

ENT MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA

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ABSTRACT

Primary Ciliary Dyskinesia (PCD) is a heterogeneous, rare genetic disease that can be present in up to 5% of the patients with recurrent respiratory infections. The underlying pathogenesis is disrupted ciliary function which results in delayed mucus transportation leading to chronic inflammation in the upper and lower respiratory tract. Almost all PCD patients have otolaryngologic manifestations, characterized by recurrent ear and sinus infections, chronic inflammation at this level, sensorineural and conductive hearing loss, and sleep-disordered breathing. This article reviews the diagnostic and therapeutic aspects of these manifestations.

Keywords: Primary Ciliary Dyskinesia, otitis, sinusitis, chronic rhinosinusitis, nasal polyposis, otitis media with effusion, sleep apnea.

INTRODUCTION

Primary Ciliary Dyskinesia (PCD) is a rare heterogeneous genetic disease with a prevalence of 1: 10,000 to 1: 20,000 live births, although it is estimated to be much higher, since it is calculated from symptomatic patients; and although it is considered a rare disease, it may be present in up to 5% of patients who have recurrent respiratory infections. Only 50% of patients present situs inversus. The pathogenesis is by-product of an alteration of the ciliary function that causes an alteration of mucus transport, resulting in a chronic inflammatory condition mainly in the upper and lower airway (1).

CLINICAL PICTURE AND TREATMENT

The clinical ENT manifestations in patients with PCD are almost always present, and are characterized by recurrent ear infections and paranasal cavities, chronic inflammation at this level, sensorineural and conductive hearing loss and respiratory alterations during sleep (2).

Recurrent Otitis Media

The presence of defects in ciliary motility produces significant alterations in the ventilation of the middle ear, either due to failure in mucociliary transport in the auditory tube, or chronic rhinosinusitis inflammatory alterations (3). This tubal dysfunction favors the presence of repeated bacterial infections in the middle ear. It is estimated that between 80% and 90% of patients with PCD are carriers of recurrent otitis media (OMAR) (4).

Acute episodes are by-product of the same germs as those that produce AOM in the general population, so they must be treated in the same way.

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The recommendation for the placement of ventilation tubes after 4 episodes per year or 3 episodes in less than 6 months should be discussed case by case in patients with PCD, since a persistent otorrhea has been found after tube placement of up to 50% (compared to less than 10% in the general population). Initial conservative treatment is preferred, although these patients must have frequent otoscopic control, since they have a higher risk of progression to chronic inflammatory pathology (otitis media with effusion) and to exhibit tympanic structural alterations that could be irreversible in the long term (5).

Otitis Media with Effusion (OME)

OME is defined as the presence of mucous or serous fluid in the middle ear for more than 12 weeks. This condition is not infectious, but rather inflammatory, and usually by-product to the presence of chronic tubal dysfunction.

It has also been associated with the presence of bacterial biofilms in the mucosa of the middle ear, the rhino pharynx, and the adenoid tissue. The most important symptoms of OME are hearing loss and a blocked ear sensation, which may go unnoticed in younger children.

It has been seen that over 85% of patients with PCD present OME at some point, and that this has a worse clinical evolution, since it can even be maintained until adulthood, compared to the general population, in which it is generally resolves spontaneously around 8 years of age (6, 7).

Hearing loss by-product of OME is associated with worse language development and poor school performance in children who suffer from it, so it should be monitored frequently in patients with PCD.

OME treatment in these patients should be considered case by case, since the placement of ventilation tubes is associated with persistent otorrhea in approximately 50% of cases. However, the improvement in hearing is immediate and significant after surgery, making this a very effective treatment modality (7).

Sensorineural hearing loss

It has been seen that patients with PCD have a higher rate of sensorineural and mixed hearing loss than the general population, aggravating the auditory problem and making it less susceptible to conservative and / or surgical treatments due to the presence of the neural component. The cause of this is unknown, but it is believed to be by-product of the compromised ciliated cells of the inner ear (however, not all patients with PCD have sensorineural hearing loss), or ototoxicity to the inner ear due to recurrent infections since bacterial toxins are able to penetrate the inner ear. This theory seems more plausible (10, 11).

This requires annual audiometric monitoring in these patients plus otoscopic control.

Chronic rhinitis

Nasal congestion and rhinorrhea are present in more than 80% of patients with PCD. These are symptoms that start very early and remain until adulthood. They are often confused with allergic rhinitis symptoms, especially in the face of partial response to topical steroid therapy. However, persistent symptoms despite adequate treatment should raise suspicion of PCD. The best treatment strategy in these cases is to facilitate fluidization of the secretions using frequent washes with hypertonic saline. No significant difference between using high volume / low pressure washes and low volume / high pressure washes has been demonstrated. Its daily use is recommended, ideally 2 times a day.

Topical nasal steroids can be used to decrease local inflammation by-product of accumulation of secretions and bacterial overgrowth (12, 13).

Rhinosinusitis a repetición

Around 60% of the patients with PCD have recurrent bacterial rhino sinus infections. This situation is more frequent in older children. The germs are not the same as in the general population, since the presence of an underlying chronic disease exacerbation is the rule. The germs detected in the cultures are *Haemophilus influenzae*, followed by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The latter three are more frequent in patients with chronic rhinosinusitis (14, 15).

Chronic rhinosinusitis

Chronic rhinosinusitis pathology is practically a constant feature in patients with PCD. It is associated with significant alterations in quality of life, worse results to low respiratory compromise treatment, and obstructive sleep pathology. It is considered that more than 80% of patients with PCD present chronic rhinosinusitis symptoms, and that they require multiple antibiotic treatments throughout their lives (8).

Between 18 and 33% present nasal polyps that usually begin during adolescence. Symptoms include nasal congestion, rhinorrhea, posterior discharge, facial pain and hyposmia / anosmia. When this symptomatology persists for more than 12 weeks, and there is objective clinical or radiological evidence of rhino sinus involvement, chronic rhinosinusitis is considered. If we take into account the radiological findings, practically 100% of patients present chronic inflammatory changes in the

paranasal cavities CT, and can be seen from 6 months of age. A frequent radiological finding in children with PCD is the presence of hypoplasia of the frontal and sphenoid sinuses, so much so that this finding raises suspicion of the disease (9). It has also been shown that patients with hypoplasia of paranasal cavities have a lower level of nitric oxide, which is a marker of the disease, and which is one of the innate local defense mechanisms of the upper respiratory tract. Nitric oxide regulates intracellular signals that increase the ciliary beat rate and has direct cytotoxic effects on the bacterial cell membrane, DNA and other bacterial enzymes (10). There is an inverse correlation between the levels of nitric oxide measured and the severity of rhinosinusitis, although it has not yet been established whether low levels of nitric oxide are a cause for, or a consequence of, severe rhinosinusitis.

Rhinosinusitis treatment for patients with PCD has been historically based on the results of rhinosinusitis treatment of patients with cystic fibrosis, and consists mainly of applying preventive measures to try to reduce bacterial exacerbations and fluidize secretions. In this regard, repeated immunizations against pneumococcus and influenza virus are recommended in all patients. Nasal washes with hypertonic saline and the use of topical anticholinergics have shown utility in the improvement of symptoms, in spite of the absence of evidence in the literature that demonstrates this. In the same way, the use of topical corticosteroids is recommended in all patients to reduce local inflammatory involvement and improve ventilation of the paranasal cavities. It has been shown that prolonged use of macrolides inhibits the migration of neutrophils, accelerates neutrophils apoptosis, modifies the release of cytokines, inhibits the release of destructive enzymes by *P. aeruginosa*, alters the structure of biofilms, improves the mucociliary transport, reduces hypersecretion of the goblet cells of the epithelium, and improves the viscoelastic properties of mucus. Its use is recommended in patients with poor response to initial treatment. The time of use is variable, but usually starts off at 3 months and the response is reevaluated after that period (11).

Bacterial exacerbations should be treated promptly with antibiotic therapy to cover the most frequent germs (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*). It is recommended to culture sputum and nasal secretions at least every 3 months. If *P. aeruginosa* is detected, it is recommended to perform a treatment similar to that of patients with cystic fibrosis, but the evidence of its effectiveness in patients with PCD has not yet been established.

In patients in whom medical treatment fails, surgical treatment is recommended. Functional surgery of paranasal cavities (in which the natural sinus ventilation holes are extended) has shown significant symptomatic improvement in patients with rhinosinusitis with nasal polyp, in patients with recurrent headache and facial pain, in pulmonary exacerbations that correlate with rhinosinusitis exacerbations, and in patients in whom there is a worsening of lung function and a rhinosinusitis compromise that does not respond to medical treatment (12).

Respiratory disorders during sleep

High respiratory obstruction is an almost constant manifestation of PCD. It has been shown that patients with PCD have a higher rate of obstructive sleep apnea / hypopnea

compared with healthy controls. This may be due to chronic inflammation of the nasal mucosa, the presence of nasal polyps, obstructive thick secretions, and a higher rate of adenoid hyperplasia seen in patients with PCD vs controls. Nocturnal hypoventilation by-product of sleep apnea / hypopnea can have effects on the evolution of pulmonary inflammatory pathology, present in practically all these patients, so it is a fact that should be taken into account at the time of evaluation (13).

CONCLUSION

Patients with PCD present ENT involvement in almost 100% of the cases. This compromise is precocious, and its presence should arouse suspicion in the treating physician to promptly direct the study and make an early diagnosis to avoid irreversible sequelae. It should not be forgotten that only 50% of patients with PCD have Kartagener's syndrome. Initial treatment is preventive and should be performed on all patients with positive diagnosis.

Once the chronic inflammatory pathology of the ears, nose and paranasal cavities has been established, its treatment is complex and multifactorial, and literature with evidence is scarce, based on small cohorts and expert opinions.

Given the low frequency of the disease, it is important to develop a multicenter database, hopefully internationally, to collect evidence that modulates our diagnostic and therapeutic process in the future.

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