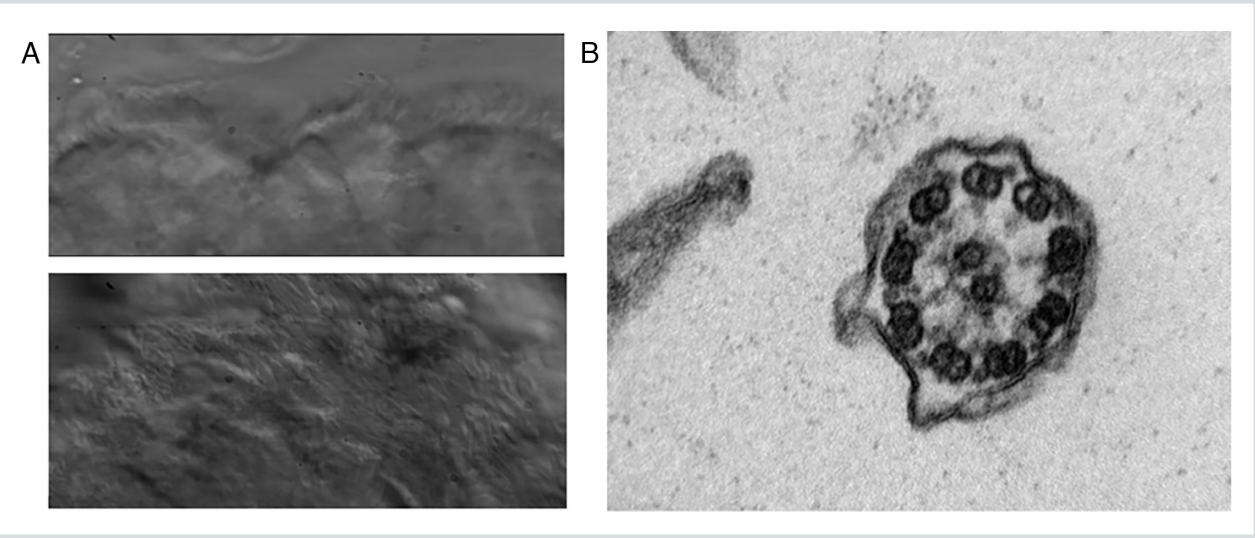

Figure 2. **A:** view of ciliated respiratory epithelium with a lateral view (upper image) and view from above (lower image) through high-speed video microscopy. **B:** view of a normal cilium through ciliary ultrastructural study with electron microscopy.

Culture of respiratory epithelial cells

In secondary ciliary dyskinesia, ciliary motility and ultrastructural changes may be observed, but they will no longer be present when the sample is re-examined after cell culture. This can be performed according to several techniques[40]. However, they are very laborious and complex procedures with a low success rate. The air-liquid interface (ALI) technique allows to obtain a sufficient number of cells for subsequent re-analysis of ciliary motility, EM, and IF[41].

EM

Preparation of the specimen for subsequent EM visualization is a complex process that includes fixations, washing, and embedding and should be performed in a specialized center (Fig. 2B). For a correct interpretation of the results, it is also necessary that the patient has not suffered from an acute respiratory infection in the past 4-6 weeks.

A European consensus on the interpretation of findings found in EM has recently been published. The defects are classified into two groups: Class 1, which is diagnostic on its own for PCD, and Class 2, which requires another test to support the diagnosis, as they can easily be confused with secondary defects. Class 1 defects include dynein outer arm deficiency, dynein outer and inner arm deficiency, and microtubule disorganization with dynein inner arm defect. Class 2 defects include: central pair defects (absence of one or two of the microtubules, "8+1" structure), basal body mislocalization with few or no cilia, and microtubule disorganization with IDAs present or lack

of ODAs (together with/without inner arms) in 25-50% of sections[42]. Patients without PCD have up to 10% secondary defects.

In 30% of patients with PCD, an alteration in ciliary motility is observed without finding any defect in the ciliary ultrastructure. The development of new EM techniques (cryo-EM, electro-tomography) opens a new field to improve resolution and diagnosis[43].

There is a relationship between anomalies in the frequency or pattern of ciliary beating, genetic variants, and some ciliary ultrastructure defects (Table 3).

IF

IF is a technique of recent application for the diagnosis of PCD that allows an indirect view of the ciliary proteins through fluorescence and using specific antibodies to detect the absence of any of them (Fig. 3)[44]. Different antibodies are being developed to detect more protein deficits. For this reason, in some studies, it is postulated as a complementary technique to EM or as a substitute for it when EM is unavailable or there is no experience[45].

Genetic study

PCD is an autosomal recessive disease, although some X-linked genes (*OFD1*, *RPGR*, and *DNAAF6*) and recently some autosomal dominant genes (*FOXJ1*, *TUBB4B*) have been identified[3].

The definitive diagnosis of PCD is made by genetic study. At present, more than 50 genes are known, of which 70-80% of individuals with PCD have a biallelic variant in one of them. Genetic defects have been related to specific cilia proteins and, in most cases, to alterations in EM and IF. Table 3 shows the correlation between the different genes described in the level of nNO and the findings in the motility study and EM[3,46-48].

TREATMENT

General measures

There is currently no curative treatment for PCD, so treatment focuses on improving the symptoms. The goals of treatment are to improve mucociliary clearance, treat upper and lower respiratory tract infections with the most appropriate antibiotic therapy, detect and treat complications early, and optimize treatment for otitis media and sinusitis.

As general measures, receiving pneumococcal and annual influenza vaccination are recommended. Active and passive exposure to tobacco should be avoided, exposure to respiratory pathogens and pollution should be minimized, and the use of antitussive medications should be avoided.

The use of bronchodilators and inhaled corticosteroids is recommended only in the presence of concomitant asthma[49].

Mucociliary clearance

Respiratory physiotherapy and physical exercise

Physiotherapy varies according to the patient's age, clinical condition, resources, and the

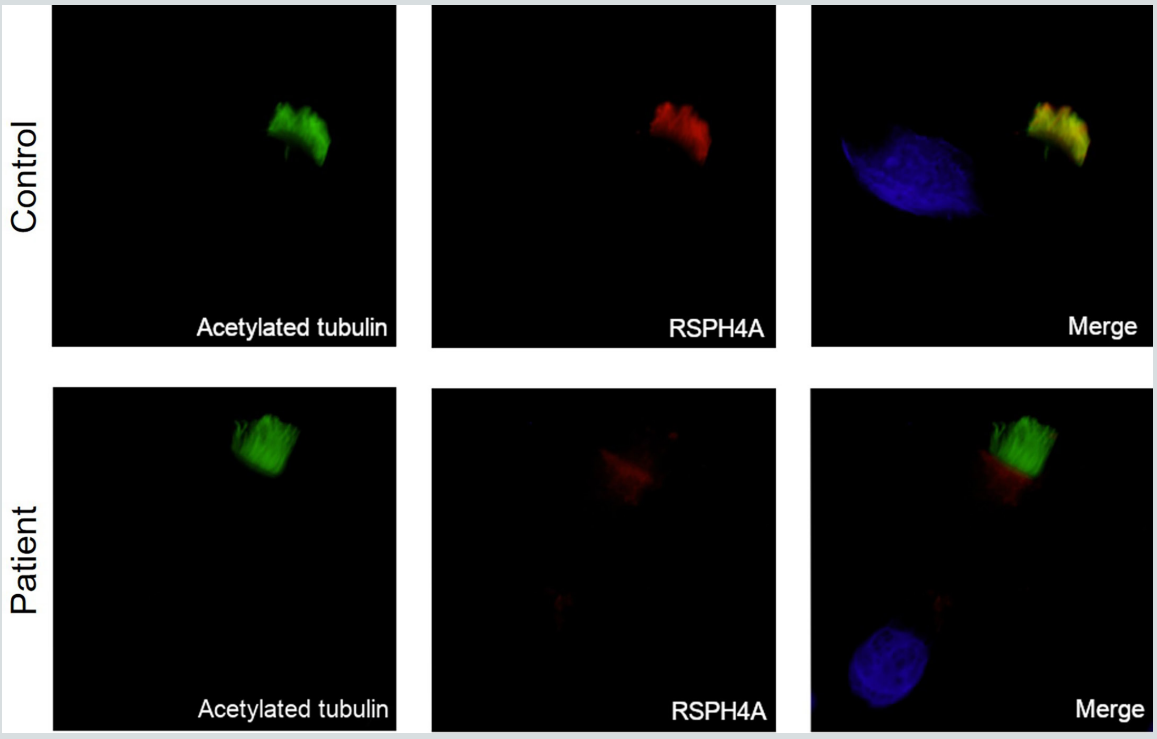

Figure 3. Example of immunofluorescence result in a patient with primary ciliary dyskinesia and homozygous pathogenic variant in the *RSPH4A* gene. The first column shows cilia by acetylated α-tubulin (green); the second column shows the protein RSPH4A (red); and the third column shows the final merged image with the nuclei stained with DAPI. The patient showed absent RSPH4A protein in ciliary axoneme.

experience of the physiotherapist. Its main objective is to keep the airway clear of secretions to reduce pulmonary infections and improve the patient's lung function. There are no data to suggest that one technique is superior to another. Two 20-min sessions per are recommended, increasing in case of respiratory exacerbations. Instrumental techniques may be useful in some patients and physical exercise is recommended in all patients[50].

Drugs to improve mucociliary clearance

Hypertonic saline increases airway osmolarity and thus improves mucociliary clearance. This effect is widely proven in CF patients, but only recently has a randomized study been performed in patients with PCD. No significant improvement in quality-of-life scores was confirmed, but an improvement in health perception scales was observed[51].

The CLEAN-PCD study (Phase 2), designed to evaluate the efficacy, safety, and quality of life of an epithelial sodium channel inhibitor (idrevloride) with or without hypertonic saline, has shown a significant improvement in lung function 28 days after treatment in the drug administration group[52].

Recombinant human DNase is an enzyme that destroys the DNA of degraded neutrophils found in respiratory secretions, thus

improving their viscosity and clearance. Randomized studies in adult patients with non-CF bronchiectasis show no benefit in quality of life, sputum characteristics, or lung function, in contrast to patients with CF[53]. In one study, it was even associated with a worsening of FEV_1 and increased pulmonary exacerbations[54]. For this reason, it is not used in routine practice, but its use can be considered in individualized cases.

Other mucolytic agents

The use of mucolytics such as N-acetylcysteine is not indicated since its efficacy in oral or nebulized form has not been demonstrated.

Antibiotic treatment

Another base of treatment is the early detection of respiratory infections. Frequent sputum cultures, pharyngeal swabs, or nasopharyngeal aspirates (every 3-4 months) are essential to detect bronchial colonization (including non-tuberculous mycobacteria) and treat it with appropriate antibiotics, depending on the results[55].

Mild-to-moderate exacerbations can be treated with oral antibiotics for 14-21 days. If the exacerbation is severe, there is no improvement of symptoms, or a very resistant bacterium is isolated, endovenous treatment for 10-14 days will be chosen. It is recommended to increase that mucociliary clearance during the treatment period to accelerate the clearance of mucus and bacteria from the airways.

The expert consensus published in 2021 recommends treatment in case of isolation of *P. aeruginosa*, methicillin-resistant *S. aureus,* and *Burkholderia cepacia* regardless of whether clinical symptoms are present or not and only treat in case of symptoms isolations of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and methicillin-sensitive *S. aureus*[56].

If *P. aeruginosa* is isolated, eradication treatment is similar to that used in CF, although evidence of its efficacy has not yet been demonstrated in patients with PCD[57].

If respiratory infections are frequent, the use of prophylactic antibiotics may be considered. In these cases, the use of inhaled antibiotics can be evaluated, although there are no studies to prove their efficacy in children with non-CF bronchiectasis or PCD. A multicenter randomized controlled trial of 6 months of azithromycin as prophylaxis in patients with PCD, including both adult and pediatric patients, demonstrated a 50% reduction in the rate of exacerbations with a good tolerability profile. Although its potential toxicities (ototoxicity, QT interval prolongation) and bacterial resistances should be considered if administered for long periods of time for common pathogens (*S. aureus*, *S. pneumoniae*, *H. influenzae*) and atypical mycobacteria[58].

Otolaryngological treatment

Chronic suppurative otitis media

The main treatment for suppurative otitis media is systemic and topical antibiotics,

focusing on the prevalence of *Streptococcus pyogenes*, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *S. aureus*. In cases of recalcitrant acute otitis, myringotomy should be considered to obtain a middle ear culture.

The use of transtympanic ventilation tubes is controversial. Possible complications following tube insertion include chronic mucoid discharge, transient or persistent perforation of the tympanic membrane, cholesteatoma, or tympanosclerosis. Intervention may be beneficial if the patient has chronic otitis that is refractory to antibiotic treatment and is associated with significant hearing loss and/or damage to the tympanic membrane or middle ear structures. Another option in the case of accentuated hearing loss is the transient use of hearing aids[59,60].

Chronic rhinosinusitis

Therapeutic strategies include saline nasal irrigation, topical nasal steroids, and antibiotics. Nasal irrigation with iso or hypertonic saline is a beneficial and safe method in PCD, as it is in the general population. It can clear stagnant mucus and is inexpensive, well-tolerated, and practical. Topical anticholinergics may be useful in some cases.

Endoscopic sinus surgery (with or without inferior turbinate meatotomy) is indicated in cases of nasal obstruction, headache, polyposis and/or facial pain, lateral medialization of the nasal wall, pulmonary exacerbations correlated with sinusitis or sinusitis with poor response to conservative medical treatment[59].

Surgical treatment

Lobectomy or segmentectomy is not routinely indicated in PCD. The indications for such an intervention are the same as in non-CF bronchiectasis: severe localized bronchiectasis with recurrent febrile processes or severe hemoptysis despite aggressive medical treatment.

In severe cases with advanced lung function decline, lung transplantation may be indicated[57].

Other treatments and future prospects

Many patients with PCD require fertility treatments. The most commonly used technique in men is intracytoplasmic sperm injection. In women, pregnancy should be monitored because of the increased risk of ectopic pregnancy. *In vitro* fertilization can be performed in cases where there is tubal dysfunction[57].

PCD is a disease that has a significant impact in the quality-of-life scales. The mothers of affected patients also score higher on stress scales. Therefore, in many cases, psychological support may be necessary in addition to education for patients and their families[61].

The creation of specialized PCD networks in the United States and Europe (PCD - Clinical Trial Network)[62] has allowed the development of clinical trials with new therapies.

Pre-clinical trials of nebulized messenger RNA to correct some gene variants, such as *CCDC40* and *DNAI1*, are a treatment that will surely become a reality for these patients. In the future, the development of gene therapies is expected to provide a treatment to restore ciliary function[3,49].

PROGNOSIS AND FOLLOW-UP

In general, people with PCD have a normal life expectancy. The rate of lung function decline is much slower than in CF patients. Situs inversus is generally not associated with other congenital malformations. With a healthy lifestyle including abstinence from smoking, respiratory physiotherapy, and early and appropriate treatment of respiratory superinfections, the prognosis is generally favorable, although there are subgroups of patients with a more rapid decline. Delayed diagnosis is associated with poorer long-term quality of life.

Follow-up should be multidisciplinary, including pulmonologist and nurse specialist, otorhinolaryngologist, respiratory physiotherapist, and other specialties according to each case.

Follow-ups with the pulmonologist are indicated every 3-6 months in children and every 6-12 months in adults. Regarding respiratory monitoring, oximetry, spirometry, sputum culture collection (or induced sputum, pharyngeal smear, nasopharyngeal aspirate), and upper airway microbiology should be performed at least 4 times a year, and culture for mycobacteria at least once a year or when there is clinical or pulmonary function deterioration of unknown cause[56]. The need to perform controls with pulmonary imaging tests is discussed (routine controls versus cases with poor evolution to assess the extent of bronchiectasis and disease progression). There are no consensus guidelines for radiological controls in PCD[55,63].

In addition, audiometry controls should be performed every 6-12 months in children, and when there is symptomatology in adults, nutritional status should also be taken into account as these patients usually have a low body mass index[55,64].

CONCLUSION

PCD is a rare disease with symptoms in common with other diseases and is therefore often underdiagnosed. Early diagnosis is essential to improve outcomes. Diagnosis is based on ciliary motility study, EM, IF, and genetic studies. The predictive PICADAR score and nNO measurement are useful screening tests with high sensitivity and specificity. Present treatment is symptomatic and similar to other diseases, such as CF and bronchiectasis. However, new therapies targeting specific mutations are being developed, making the correct diagnosis of this disease even more important.

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CONFLICTS OF INTEREST

None.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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