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Primary Ciliary Dyskinesia: Pathogenesis, Diagnosis, and Management

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Abstract

Primary ciliary dyskinesia (PCD), also known as congenital Kartagener's syndrome, is a multifactorial pleiotropic disorder that commonly affects patients throughout their life, from fetal development to death. It owes its clinical presentation to the number of genetic defects that lead to abnormally functioning or nonfunctional cilia throughout the body. In particular, it affects the respiratory system and the nasopharyngeal ducts significantly. Much like Cystic Fibrosis (CF), which presents with the buildup of mucus and the presence of unwanted bacterial biofilms, impaired cilia in PCD patients often leads to life-long respiratory distress, bronchiectasis, and persistent respiratory infections. At birth, PCD patients can also present with situs abnormalities, as the cilia during critical developmental stages concerning left-right partitioning fail to move fluid containing developmental signaling compounds leading to misplaced primordial structures. The genetics and the etiology of this disease are not yet fully understood and are actively being studied, but the most common phenotypes are defects to the ciliary outer arm, inner arm, and micro-tubular arrangements. Furthermore, due to the complex, multifaceted nature of this disease and its symptoms, management of PCD is complex and likely involves a combination of both pharmaceutical and non-pharmaceutical approaches. This review highlights the pathogenesis and pathophysiology of PCD and the appropriate diagnostic methods and management of PCD as a means of providing clinically useful information as the study of this disease rapidly advances.

Introduction

PCD is a genetically heterogeneous autosomal recessive disorder involving multiple body systems with an estimated prevalence of 1 in 16,000-30,000 (Shapiro et al. 2014). The genetic mutations result in the production of cilia with a spectrum of functionality ranging from impaired mobility to complete non-functionality. This results in failure of mucociliary clearance, primarily affecting airway structures. Patients commonly present with neonatal respiratory distress, continuing to persistent wet cough, recurrent upper and lower respiratory infections, perennial rhinosinusitis, otitis media, bronchiectasis, and infertility (Leigh et al. 2009). Cilia play a pivotal role in organogenesis laterality, and consequently, PCD cases often present with situs anomalies. Situs inversus totalis, a congenital disorder where visceral organs' positions are mirrored from their original position in the body cavity and the most common congenital anomaly, is seen in approximately 50% of cases. Less common but relevant phenotypes of PCD are situs ambiguous and congenital heart defects (CHD). The latter can occur in conjunction with situs abnormalities and this is defined as heterotaxy (Shapiro et al. 2014).

PCD is found to be multifactorial and caused by mutations of different genes simultaneously (Horani et al. 2016). The mutant genes usually associated with PCD are responsible for the correct structuring, functioning, and assembly of ciliary complexes. An example of this would be the DNAI1 gene, a member of the dynein intermediate chain family, which contributes to the ultrastructure of the outer dynein arm (Guichard et al.

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2001). Further studies have shown that a mutation in DNAI1 linked ciliary dysfunction to situs inversus (Guichard et al. 2001). Other PCD associated genes include DNHA5, a gene contributing to the outer dynein arm structure and the ciliary power stoke, along with DNAAF2, DNAI2, HEATR2, CCDC103, LRRC6, etc. Mutations in these genes are thought to be responsible for the clinical symptoms of PCD, which can range widely and appear shortly after birth in neonates (Horani et al. 2016). With adulthood, these symptoms slowly evolve, becoming more chronic and severe, revealing new clinical manifestations with time. The most prevalent manifestation of PCD is recurrent upper and lower respiratory tract infections and respiratory distress in infants (Knowles et al. 2013). Upon reaching school-age, children present with a chronic wet cough, and the development of bronchiectasis becomes more likely. Patients of all ages describe a yearlong nasal congestion and often present with persistent episodes of pneumonia throughout their lifetime (Mirra, Werner, and Santamaria 2017). In adulthood, infertility is very common amongst PCD patients due to the lack of sufficient motility of spermatozoa in affected males and disrupted movement of the ovum through the uterine tube in affected females, often leading to ectopic pregnancies (Knowles et al. 2013).

Though there is no internationally agreed-upon standard by which we diagnose PCD, there exist a number of tests that can be performed to confirm a diagnosis. The gold standard for diagnosis of PCD is transmission electron microscopy (TEM) (Shoemark et al. 2020). With TEM or other forms of high-magnification video microscopy, the goal is to identify ultrastructural defects in the cilia; however, due to the difficulty in obtaining adequate samples of cilia and the technical skill required in operating electron microscopes and evaluating images of the ultrastructure of cilia, TEM, though rigorous, is not a feasible diagnostic tool in underserved areas or for the growing number of patients who present with normal ciliary EM images (Knowles et al. 2013). Novel screening methods for PCD include the nNO test which measures nasal nitric oxide (NO) and patients with PCD have been reported to have nNO levels 10-20% of normal values (Knowles et al. 2013). nNO tests are usually performed in conjunction with sweat chloride tests and comprehensive genetic testing to diagnose differentially between defects in the CFTR gene for CF differentially and PCD (Knowles et al. 2013; Leigh, Zariwala, and Knowles 2009). Though computed tomography (CT) imaging is rarely done for children, CT and magnetic resonance imaging (MRI) can also be used to confirm diagnosis of situs inversus as well as other lung abnormalities seen in PCD (Kennedy, Omran, et al. 2007).

Though there is no cure for PCD in general, the onset of bronchiectasis can be delayed with antibiotic therapy, and management of the disease usually follows the same treatment of lung disease as seen in CF. The mainstay of treatment for PCD is regulation of the recurrent respiratory infections via bronchodilators, physiotherapy, and antibiotics [11]. Mucolytic agents and expectorants are also advised. With regards to situs inversus and dextrocardia, most situs abnormalities are asymptomatic and surgery is avoided. Surgery can be employed for resection of the lung and for lung transplantation, but is usually only considered at late-stage bronchiectasis and lung disease (Meeks and Bush, n.d.).

There exists a wealth of information surrounding PCD, but physicians still may struggle with managing this disease and its different presentations among various age groups. The following review highlights the diagnostic criteria of PCD and the congenital abnormalities it may bring, its pathophysiology over different stages in life, methods of diagnosis of PCD, and the various methods of management that have developed in the past years.

Pathogenesis

In humans, cilia are cylindrical projections from the apical surface of epithelial cells. They are found on a variety of surfaces of the body as well as in early embryonic development. Based on functionality, cilia fall into 3 categories primary, motile, and nodal. The defects seen in PCD are limited to the motile and nodal cilia, which is the etiology of the disease's symptoms (Bhatt and Hogg 2020). The motile cilia are found in the conduction zone of the airway, sinuses, middle ear, brain ependyma, fallopian tubes, and spermatozoa. The active movement of the 9 + 2 orientation of microtubules in relation to each other produces a half cone trajectory. As the many cilia beat in this fashion, a metachronal rhythm and unidirectional fluid flow are created, allowing for movement in the desired direction.

In contrast, during gastrulation, nodal cilia are present on the bilaminar disc's ventral surface adjacent to the primitive node. The 9 + 0 orientation of the microtubules creates a rotational movement in a clockwise

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direction. These transient cells result in the leftward flow of fluid over the primitive node and determine the left-right laterality of organs (Poprzeczko et al. 2019).

Airway Pathologies

In the respiratory tract, a protective layer of mucus lines the conducting airways and sinuses at the air-epithelium interface that functions as a physiological barrier to aerosolized particles, bacteria, and viruses. The epithelium's motile cilia propel the mucus against gravity and expel the mucus, along with trapped particulates, through the oral orifices; this is known as mucociliary clearance (MCC) (Kaushik et al. 2021). Any impairment of this system increases the chances of acquiring respiratory infections or chronic respiratory diseases. The importance of this system is evident in PCD, challenging patients often from birth. Between 70-80% of PCD neonates display a transient period of respiratory distress, possibly from the inadequate clearance of amniotic fluid from the lungs (Noone et al. 2004). The failure to adequately remove the mucus develops into a chronic wet cough in infancy, as the body attempts to work against gravity and persists throughout life. A complex bacterial community cultivates within the airways resulting in recurrent infections in the bronchioles, sinuses (rhinosinusitis), and middle ear (otitis media), which are principal features reported in virtually all PCD patients (Noone et al. 2004). The chronically episodic bronchitis results in another principal manifestation of PCD, bronchiectasis. The severity of bronchiectasis seems correlated with age, which is substantiated by the repeated damage to the epithelium over time (Leigh et al. 2009).

Laterality defects

The failure or impairment of nodal cilia during early development alters the left-right laterality of internal organs. The random arrangements of organs are a common feature of PCD, with approximately 60% in pediatric and 50% in adult cases. Additional laterality defects have been reported in PCD as heterotaxy in approximately 6% of patients (Kennedy and Plant 2014). The heterotaxy anomalies found in PCD are abdominal situs inversus, life-sided polysplenia, and asplenia. An important consideration of PCD patients presenting with heterotaxy is the increased incidence of cardiac and vascular disarrangements, which are correlated with increased morbidity. These laterality defects are rarely isolated to a single organ and often occur in combination with each other and on a spectrum of severity (Kennedy, Omran, et al. 2007).

Reproductive issues

Among PCD patients, infertility is a typical phenotype occurring in over half of cases. The incidence among males is higher (75%), which is expected due to the heavy reliance on motile cilia to propel spermatozoa to the ovum. In contrast, female infertility is more complex and less understood. Reduced reliance on motile cilia to move the ovum into the correct location for fertilization may contribute to the complexity of female infertility. Female infertility occurs in roughly 60% of cases, but these patients have reported the use of benchtop fertilization technology to successfully conceive and result in healthy births (Vanaken et al. 2017). In females, the risk for ectopic pregnancies is higher, but the mechanism behind this correlation is not well-studied. One possible explanation for this finding is that the impaired cilia along the lining of the uterine tubes fail to move the egg along its path to the endometrial cavity leading to early fertilization and implantation in the ampulla (Blyth and Wellesley 2008).

Other pathologies

Ciliary defects can also present issue in other parts of the body. For example, the build up of mucus in the ear and the impaired motility of cilia in the pharyngotympanic of the middle ear can lead to conductive hearing loss due to acute otitis media. Ontologically, studies have also shown that PCD can lead to otorrhea, tympanic perforation, and complete hearing loss (Prulière-Escabasse et al. 2010). However, longitudinal studies show that hearing loss is resolved over time and, by adolescence, most otological issues can be resolved with regular antibiotic therapy (Majithia et al. 2005). Cilia can also be found in the ventricles of the brain, lining the ependymal cells that move cilia from the choroid plexus and the ventricles to the sinuses of the brain. Though the direct link between neonatal hydrocephalus and PCD is unknown, there have been clinical reports indicating an associated risk between the two; one possible explanation for the connection is that the immotile ependymal cilia cause stagnation of the cerebrospinal fluid and ventricular dilatation (Greenstone et al. 1984).

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Moderate to severe headaches have also been suggested as possible symptoms of impeded fluid in the sinuses of the head and face (McManus et al. 2003).

Diagnostic Methods

Although there exists no definitive standard for diagnosis of PCD, efforts have been made by organizations interested in the study and cure of this disease, such as the European Respiratory Society (ERS) or the Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia (BESTCILIA), to outline diagnostic methods and clinical algorithms when approaching PCD patients (Kuehni and Lucas 2017; Werner, Onnebrink, and Omran 2015; Kobbernagel et al. 2020). A discussion of these methods follows.

Saccharine test

Historically, the saccharine test was utilized to assess for PCD in neonates, children, and adolescents. The test involves placing a small 1mm micropellet of saccharine, a water-soluble artificial sweetener, into the inferior turbinate alongside the nasal cavities (Olm, Caldini, and Mauad 2015). The time between the placement of the saccharine and the eventual sensation of taste experienced by the patient as the saccharine particles encounter the pharynx is measured. It must be noted that the patient's ability to taste saccharine at all must be tested prior to the test; during the test, the patient must maintain the position of his head bent forward and refrain from eating, drinking, sneezing, coughing, and speaking. In some variations of the test, the patient is asked to swallow every 3 minutes after the saccharine is placed, and a time of 6 to 10 minutes until the taste of saccharin is detected is considered normal (Slavin et al. 2005). A time of 30 minutes or greater taken to taste the saccharine indicates abnormalities with mucociliary transport and can lead to a possible diagnosis of PCD (Bush et al. 1998). Some studies have shown different sensitivities for this test, and the maximum clinical threshold for saccharine tasting time indicating ciliary dysfunction has been 60 minutes (Olm, Caldini, and Mauad 2015). Due to the loss of functionality of the cilia. those with PCD are expected to take longer to taste the saccharine; however, increased saccharine tasting time can also be due to acute respiratory viral or bacterial infection, congenital malformations within the nose and pharynx such as septal deviation, or the presence of granulomas in the nasopharynx, as seen in rhinoscleroma. Due to the difficulty of administering this test, especially in children under the age of 12, the saccharine test is suggested to be used primarily as a screening test. Furthermore, due to the unreliability of the test with high false positives when patients present with respiratory infection (which is a recurring issue with diagnostic respiratory tests for PCD) and with false negatives, as an abnormal saccharine taste testing time does not always capture ciliary defects such as dyskinetic ciliary beating, the saccharine test cannot be recommended as a diagnostic test in clinical settings where more powerful methods are easily available (Barbato et al. 2009).

Nasal and fractional exhaled nitric oxide, and sweat chloride tests

The ERS included the nasal and fractional nitric oxide tests in their guidelines for diagnosis for PCD in 2009 and since then it has become the primary method for screening for PCD (Barbato et al. 2009). It involves the analysis of nitric oxide (NO) levels either in the upper respiratory tracts nasally or in the lower respiratory tracts at the levels of the bronchi and alveoli (Walker et al. 2012). Measurements of nNO involve the use of a chemiluminescence analyser which collects air from an aspirating tube inside the nostrils of a patient as their breath is held; in the case of alveolar and bronchial NO measurements, exhaled air is measured and mathematical models estimate the levels of production of NO from the conducting and alveolar respiratory compartments (Wodehouse et al. 2003; Walker et al. 2012). Variations of this test involve humming, conventional tidal breathing, or very rapid tidal breathing (VRTB) during aspiration and collection to increase sinus ventilation and facilitate the procedure for neonatal or uncomfortable patients (Weitzberg and Lundberg 2002; Holgersen, Marthin, and Nielsen 2019). It must be noted that changes to the method of collection can warp nNO levels across patient age groups and no current standard or preferred method is suggested. This tidal breathing method works better in young patients who are resistant to the the velum closure maneuver used normally in nNO tests; in general, however, measuring nNO in young patients and neonates can lead to skewed results as the necessary developmental stages required for NO production may not have been yet completed (Lucas and Walker 2018). Unlike with CF, where neonatal genetic screening and sweat chloride tests can indicate the disease at or near birth, low nNO at birth cannot be conclusive, and tests must be continually administered if PCD is suspected. The nNO test is based on the finding that 95% patients who

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present with PCD have nNO levels of about 20.0 ml/min which is 10 to 20% lower than levels in unaffected patients (Leigh et al. 2013). Walker et al. provide some hypotheses for explaining why NO levels are low in PCD patients (which are also low in patients with respiratory infections and CF) and suggest that in such diseases, the biosynthesis of NO is decreased in the respiratory epithelium, or that the buildup of mucus and lack of functional cilia traps NO in the respiratory sinuses and tracts (namely the paranasal sinuses), but more research needs to be completed to explain this phenomena (Walker et al. 2012). It is known, however, that during respiratory infection, nNO is elevated due to its antiviral effects and its role as a signalling molecule and is often elevated in those affected by asthma and COPD (Kharitonov, Yates, and Barnes 1995). As such, the nNO test is a useful test in ruling out these diseases but not effective in ruling out CF. To rule out CF, a quantitative pilocarpine iontophoresis sweat test or a sweat chloride test along with testing for defects in the CFTR receptor and the corresponding gene must be performed in conjunction with nNO tests (Leigh et al. 2013).

Transmission electron microscopy and high-speed video microscopy

Transmission electron microscopy (TEM), unlike the other clinical diagnostic methods discussed, is different in that it can directly measure the level of ciliary impairment and offers the highest power in the diagnosis of PCD. Defects in the genes that code for the ultrastructure of the cilia can be observed phenotypically after taking a brush biopsy, bronchial biopsy, or a turbinate biopsy and observed in multi-plane cross-sections under a TEM (Roomans et al. 2006). Another advantage that TEM provides is its ability to distinguish between PCD and Secondary Ciliary Dyskinesia, which describes the presence of irregularly functioning cilia as due to respiratory infections or secondary causes. In particular, TEM can distinguish between specific ciliary defects such as outer arm defects, inner arm defects, micro-tubular arrangements, and non-specific defects such as disorientation and disorganization of the cilia (Pizzi et al. 2003). Though TEM is the closest diagnostic method to being a gold-standard, some patients can still present without immediate ciliary structural defects, which is where analysis of the movement of cilia is sometimes advantageous (Shoemark et al. 2012). Ciliary beat frequency and ciliary beat patterns are directly related to ciliary function, and analysis of the frequency and beat pattern of cilia via high-speed-microscopy along with TEM is often recommended as a primary diagnostic tool for PCD (Raidt et al. 2014). Through rigorous analysis of high-speed video microscopy (HVM) is often done by a trained practitioner, computational tools exist that can automate the analysis and detection of irregular or PCD-like patterns (Parrilla et al. 2012). HVM usually follows brush biopsy of the nasal epithelium and real-time recording of cilia with a camera with 120 fps or greater. It must be noted, however, that HVM protocol amongst different PCD centers differ, especially in terms of instruments used, magnification and resolution of camera used, mean thresholds of normal and abnormal ciliary beat frequency, and even techniques for brush biopsy. Raidt et al., in an effort to standardize the HVM procedure for PCD, provide a repository of high-speed videos of ciliary beats and different frequencies of cilia from both patients with normal cilia and patients with genetic defects of various kinds, affecting different parts of the cilia organelle (Raidt et al. 2014). As PCD often arises from a multitude of genetic defects, both TEM and HVM are performed in conjunction with genetic tests to confirm the specific combination of genotypic defects that may have led to the phenotypic defects seen in microscopy and on video. Due to its efficacy, however, HVM can be performed on the same day as the clinical visit in conjunction with nNO tests, prior to TEM and genetic testing, and this combination is recommended as the primary line of testing (Rubbo et al. 2019). Nevertheless, one issue associated with TEM and HVM are that the required tools and technical skills needed to carry out the procedures are not always available in under-served areas.

Clinical imaging

PCD is unique in that it is a disease that is often under-diagnosed or mis-diagnosed for patients from birth up to adulthood because of the similarity of its clinical presentation to diseases like CF, bronchiectasis, or regular and expected respiratory infections. Though heterotaxy and situs abnormalities can easily detected by physical examination, CT and MRI imaging can undoubtedly confirm such congenital disabilities. However, clinical imaging excels in identifying a possible PCD diagnosis to those who have non-CF bronchiectasis and were possibly left undiagnosed with PCD as children. CT imaging of affected adults usually show atelectasis, situs inversus, and severe mucal buildup in the middle and lower lobes (Kennedy, Noone, et al. 2007; Dettmer et al. 2018). Although CT imaging cannot immediately diagnose someone with PCD, imaging to determine the degree and variance of bronchiectasis is helpful in identifying possible genetic screens and tests.

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Developing diagnostic methods

As PCD continues to be explored clinically, emerging methods for diagnosis are rapidly being developed. One developing front of research in prenatal diagnosis. Wessels et al. describe two families with newborns affected by PCD along with fetal cerebral ventriculomegaly and post-natal respiratory distress. They postulate that the ventricular dilation might be a consequence of the dyskinetic beating of the cilia lining the ventricular ependyma of the brain and spinal cord leading to hydrocephalus and ventriculomegaly (Wessels, Hollander, and Willems 2003). It is possible that this dilation can be detected prior to birth via imaging studies such as CT or sonography and be used as a possible early marker for PCD (Roomans et al. 2006). One underutilized diagnostic tool that has recently been gaining traction in PCD workup and clinical algorithms is pulmonary radio-aerosol mucociliary clearance (MCC). MCC is a test that involves the uptake of a radioactive aerosol, such as one containing Technetium-99, and imaging the lung using a gamma camera. The percentage of the radioaerosol cleared over time is measured and low clearance implies the possibility of PCD. This test is also useful in that it is more feasible to administer in young children and, like the nNO test, does not rely on the analysis of the ultrastructure of the cilia (Walker et al. 2014). However, as with any gamma-based imaging modality, this test requires the use of a cyclotron and is not feasible in resource-poor areas and exposes patients to ionizing radiation. Other avenues of research involve the automation of the interpretation of the results from the above presented diagnostic methods or algorithms for quick identification of PCD. One such binary questionnaire, PICADOR (PrImary CiliARy DyskinesiA Rule), shows good accuracy and validity for making diagnostic decisions based solely on the presenting symptoms of the patient, such as whether or not they present with a wet cough, situs inversus, hearing loss symptoms, and other common PCD presenting symptoms (Behan et al. 2016).

Management

Due to the lack of sufficient scientific research and the rare nature of the disease, no standardized management plan for PCD has been designed yet. Most of the existing clinical management methods utilized by physicians rely on recent PCD targeted studies as well as extrapolated research from sister disorders such as CF. Regardless of the apparent differences in pathophysiology of these two disorders, the similarity of certain manifestations such as poor airway mucus clearance and recurrent lung infections can be managed similarly. Devising an efficient treatment plan for patients afflicted by this disease first involves acknowledging the broad scope of its effect on patients. Because it is unlikely that a singular drug or a surgical method will be developed within the foreseeable future that can eliminate all of the clinical symptoms of PCD, managing it will involve the orchestration of multiple approaches, each treating the individual aspects of its presentation. Due to the multifaceted nature of the disease, diagnosing and treating a patient with PCD will require the input and collaboration of a multitude of differently specialized physicians including otolaryngologists, cardiologists, pulmonologists and radiologists. As listed before, PCD can be associated with many different symptoms including: upper and lower tract respiratory infections, pneumonia, later onset bronchiectasis, otitis media, infertility, airway mucus obstruction, nasal congestion, low energy levels, less tolerance for high intensity activities, and commonly situs invertus with dextrocardia. Furthermore, the earlier PCD is diagnosed, the better the chances are of managing the patient's symptoms and preventing many occurrences of infections and permanent damage.

Pharmacological

Antibiotics

Along with airway clearance techniques, antibiotic therapy is usually advised for patients diagnosed with recurrent lung infections and bronchiectasis. Macrolides prescribed in the long term have been linked to a substantial decrease in the frequency of bronchiectasis exacerbations. Amongst macrolides, azithromycin has proven the most effective as compared to erythromycin and roxithromycin in improving quality of life and lung function (Li et al. 2018). Later studies also fortified these finding when patients were prescribed azithromycin for a 6 month duration. By the end of the study, results revealed a considerable 50% drop in exacerbations reported (Kobbernagel et al. 2020). However, the long term effects of administering macrolides needs to be studied more extensively due to the high probability of emerging bacterial drug resistance and azithromycin's side-effects such as diarrhea (Kobbernagel et al. 2020; Hnin et al. 2015).

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Vitamin D supplement

A pioneer study recently correlated hypovitaminosis D with patients diagnosed with PCD. Almost 72% of the 22 patients in the study revealed Vitamin D insufficiency along with a reported lower quality of life. It is still unclear what the exact relationship between the two is; however, it is highly advised to monitor the patient's Vitamin D levels and incorporate supplementation of it into their management plan (Mirra et al. 2015).

Non-pharmacological

High-frequency chest-wall oscillation vest therapy

For the management of bronchiectasis, high-frequency chest wall oscillation vest therapy (HFCWO) is showing very promising outcomes in relation to airway clearance. After being placed on HFCWO therapy for a year, patients reported being much more capable of clearing their own airway pathways and noted a general improvement in respiratory health. There was also a significant drop in the number of hospitalizations before and after one year of therapy. A much lower use of oral antibiotics for breathing problems were also noted as soon as one month after starting the therapy. In addition to that, there was an average of 4% increase in both FEV1 and FVC measurements at the end of the one year study. All in all, HFCWO as an airway clearance technique has proven to yield very encouraging results in a relatively short period of time, ultimately leading to a better quality of life (Barto et al. 2020).

Dental management

A recent study, first of its kind, on a small group of patients with ciliopathic anomalies such as PCD, revealed abnormalities in teeth development due to the dysfunctional primary cilia. Even though this study was done on a small scale, it advises the placement of PCD diagnosed patients on preventative and dental healthcare measurements with routine observation as soon as possible to minimize abnormalities (Pawlaczyk-Kamieńska et al. 2020).

Exercise

About a third of patients with PCD have shown decreased aerobic fitness in a study assessing physical capacity by measuring peak oxygen uptake (VO2peak) of children and young adults. This naturally leads to a more sedentary lifestyle and the inability to partake in rigorous physical activities. It is recommended that patients incorporate regular exercise into their daily lives to build stronger endurance and better assist with airway clearance whilst also avoiding lifestyle-derived diseases (Madsen et al. 2013).

Surgical

Endoscopic sinus surgery

In a study regarding chronic rhinosinusitis (CRS) in patients diagnosed with PCD, endoscopic sinus surgery (ESS) with adjuvant therapy generated promising results. The adjuvant therapy included two weeks of administering systemic antibiotics targeting the bacteria found in the patient's sinus swabs along with saline nasal irrigation twice a day and a three month application of topical nasal steroids. After 12 months, the therapy led to an alleviation in their symptoms, a delay in chronic infections due to Pseudomonas aeruginosa, and an overall improved lung function (Alanin et al. 2017).

Middle ear ventilation tubing

Another major manifestation of PCD, as mentioned before is Otitis media with effusion that appears in almost all PCD patients starting from early age and persisting throughout adulthood. Surgical treatment involving the insertion of middle ear ventilation tubes (VTs) proved successful in PCD diagnosed children with mild to moderate hearing loss. Hearing abilities returned to normal in 80% of cases with newly inserted VTs. It is important to note that a high percentage of post-operative otorrhea episodes were reported in the children's group; however, most were easily managed with therapy with no major complications (Wolter et al. 2012).

Lung resection

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One of the more controversial approaches to the management of PCD with severe localized bronchiectasis and infections is lung resection of the affected part. However, a recent study identified and compared the lung function and characteristics of lobectomised versus non-lobectomised patients using the international PCD cohort made up of almost 3000 patients. After studying different parameters such as FVC and FEV1, it was concluded that lobectomy showed no significant improvement of lung function. On the contrary, patients that underwent the surgery revealed a lower FVC as compared to the control group of non-lobectomised patients, and consequently a speedier decline in lung function. Lobectomised patients were also much more likely to come in after the surgery for bronchiectasis and lung infections. Due to the lack of information and awareness, most of these surgeries were conducted on patients before the diagnosis of PCD. This was probably done in hopes of alleviating respiratory issues, such as is sometimes done with bronchiectasis and cystic fibrosis patients. If the lung resection might have shown positive outcomes for cystic fibrosis patients, it has only led to adverse effects and a worsening of PCD patient's lung conditions. In all cases, a lung resection needs to be carefully thought out and the risks compared to its unguaranteed and rare benefits should be weighed out, particularly in PCD patients (Kouis et al. 2019).

Conclusion

PCD is an actively studied, genetically complex disease, which presents with a common array of symptoms. Recent research into the biology and structure of motile cilia provides a window into the underlying mechanisms involved in manifesting symptoms and why the respiratory tract and sinuses are particularly affected. Further genetic analysis of patients has identified multiple genes involved in producing pathological cilia allowing for the preliminary categorization of mutations and related symptoms. To date, there is no standardized protocol for the diagnosis of PCD; currently, diagnosis involves a combination of careful clinical history, clinical imaging, and lab testing. However, there is a somewhat coordinated global effort to develop a combination of tests that attempts to increase the accessibility and accuracy of early diagnosis. The management of the disease is in similar territory as diagnosis; there is no standardized protocol. Management varies with the severity of the disease but generally consists of two general approaches: allopathic and conservative. The allopathic component of management focuses on controlling the infectious and inflammatory aspects of the disease. Simultaneously, the conservative component focuses on managing the symptoms associated with mucus removal, including body manipulation physiotherapy or percussive techniques. The complexity of this disease is slowly unravelling as research progresses. Research is moving towards more affordable and accurate diagnostic techniques, leading to more focused individualized treatment and better patient outcomes.

References

1. Alanin, Mikkel Christian, Kasper Aanaes, Niels Høiby, Tania Pressler, Marianne Skov, Kim Gjerum Nielsen, Helle Krogh Johansen, and Christian von Buchwald. 2017. "Sinus Surgery Can Improve Quality of Life, Lung Infections, and Lung Function in Patients with Primary Ciliary Dyskinesia." In *International Forum of Allergy & Rhinology*, 7:240–47. 3. Wiley Online Library.
2. Barbato, A1, T Frischer, CE Kuehni, D Snijders, I Azevedo, G Baktai, L Bartoloni, et al. 2009. "Primary Ciliary Dyskinesia: A Consensus Statement on Diagnostic and Treatment Approaches in Children." *European Respiratory Journal* 34 (6): 1264–76.
3. Barto, Tara Lynn, Diego Jose Maselli, Sarah Daignault, John Stiglich, Jared Porter, Carlye Kraemer, and Gary Hansen. 2020. "Real-Life Experience with High-Frequency Chest Wall Oscillation Vest Therapy in Adults with Non-Cystic Fibrosis Bronchiectasis." *Therapeutic Advances in Respiratory Disease* 14: 1753466620932508.
4. Behan, Laura, Borislav D Dimitrov, Claudia E Kuehni, Claire Hogg, Mary Carroll, Hazel J Evans, Myrofora Goutaki, et al. 2016. "PICADAR: A Diagnostic Predictive Tool for Primary Ciliary Dyskinesia." *European Respiratory Journal* 47 (4): 1103–12.
5. Bhatt, Reena, and Claire Hogg. 2020. "Primary Ciliary Dyskinesia: A Major Player in a Bigger Game." *Breathe* 16 (2).
6. Blyth, M, and D Wellesley. 2008. "Ectopic Pregnancy in Primary Ciliary Dyskinesia." *Journal of Obstetrics and Gynaecology* 28 (3): 358–58.

7. Bush, A, P Cole, M Hariri, I Mackay, G Phillips, C O'callaghan, R Wilson, and JO Warner. 1998. "Primary Ciliary Dyskinesia: Diagnosis and Standards of Care." *European Respiratory Journal* 12 (4): 982–88.
8. Dettmer, Sabine, Felix Ringshausen, Jens Vogel-Claussen, Jan Fuge, Amir Faschkami, Hoen-oh Shin, Nicolaus Schwerk, Tobias Welte, Frank Wacker, and Jessica Rademacher. 2018. "Computed Tomography in Adult Patients with Primary Ciliary Dyskinesia: Typical Imaging Findings." *PLoS One* 13 (2): e0191457.
9. Greenstone, MA, RW Jones, A Dewar, BG Neville, and PJ Cole. 1984. "Hydrocephalus and Primary Ciliary Dyskinesia." *Archives of Disease in Childhood* 59 (5): 481–82.
10. Guichard, Cécile, Marie-Cécile Harricane, Jean-Jacques Lafitte, Philippe Godard, Marc Zaegel, Vincent Tack, Guy Lalau, and Patrice Bouvagnet. 2001. "Axonemal Dynein Intermediate-Chain Gene (Dnai1) Mutations Result in Situs Inversus and Primary Ciliary Dyskinesia (Kartagener Syndrome)." *The American Journal of Human Genetics* 68 (4): 1030–35.
11. Hnin, Khin, Chau Nguyen, Kristin V Carson-Chahhoud, David J Evans, Michael Greenstone, and Brian J Smith. 2015. "Prolonged Antibiotics for Non-Cystic Fibrosis Bronchiectasis in Children and Adults." *Cochrane Database of Systematic Reviews*, no. 8.
12. Holgersen, Mathias G, June K Marthin, and Kim G Nielsen. 2019. "Proof of Concept: Very Rapid Tidal Breathing Nasal Nitric Oxide Sampling Discriminates Primary Ciliary Dyskinesia from Healthy Subjects." *Lung* 197 (2): 209–16.
13. Horani, Amjad, Thomas W Ferkol, Susan K Dutcher, and Steven L Brody. 2016. "Genetics and Biology of Primary Ciliary Dyskinesia." *Paediatric Respiratory Reviews* 18: 18–24.
14. Kaushik, Manish Singh, Soura Chakraborty, Shobi Veleri, Suneel Kateriya, and others. 2021. "Mucociliary Respiratory Epithelium Integrity in Molecular Defense and Susceptibility to Pulmonary Viral Infections." *Biology* 10 (2): 95.
15. Kennedy, Marcus P, Peadar G Noone, Margaret W Leigh, Maimoona A Zariwala, Susan L Minnix, Michael R Knowles, and Paul L Molina. 2007. "High-Resolution CT of Patients with Primary Ciliary Dyskinesia." *American Journal of Roentgenology* 188 (5): 1232–38.
16. Kennedy, Marcus P, Heymut Omran, Margaret W Leigh, Sharon Dell, Lucy Morgan, Paul L Molina, Blair V Robinson, et al. 2007. "Clinical Perspective." *Circulation* 115 (22): 2814–21.
17. Kennedy, Marcus P, and Barry J Plant. 2014. "Primary Ciliary Dyskinesia and the Heart: Cilia Breaking Symmetry." *Chest* 146 (5): 1136–38.
18. Kharitonov, SA, D Yates, and PJ Barnes. 1995. "Increased Nitric Oxide in Exhaled Air of Normal Human Subjects with Upper Respiratory Tract Infections." *European Respiratory Journal* 8 (2): 295–97.
19. Knowles, Michael R, Leigh Anne Daniels, Stephanie D Davis, Maimoona A Zariwala, and Margaret W Leigh. 2013. "Primary Ciliary Dyskinesia. Recent Advances in Diagnostics, Genetics, and Characterization of Clinical Disease." *American Journal of Respiratory and Critical Care Medicine* 188 (8): 913–22.
20. Kobbernagel, Helene E, Frederik F Buchvald, Eric G Haarman, Carmen Casaulta, Samuel A Collins, Claire Hogg, Claudia E Kuehni, et al. 2020. "Efficacy and Safety of Azithromycin Maintenance Therapy in Primary Ciliary Dyskinesia (BESTCILIA): A Multicentre, Double-Blind, Randomised, Placebo-Controlled Phase 3 Trial." *The Lancet Respiratory Medicine* 8 (5): 493–505.
21. Kouis, Panayiotis, Myrofora Goutaki, Florian S Halbeisen, Ifigeneia Gioti, Nicos Middleton, Israel Amirav, Angelo Barbato, et al. 2019. "Prevalence and Course of Disease After Lung Resection in Primary Ciliary Dyskinesia: A Cohort & Nested Case-Control Study." *Respiratory Research* 20 (1): 1–12.
22. Kuehni, Claudia E, and Jane S Lucas. 2017. "Diagnosis of Primary Ciliary Dyskinesia: Summary of the ERS Task Force Report." *Breathe* 13 (3): 166–78.
23. Leigh, Margaret W, Milan J Hazucha, Kunal K Chawla, Brock R Baker, Adam J Shapiro, David E Brown, Lisa M LaVange, et al. 2013. "Standardizing Nasal Nitric Oxide Measurement as a Test for Primary Ciliary Dyskinesia." *Annals of the American Thoracic Society* 10 (6): 574–81.
24. Leigh, Margaret W, Jessica E Pittman, Johnny L Carson, Thomas W Ferkol, Sharon D Dell, Stephanie D Davis, Michael R Knowles, and Maimoona A Zariwala. 2009. "Clinical and Genetic Aspects of Primary Ciliary Dyskinesia/Kartagener Syndrome." *Genetics in Medicine* 11 (7): 473–87.

25. Leigh, Margaret W, Maimoona A Zariwala, and Michael R Knowles. 2009. "Primary Ciliary Dyskinesia: Improving the Diagnostic Approach." *Current Opinion in Pediatrics* 21 (3): 320.
26. Li, Wen, Zhong Qin, Jie Gao, Zhibin Jiang, Yihui Chai, Liancheng Guan, and Yunzhi Chen. 2018. "Azithromycin or Erythromycin? Macrolides for Non-Cystic Fibrosis Bronchiectasis in Adults: A Systematic Review and Adjusted Indirect Treatment Comparison." *Chronic Respiratory Disease* 16: 1479972318790269.
27. Lucas, Jane S, and Woolf T Walker. 2018. "NO Way! Nasal Nitric Oxide Measurement in Infants." Eur Respiratory Soc.
28. Madsen, Astrid, Kent Green, Frederik Buchvald, Birgitte Hanel, and Kim Gjerum Nielsen. 2013. "Aerobic Fitness in Children and Young Adults with Primary Ciliary Dyskinesia." *PloS One* 8 (8): e71409.
29. Majithia, A, J Fong, M Hariri, and J Harcourt. 2005. "Hearing Outcomes in Children with Primary Ciliary Dyskinesia—a Longitudinal Study." *International Journal of Pediatric Otorhinolaryngology* 69 (8): 1061–64.
30. McManus, I Christopher, Hannah M Mitchi*f*roson, Eddie MK Chung, Georgina F Stubbings, and Naomi Martin. 2003. "Primary Ciliary Dyskinesia (Siewert's/Kartagener's Syndrome): Respiratory Symptoms and Psycho-Social Impact." *BMC Pulmonary Medicine* 3 (1): 1–12.
31. Meeks, M, and A Bush. n.d. "Primary Ciliary Dyskinesia (PCD) Pediatr Pulmonol. 2000; 29: 307–316. Doi: 10.1002/(SICI) 1099-0496 (200004) 29: 4< 307:: AID-Ppul11> 3.0." CO.
32. Mirra, Virginia, Carlo Caffarelli, Marco Maglione, Rossella Valentino, Giuseppe Perruolo, Claudia Mazzarella, Laida Lisa Di Micco, Silvia Montella, and Francesca Santamaria. 2015. "Hypovitaminosis d: A Novel Finding in Primary Ciliary Dyskinesia." *Italian Journal of Pediatrics* 41 (1): 1–6.
33. Mirra, Virginia, Claudius Werner, and Francesca Santamaria. 2017. "Primary Ciliary Dyskinesia: An Update on Clinical Aspects, Genetics, Diagnosis, and Future Treatment Strategies." *Frontiers in Pediatrics* 5: 135.
34. Noone, Peadar G, Margaret W Leigh, Aruna Sannuti, Susan L Minnix, Johnny L Carson, Milan Hazucha, Maimoona A Zariwala, and Michael R Knowles. 2004. "Primary Ciliary Dyskinesia: Diagnostic and Phenotypic Features." *American Journal of Respiratory and Critical Care Medicine* 169 (4): 459–67.
35. Olm, Mary Anne Kowal, Elia Garcia Caldini, and Thais Mauad. 2015. "Diagnosis of Primary Ciliary Dyskinesia." *Jornal Brasileiro de Pneumologia* 41 (3): 251–63.
36. Parrilla, Eduardo, Miguel Armengot, Manuel Mata, Julio Cortijo, Jaime Riera, José L Hueso, and David Moratal. 2012. "Optical Flow Method in Phase-Contrast Microscopy Images for the Diagnosis of Primary Ciliary Dyskinesia Through Measurement of Ciliary Beat Frequency. Preliminary Results." In *2012 9th IEEE International Symposium on Biomedical Imaging (ISBI)*, 1655–58. IEEE.
37. Pawlaczyk-Kamieńska, Tamara, Hanna Winiarska, Tomasz Kulczyk, and Szczepan Cofta. 2020. "Dental Anomalies in Rare, Genetic Ciliopathic Disorder—a Case Report and Review of Literature." *International Journal of Environmental Research and Public Health* 17 (12): 4337.
38. Pizzi, Sara, Salvatore Cazzato, Filippo Bernardi, Walther Mantovani, and Giovanna Cenacchi. 2003. "Clinico-Pathological Evaluation of Ciliary Dyskinesia: Diagnostic Role of Electron Microscopy." *Ultrastructural Pathology* 27 (4): 243–52.
39. Poprzeczko, Martyna, Marta Bicka, Hanan Farahat, Rafal Bazan, Anna Osinka, Hanna Fabczak, Ewa Joachimiak, and Dorota Wloga. 2019. "Rare Human Diseases: Model Organisms in Deciphering the Molecular Basis of Primary Ciliary Dyskinesia." *Cells* 8 (12): 1614.
40. Prulière-Escabasse, Virginie, André Coste, Pierre Chauvin, Brigitte Fauroux, Aline Tamalet, Erea-Noel Garabedian, Estelle Escudier, and Gilles Roger. 2010. "Otologic Features in Children with Primary Ciliary Dyskinesia." *Archives of Otolaryngology–Head & Neck Surgery* 136 (11): 1121–26.
41. Raidt, Johanna, Julia Wallmeier, Rim Hjeij, Jörg Große Onnebrink, Petra Pennekamp, Niki T Loges, Heike Olbrich, et al. 2014. "Ciliary Beat Pattern and Frequency in Genetic Variants of Primary Ciliary Dyskinesia." *European Respiratory Journal* 44 (6): 1579–88.
42. Roomans, Godfried M, Andrejs Ivanovs, Eyman B Shebani, and Marie Johannesson. 2006. "Transmission Electron Microscopy in the Diagnosis of Primary Ciliary Dyskinesia." *Upsala Journal of Medical Sciences* 111 (1): 155–68.

43. Rubbo, Bruna, Amelia Shoemark, Claire L Jackson, Robert Hirst, James Thompson, Joseph Hayes, Emily Frost, et al. 2019. "Accuracy of High-Speed Video Analysis to Diagnose Primary Ciliary Dyskinesia." *Chest* 155 (5): 1008–17.
44. Shapiro, Adam J, Stephanie D Davis, Thomas Ferkol, Sharon D Dell, Margaret Rosenfeld, Kenneth N Olivier, Scott D Sagel, et al. 2014. "Laterality Defects Other Than Situs Inversus Totalis in Primary Ciliary Dyskinesia: Insights into Situs Ambiguus and Heterotaxy." *Chest* 146 (5): 1176–86.
45. Shoemark, Amelia, Mieke Boon, Christoph Brochhausen, Zuzanna Bukowy-Bieryllo, Maria M De Santi, Patricia Goggin, Paul Griffin, et al. 2020. "International Consensus Guideline for Reporting Transmission Electron Microscopy Results in the Diagnosis of Primary Ciliary Dyskinesia (BEAT PCD TEM Criteria)." *European Respiratory Journal* 55 (4).
46. Shoemark, Amelia, M Dixon, B Corrin, and A Dewar. 2012. "Twenty-Year Review of Quantitative Transmission Electron Microscopy for the Diagnosis of Primary Ciliary Dyskinesia." *Journal of Clinical Pathology* 65 (3): 267–71.
47. Slavin, Raymond G, Sheldon L Spector, I Leonard Bernstein, Sinusitis Update Workgroup, Michael A Kaliner, David W Kennedy, Frank S Virant, et al. 2005. "The Diagnosis and Management of Sinusitis: A Practice Parameter Update." *Journal of Allergy and Clinical Immunology* 116 (6): S13–47.
48. Vanaken, Gert Jan, Laurence Bassinet, Mieke Boon, Rahma Mani, Isabelle Honore, Jean-Francois Papon, Harry Cuppens, et al. 2017. "Infertility in an Adult Cohort with Primary Ciliary Dyskinesia: Phenotype–Gene Association." *European Respiratory Journal* 50 (5).
49. Walker, Woolf T, Claire L Jackson, Peter M Lackie, Claire Hogg, and Jane S Lucas. 2012. "Nitric Oxide in Primary Ciliary Dyskinesia." *European Respiratory Journal* 40 (4): 1024–32.
50. Walker, Woolf T, Aneurin Young, Michael Bennett, Matthew Guy, Mary Carroll, John Fleming, Joy Conway, and Jane S Lucas. 2014. "Pulmonary Radioaerosol Mucociliary Clearance in Primary Ciliary Dyskinesia." *European Respiratory Journal* 44 (2): 533–35.
51. Weitzberg, Eddie, and Jon ON Lundberg. 2002. "Humming Greatly Increases Nasal Nitric Oxide." *American Journal of Respiratory and Critical Care Medicine* 166 (2): 144–45.
52. Werner, Claudius, Jörg Große Onnebrink, and Heymut Omran. 2015. "Diagnosis and Management of Primary Ciliary Dyskinesia." *Cilia* 4 (1): 1–9.
53. Wessels, Marja W, Nicolette S den Hollander, and Patrick J Willems. 2003. "Mild Fetal Cerebral Ventriculomegaly as a Prenatal Sonographic Marker for Kartagener Syndrome." *Prenatal Diagnosis: Published in Affiliation With the International Society for Prenatal Diagnosis* 23 (3): 239–42.
54. Wodehouse, T, SA Kharitonov, IS Mackay, PJ Barnes, R Wilson, and PJ Cole. 2003. "Nasal Nitric Oxide Measurements for the Screening of Primary Ciliary Dyskinesia." *European Respiratory Journal* 21 (1): 43–47.
55. Wolter, Nikolaus E, Sharon D Dell, Adrian L James, and Paolo Campisi. 2012. "Middle Ear Ventilation in Children with Primary Ciliary Dyskinesia." *International Journal of Pediatric Otorhinolaryngology* 76 (11): 1565–68.