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Clinical Manifestations and Management of Primary Ciliary Dyskinesia in ENT Practice

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ABSTRACT

Primary ciliary dyskinesia (PCD) comprises a wide range of phenotypes related to the impaired function of epithelial cilia. Histologically altered or absent cilia lead to multiple and variable consequences at the clinical level. Several research and clinical interest have surrounded respiratory ciliated epithelium because of its key role in clearing mucus from the ear, nose, and respiratory tract. Our aim was to provide a current state of the art on the ENT signs and symptoms of primary ciliary dyskinesia and their practical management. We systematically searched the following databases from 2011 until 2021: Cochrane Central Register of Controlled Trials, PubMed, and ScienceDirect. The searches were performed by 2 independent investigators. After removing duplications, articles were selected after the evaluation of the publications by reading their titles and abstracts. Eventually, full-text reading took place. Early onset of upper and lower respiratory symptoms in a full-term born child is suggestive of ciliary dyskinesia, especially in the absence of a usual triggering factor (passive smoking, allergy). The cornerstone of care is improving mucociliary clearance, using nasal and sinus irrigations, autoinflaction devices for middle ear effusion, physiotherapy and/or physical exercise for upper airway recovery. Decongestants, mucolytics, steroids, and antihistamines are part of the therapeutic arsenal with a low level of evidence. Early eradication of airway infections should be based on bacteriological analysis. Surgical interventions are common and mainly aim at restoring drainage. in summary, PCD is associated with ENT manifestations from the first days of life. The key to management is restoring adequate drainage of the upper airway and ENT cavities, using medical and surgical interventions.

Keywords: Chronic rhinitis, chronic rhinosinusitis, management, otitis media with effusion, primary ciliary dyskinesia

Introduction

Primary ciliary dyskinesia (PCD) is an inherited motor ciliopathy, in which the beating of the respiratory cilia is absent, slow, or abnormal, leading to a deficit in mucociliary clearance and significant respiratory and ENT pathologies.[1]

Clinically, PCD is primarily characterized by recurrent or chronic infections of the upper and lower respiratory tract, the development of bronchiectasis, chronic cough, chronic nasal congestion, recurrent or chronic otitis media, and chronic sinusitis beginning from childhood.[2]

Primary ciliary dyskinesia is rare, and its prevalence is difficult to establish, ranging from 1 : 10 000 to 1 : 20 000. However, the actual prevalence of PCD is probably higher because the diagnosis is difficult and often missed or delayed due to lack of clinical suspicion and difficulties in confirming this diagnosis. This results in a significant delay in diagnosis or inadequate treatments.[3]

Diagnosis of primary ciliary dyskinesia is based on a combination of tools such as genetic analysis, measurement of nasal NO, transmission electron microscopy, high-speed video microscopy analysis after cell culture, and

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immunofluorescence. Guidelines of the American Thoracic Society and the European Respiratory Society agree that a positive genetic analysis or an ultrastructural defect observed by transmission electron microscopy confirms the diagnosis of PCD.[4]

The objective of this article is to carry out a current state of the art on the clinical manifestations and management of primary ciliary dyskinesia in the practice of otorhinolaryngology.

Methods

The Cochrane Central Register of Controlled Trials, PubMed, and ScienceDirect databases were searched using keywords, subject headings, and Medical Subject Headings. The search was completed on February 15, 2022. We used keywords, including Primary ciliary dyskinesia AND ENT OR ear OR sinus OR ventilation tube OR middle ear ventilation OR sinonasal OR nasal AND treatment OR manifestations, to identify all previously published studies that investigated the clinical manifestations and management of primary ciliary dyskinesia. The search was adapted to each database, and we included clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews. The reference lists of the identified studies were searched manually for additional related papers. A repeated search using the same strategy was performed on February 15, 2022, and revealed the same results. Titles and abstracts of all articles extracted from the primary search were screened after removing duplicates. The full texts of relevant papers were reviewed for eligibility by 2 authors independently. Finally, 32 articles were selected.

ENT Clinical Manifestation of PCD

Primary ciliary dyskinesia is a disease affecting the structure and/or function of the mobile cilia, thereby causing a disorder of mucociliary clearance with an accumulation of mucus and bacteria in the airways. The upper respiratory tract and the middle ear are covered with ciliated epithelium. One of the characteristics of PCD is the retention, from the neonatal period, of secretions and chronic infections in the middle ear, nose, and facial sinuses (Table 1).[3,5]

The clinical presentation of PCD is heterogeneous, and the symptoms of this disease are nonspecific. Therefore, although most patients with PCD have symptoms of preschool onset, diagnosis is often delayed.[6] Sommer et al[7] found that the majority of patients had seen a doctor more than 50 times before being diagnosed with PCD, with the average age of diagnosis for PCD being 10.9 years.

Main Points

- Primary ciliary dyskinesia is underdiagnosed, and mean time to diagnosis is 11 years.
- Recent guidelines for management of primary ciliary dyskinesia in ENT practice are summarized.
- ENT care is paramount for the quality of life of primary ciliary dyskinesia patients.
- Coordination of medical and surgical treatments is key for primary ciliary dyskinesia patients.

Table 1. The Early Onset (Before Attending Daycare) in a Full-term Born Child is Suggestive of Ciliary Dyskinesia, Especially with a History of Neonatal Respiratory Distress and/or Neonatal Cough, and in the Absence of a Usual Triggering Factor (Passive Smoking, Allergy)

ENT Manifestations of PCD	
Nose / Sinus	Early onset (preschool)
	Perennial
	Despite medical treatment
	Recurrence after surgery
Ears	Early onset (preschool)
	Perennial
	Hearing loss
	Despite medical / surgical treatment
Upper airway	Chronic cough
	Sleep apnea

The ENT manifestations of PCD are very common and contribute significantly to the general morbidity of the disease. They are often recurrent during early childhood, despite well-conducted antibiotic treatment.[8]

The majority of PCD patients have chronic rhinosinusitis (CRS), which is defined by inflammation of the entire nasal mucosa and paranasal sinuses. Chronic rhinosinusitis causes symptoms such as nasal congestion, facial pain, mucopurulent anterior or posterior rhinorrhea, hyposmia, or anosmia. These symptoms are considered chronic if they persist for more than 12 weeks and if signs of rhinosinusitis are demonstrated by endoscopy or imaging. Sinonasal polyposis may also be associated,[5,8] usually occurring in older children and affecting 15-56% of adults.[6,9] The nasal symptomatology associated with PCD is generally present throughout the year and is not influenced by seasonal change, unlike allergic rhinitis.[8] Chronic rhinorrhea and nasal congestion are often present since the neonatal period.[7,10-12] Although it is a non-specific sign, clinical examination of the nasal cavities in patients with PCD frequently shows mucopurulent secretions in the nasal floor and swelling of the inferior turbinates.[8] Hydrocephalus is uncommon in patients with PCD, but has been associated with ciliary aplasia, as it has been reported in 10% of patients with CCNO mutations.[14] Hydrocephalus is the consequence of a dysfunction of the mobile cilia of the cerebral ventricles and of the ependymal duct, and can cause chronic headaches that can be mistakenly attributed to sinusitis.[13]

Pan-sinusitis is found on imaging (CT scan) in most adult PCD patients, and is often associated with sinus hypoplasia or agenesis (mainly frontal sinuses). Bilateral ethmoid sinus mucoceles have also been described in children with PCD.[15,16] In terms of pathogens, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* were the most frequently found bacteria in patients with PCD.[17]

Primary ciliary dyskinesia is also expressed by very frequent involvement of the middle ear. Otologic manifestations of PCD include but are not limited to, chronic otitis media with

effusion, recurrent otitis media, and hearing loss. Patients frequently present with persistent otorrhea, especially after ventilation tube insertion. Clinical examination of the ear may be normal or show chronic otitis media with effusion, acute otitis media, tympanosclerosis, as well as otorrhea in the external auditory canal if the tympanic membrane is ruptured spontaneously or by the ventilation tube insertion. Hearing loss caused by chronic otitis media with effusion is mild to moderate in severity and is usually insidious in young children with PCD.[8] However, even mild hearing loss in the first years of a child's life can affect language acquisition as well as the child's listening skills at school, which can affect children's performance at school. Chronic otitis media with effusion affects at least 80% of children with PCD and is often persistent until the age of 12. Therefore, special attention should be paid to hearing loss.[7,8,18]

Upper respiratory tract and middle ear infections are common in the general pediatric population, and they can be difficult to distinguish from the nasal and otologic manifestations of PCD. This type of frequent infections may delay the diagnosis of PCD in children. In addition, the chronic ENT and respiratory symptoms associated with PCD are common to other diseases that should also be considered, such as cystic fibrosis, immunodeficiency, asthma, allergic rhinitis, prolonged bacterial bronchitis, gastroesophageal reflux, and secondary ciliary dyskinesia.[2,19] The combination of several signs suggestive of PCD makes it possible to distinguish PCD from these conditions: unexplained neonatal respiratory distress, persistent daily productive cough of early onset, daily nasal congestion of early onset, and abnormal lateralization of the viscera. About 50% of PCD patients present with situs inversus and 12% with situs ambiguous.[20]

Symptoms affecting the ENT sphere in patients with PCD may progress with age. Chronic rhinosinusitis is the main manifestation in PCD adult patients, while otological manifestations are more common in children.[7,21]

Management and Treatment of ENT Complications

The current recommendations concerning the management of PCD are extrapolated from guidelines for the management of cystic fibrosis and personal experiences of various medical centers, without real proof of benefit. The management of PCD should be multidisciplinary and carried out in centers with expertise in the disease. Consultations with a respirologist and ENT specialist are usually done every 3-6 months, depending on the severity of the disease and the patient's age (Table 2).

Currently, as there is no treatment that corrects the genetic dysfunction of mobile cilia, the goal of PCD management is to treat the symptoms, to prevent infectious exacerbations and their complications, and to delay as much as possible the functional decline of the respiratory system, while preserving as much as possible the quality of life and the socio-psychological well-being of the patients.[5]

Management of nasal and sinus involvement in PCD consists of medical and surgical treatments. The medical treatment of CRS is based on nasal and sinus irrigation with physiological liquid, respiratory drainage physiotherapy, local corticosteroid therapy, local antibiotic therapy (nebulization) or general, and sometimes anticholinergics. Nasal and sinus irrigation with isotonic or hypertonic saline is the basis of treatment, allowing to drain the secretions as well as the bacteria and the biofilm contained in the sinuses. Local intranasal corticosteroids may help decrease mucosal inflammation, especially in the presence of polyps. However, polyps in PCD patients are mostly neutrophilic; therefore, they respond less to local intranasal corticosteroids.[4,22] In infectious exacerbations of rhinosinusitis, conservative treatment is not recommended, and antibiotics are preferred, with the choice of antibiotic to be ideally guided by the nasosinus bacteriological analysis. Methods of administration of antibiotics can be oral, nebulized, or intravenous.[5,8,21]

Long-term macrolide therapy may be useful for patients with frequent respiratory exacerbations, in whom azithromycin may reduce the morbidity of exacerbations, the need for additional antibiotic therapy, and potentially prevent irreversible lung damage. In addition to their antibacterial effect, macrolides have beneficial anti-inflammatory effects and are increasingly used in various chronic respiratory pathologies, including PCD. Kobbernagel et al[23] have shown that 6-month maintenance treatment with azithromycin halves respiratory exacerbations in patients with PCD.

Endoscopic sinus surgery (meatomy, polypectomy, ethmoidectomy, turbino-septal surgery) could be of benefit in the management of PCD. The goals of sinus surgery in patients

Table 2. The Cornerstone of Care is Restoring Adequate Drainage of the Upper Airway and ENT Cavities, Using Nasal and Sinus Irrigations, Autoinflaction Devices for Middle Ear Effusion, Physiotherapy and/or Physical Exercice for Upper Airway Recovery. Decongestants, Mucolytics, Steroids, and Antihistamines are Part of the Therapeutic Arsenal with a Low Level of Evidence. Antibiotics Should be Based on bacteriological Analysis. Surgical Interventions are Common and Mainly Aim at Restoring Drainage

ENT Management of PCD	
Nose / Sinus	Saline douching (hypertonic)
	Antibiotics (nebulization, systemic)
	Functional endoscopic sinus surgery
	Endoscopic sinus surgery
Ears	Autoinflation devices
	Antibiotics (local, systemic)
	Transtympanic drainage (controversial)
	Hearing aid
	Speech therapy
	Surgery of middle ear complications
Upper airway	Respiratory drainage physiotherapy
	Antibiotics (nebulization, systemic)
	Macrolide maintenance therapy (azithromycin)
	Adenotonsillectomy
	Continuous positive airway pressure

with PCD are to treat nasal congestion, to restore nasal breathing, to improve olfaction, and to increase penetration of local treatments by improving mechanical sinus drainage.[8] Some studies also suggest that sinus surgery may reduce the respiratory bacterial load.[24] Bequignon et al[21] advise orienting the surgical procedure according to the predominant symptoms: if facial pain is in the foreground, an ethmoidectomy is performed, while in the event of predominant nasal obstruction, a turbinectomy is performed. Endoscopic sinus surgery is not a curative treatment, and persistent chronic rhinorrhea can be observed in post-operative consultations and follow-up consultations. Therefore, endoscopic sinus surgery should be used in cases of persistent rhino-sinus symptoms and/or no amelioration with long-term macrolide therapy.

Biofilms of the upper, lower, and middle ear respiratory tracts are a complex association of bacteria, irreversibly attached to the mucous surface and enclosed in an adherent extracellular matrix, originating from both the host and the bacteria. The biofilm environment contains low levels of oxygen and is not perfused by arterial blood, making it inaccessible to systemic antibiotics. These biofilms are likely to be present in patients presenting CRS, including those with PCD, and they are a reservoir of bacteria and mediators that contribute to systemic inflammation and recurrent respiratory tract infections. Therefore, some studies suggest that the sinuses can be considered as a bacterial reservoir that can infect the upper and lower respiratory tracts, and that the incorporation of naso-sinus bacteriological analyzes to guide the choice of medical and surgical treatments could improve the outcome of PCD patients. In these patients, the bacteria most commonly found in the sinuses are *H. influenzae*, *P. aeruginosa*, *Staphylococcus aureus*, and *S. pneumonia*.[8,17,25]

Management of otological complications of PCD aims to improve patients' hearing, aiming to avoid the possible sequelae of long-term hearing loss (cognitive disorders, language development disorders, and academic delay), as well as to prevent the sequelae of chronic otitis in the tympanic membranes and middle ear (tympanosclerosis, retraction pockets or atelectasis of the eardrums, cholesteatoma, erosion of the ossicles).[8,15] Chronic otitis media with effusion being very common in patients with PCD, especially in young children; therefore, hearing should therefore be monitored regularly using age-appropriate methods.[7] Oral antibiotic treatment is recommended to treat acute otitis media.[26] Use of trans-tympanic aerators for the treatment of chronic otitis media with effusion is controversial in the management of PCD, as these could be responsible for persistent and intractable otorrhea, causing discomfort and worsening hearing loss. European guidelines recommend to avoid the use of trans-tympanic ventilators in the management of patients with PCD, and treating hypoacusis by hearing aids and regular follow-up in ENT consultations.[27] Furthermore, no cases of cholesteatoma were found in PCD children with chronic otitis media with effusion managed without trans-tympanic aerators.[28] Antibiotics and local and/or general corticosteroids may be offered in the face of debilitating otorrhea, with the choice of antibiotic having to be adapt according to the results of the bacteriological culture of the otorrhea. It is important to avoid ototoxic antibiotics. Self-insufflation devices, also called nasal balloons, can also be used for the management of chronic otitis media with effusion, with limited evidence of benefit.[8,26,29-31]

Vaccination against influenza and pneumococcus is important for patients with chronic respiratory diseases, including PCD.[8] Concerning the severe acute respiratory syndrome coronavirus 2 pandemic, PCD patients were considered to be at high risk. Therefore vaccination is also recommended.[32]

Perspectives

The cornerstone of care has been to restore adequate drainage to the upper airway and ENT cavities. To collect standardized data focusing on ENT disease in PCD patients, the ENT prospective international cohort of patients with PCD (EPIC-PCD) was born. This international prospective study aims to longitudinally characterize ENT disease in PCD patients and its association with lung disease, and to identify determinants of its prognosis.[33] While observational, this multicenter study was not designed to develop new treatments. However, it helps to better identify the ENT manifestations of PCD, better define the exacerbations, better understand their evolution, the possible need for surgery, and their prognosis.

Future treatments may target ciliary function itself. PCD is genetically heterogeneous and currently includes more than 50 known genes. To date, three studies in the preclinical stage have been published, describing the partial restoration of ciliary function in ciliopathies using classical gene therapy and one study using gene editing. Gene therapy aims to replace or repair the DNAI1 gene, which encodes a component of the outer arm of dynein, associated with approximately 10-14% of PCD cases. Lentiviral and adenoviral vectors of the DNAI1 gene were delivered directly into the airways of mouse models of PCD by aerosol, showing promising outcomes. Aerosolization of DNAI1 gene through viral vectors was able to normalize ciliary beat frequency. However, before it can be applied to patients, gene therapy has to address safety concerns following alterations in genomic DNA and the resistance of differentiated airway epithelium to transduction by viral vectors.

More recently, RNA therapy or transcript therapy has been studied with the aim of restoring DNAI1 or CCDC40 protein expression in knockout mice.[34] By acting downstream of the genome, these options avoid DNA alteration and are preferably reversible. The first results of the preclinical stage in transcript therapy for CCDC40 protein are encouraging. There is no current data for RNA therapy in PCD humans.

Conclusion

Primary ciliary dyskinesia is associated with ENT manifestations from the first days of life. The current management of PCD is based mainly on expert opinions and extrapolations from cystic fibrosis patients. The key management is restoring adequate drainage of the upper airway and ENT cavities, using medical and surgical interventions. Unfortunately, there is no curative management for PCD patients. Hence, these patients must have regular follow-ups in ENT and pneumology to reduce as possible complications that could affect lung function. Management in a specialized center with a multidisciplinary approach should be prioritized for PCD patients.

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