

PRIMARY CILIARY DYSKINESIA TREATMENT

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ABSTRACT

At present, there is no specific treatment for primary ciliary dyskinesia, nor controlled and randomized clinical trials to determine how the management and monitoring of these patients should be considered. The therapeutic options are extrapolated from other diseases, such as cystic fibrosis, or non-cystic fibrosis bronchiectasis. However, the implementation of specific groups of experts, both in the USA (PDC-foundation) and in Europe (BESTCILIA or BEAT-PD), are helping to increase knowledge of the disease, opening research channels and seeking new treatments. Until we have therapies capable of correcting the basic defect of the disease, the pillars of treatment are the daily cleansing of the airways and aggressive antibiotherapy against respiratory infections. Multidisciplinary care in specialized centers where pulmonary function is monitored and the infection is prevented and treated will improve, as in cystic fibrosis, the results of patients.

Key words: primary ciliary dyskinesia, PCD, treatment.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare disease, scarcely known and with a complex diagnosis, as it does not depend on a single conclusive test but on a series of sophisticated techniques that require specific means and expert personnel. All this leads to an important underdiagnosis, or diagnostic delay (1), as well as difficulties in the control and monitoring of patients, since the multisystemic nature of the disease requires multidisciplinary care by various specialists (pulmonologists, physiotherapists, otolaryngologists, ...), pediatric and adult, experts in PCD. The coordination of this care will depend, in each country, on its own health organization, on geographic accessibility and on the preferences of patients. In this sense, the National Health Service of the United Kingdom can serve as an example. Since 2012 they have a centralized and highly specialized service consisting of four pediatric national PCD centers to which, in 2018, other complementary services for adults were incorporated. There, at least one annual review is carried out and an individualized follow-up plan is drawn up, to be developed by local primary or secondary care physicians. Additional visits are scheduled, at least every 3 months, to be carried out in one of the National Centers, or through shared care with the team of local specialists. The family being treated has a telephone counseling line managed by the professionals involved in their care (2).

In all cases, in the first years of adolescence, the patient is integrated into an adult transition program that allows him or her to acquire the knowledge and skills necessary to manage their own medical care (3). Furthermore, international networks of interrelation between the reference centers of each country begin to exist, which may favor the rapprochement between the professionals dedicated to PCD, and improve both the diagnosis of the disease and its treatment.

FOLLOW-UP AND SPECIFIC TREATMENT

At present, there is no specific treatment for PCD, nor are there controlled and randomized clinical trials. Existing protocols are limited to expert consensus (4,5) extrapolated from evidence from other diseases with defective mucociliary clearance, such as cystic fibrosis (CF), or non-CF bronchiectasis, in which the aim is to preserve lung function by eliminating mucus, prevention and early detection of respiratory infections, and aggressive treatment. CF is a different disease than PCD in its pathophysiology, evolution and prognosis (6), so it would be necessary to have own guidelines based on evidence (7).

In any case, in the last 12 years progress has been made in knowledge and disease treatment (3):

- In 2007, the European Respiratory Society (ERS) constituted a working group on PCD formed by representatives of 23 European Centers, which highlights the important existing diagnostic and therapeutic disparities (1,8), and that in 2009, published the first consensus on the diagnosis and

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treatment of this disease in children (4).

- Similarly, in the USA, in 2016, the PCD-Foundation (www.cdfdfoundation.org) presented its own consensus (5) promoting knowledge on PDC through annual conferences, community education, patient advocacy and research funding.
- Between 2012-2015, BESTCILIA Group is created, which implements the European PCD Registry (9), the international PCD cohort (iPCD) with more than 3000 patients (10) and the first clinical trial (11). They develop and validate quality of life questionnaires (QOL-PCD) specific for children and affected adults (12, 13).
- Since 2016, the BEAT-PCD network (COST Action BM1407), constituted by clinicians and researchers, and funded by the European Union, coordinates the research of PCD in Europe, in order to increase knowledge on the disease, study its progression and find therapies that lead to improvements in long-term prognosis.

In this review we set out to collect and update the key aspects of the follow-up and management of children with PCD.

EFFECTS ON GROWTH AND DEVELOPMENT

Recent data reflects reductions in height and BMI, independent of age and sex, but related to diagnostic delay, FEV1 and FVC (14). These findings suggest that early diagnosis and the inclusion of nutritional counseling and control could improve growth and delay the deterioration of lung function in these patients (7). Similarly, knowing that vitamin D deficiency is a common finding in PCD and conditions a worse quality of life (15), monitoring and treatment is recommended.

LUNG DISEASE

Respiratory tract cleansing therapies

The basic problem with PCD is the existence of poor or absent mucociliary clearance, which is why respiratory therapies that facilitate the elimination of mucus are essential to reduce stasis of secretions, atelectasis, bronchial infection-inflammation, and progression of lung disease (2). The daily cleaning of the airway and aggressive antibiotic therapy against respiratory infections are the fundamental pillars of lung disease treatment.

• Respiratory physiotherapy

There is no evidence or consensus on the most effective respiratory physiotherapy techniques that, in addition, vary center to center (4). In what all agree is to apply them as soon as PCD diagnosis is considered probable (3). Respiratory physiotherapists, as part of the multidisciplinary team, must design an individualized protocol, according to the child's age, preferences, mucus

properties and severity of the disease (3,16). It is generally recommended to perform two daily sessions, increasing the number during exacerbations (2).

• Exercise

Exercise improves the strength of the respiratory muscles and aerobic condition, reduced in patients with PCD (15), so it should be prescribed in combination with respiratory clearance therapies (3, 17). Its performance before physiotherapy increases effectiveness and has a greater bronchodilator effect than that of the β_2 -agonist drugs themselves (18).

• Inhalation therapy

In patients with CF it has been shown that certain inhaled medications alter the properties of the mucus or facilitate its elimination. However, when dealing with a different disease, like PCD, the same results cannot be guaranteed.

- *Nebulized hypertonic saline solution* improves mucociliary clearance and reduces exacerbations in adults with non-CF bronchiectasis (20), without achieving major changes in spirometry, sputum colonization or quality of life. For PCD, there is only one randomized, controlled, crossover study with 22 patients, which does not benefit from any of the parameters studied (20).
- Recombinant human DNase, commonly used in CF to lyse neutrophil DNA, has been shown to be ineffective in non-CF bronchiectasis (22). In PCD there is hardly any experience, only in isolated cases, so it cannot be recommended (17).
- Some studies speak in favor of the role of Uridine-5'-triphosphate (UTP) (22) and inhaled mannitol (23) in the improvement of lung clearance, but more tests are needed to be able to recommend them.
- β_2 agonists and inhaled corticosteroids are not routinely indicated for these patients, unless they have asthma or pathway respiratory reactivity (4, 5,17).

Management and prevention of pulmonary infections

Again, the evidence is scarce and guidelines are extrapolated from the experience with CF (4, 5), although there are microbiological differences between the two diseases. In PCD, *Haemophilus influenzae* is the most common and precocious pathogen (35-65% in children and adolescents) and *Pseudomonas aeruginosa*, although less prevalent, increases with age (from 21 to 51%) (24). The performance of sputum cultures [≥ 2 - 4 times / year, according to the consensus (4, 5)] and aggressive treatment of the new isolates, reduce the progression of the disease (3). Even so, while antibiotic therapy in exacerbations is not discussed, it is not clear whether bacterial isolates should be treated when they are not accompanied by clinical

indicators. In mild exacerbations, oral antibiotics are used and respiratory physiotherapy is increased. Serious ones may require intravenous antibiotics and hospitalization (5), with doses that could be lower than those used in CF. However, there is a case of a 10-year-old boy with respiratory exacerbation, recently been published, in which the dose of tobramycin (single daily) had to be increased to 12.8 mg / kg (similar to that used in CF)., to achieve the pharmacokinetic objectives (25). Antibiotics are selected based on the most recent sputum culture results, taking into account the patient's history of respiratory colonization. The duration of treatment is usually 14-21 days, according to the proposed guidelines for CF and non-CF bronchiectasis.

Inhaled antibiotics are usually reserved for *P. aeruginosa* infection, although they may be an option for respiratory exacerbations (5) and for symptomatic patients with moderate-severe lung disease and chronic bronchial infection. Inhaled tobramycin (300 mg nebulized, twice daily, for a period of 28 days), should be considered with the first evidence of growth of *P. aeruginosa* (26), since its presence is associated, as in CF, with worse lung function (27). Similarly, it seems prudent to segregate patients and implement strategies to prevent the spread of certain pathogens since the risks of cross infections are probably similar to those of CF (3).

When repeated cycles of antibiotics are required, prophylactic macrolide treatment could be considered (4,5). To assess its effectiveness, a multicenter, randomized, double-blind prospective study with azithromycin is currently underway (11).

Pneumococcal immunization, within the normal immunization program, and annual vaccination against the influenza virus, should be indicated in all patients, as well as immunoprophylaxis against respiratory syncytial virus (RSV) in infants with PCD, the first year of life (4, 5, 17).

Terminal disease. Complications

In advanced cases, with severe localized bronchiectasis and repeated exacerbations, in which the usual treatment fails, the possibility of a segmentectomy or lobectomy of the affected territory could be assessed. In the same way, lung transplantation can be considered in patients with terminal illness, since their survival is similar to that of the general population. In them, site anomalies could represent a barrier in the selection of the donated lung and require advanced surgical planning (28).

AFFECTION OF SUPERIOR AIRWAYS

In the upper respiratory tract, the pathology derived from mucociliary disorder affects the nasal passages, paranasal sinuses and middle ear.

Chronic rhinosinusitis (CRS) is the hallmark of PCD ($\geq 70\%$ of patients) (29) and rhinosinusitis polyposis prevails in up to 50% of adults (29), greatly altering their quality of life (13). Regarding otologic manifestations,

acute otitis media with effusion occurs in almost 100% of children <12 years (30) and, although they tend to improve over time, it is usually associated with a moderate conductive hearing loss that could hinder the acquisition of speech.

The management and treatment of these processes is extrapolated from the general population, or from CF, and is addressed in depth in another article of this journal.

NON-RESPIRATORY MANIFESTATIONS

Cardiomyopathy / Heteroataxy

Congenital heart disease, if present, usually requires corrective or palliative surgery. When combined with heteroataxy, there is an increased risk of postoperative mortality and of respiratory complications with anesthesia (30). Therefore, a careful preoperative assessment and preparation and intense perioperative respiratory management are recommended.

Infertility

Intracytoplasmic sperm injections may facilitate conception in men with immobile cilia, while in vitro fertilization and intrauterine implantation could help women with PCD and decreased fertility (31).

NEW THERAPIES

Currently, some clinical trials are investigating the effect of certain drugs for PCD, either on lung function with inhaled solutions of epithelial sodium channel inhibitors (NCT02871778, Vertex Pharmaceuticals), or in vitro, with aminoglycosides, which have been shown to stimulate readthrough of premature termination codons in 5 genes involved in the disease (32). We are, therefore, at an exciting stage in which increased knowledge of genetics and phenotyping of PCD can lead to the development of new therapeutic strategies. However, the genetic heterogeneity of PCD caused by mutations in more than 30 genes, many yet unidentified, hinders the development of therapies capable of correcting the basic defect of the disease, or of restoring the function of defective proteins, as occurs in CF. Either way, a group of researchers recently has managed to apply for the first time the "editing of genes" in this pathology, restoring the function of the DNAH11 gene *ex vivo* and replacing the inactivating mutation by a wild-type sequence in the diseased cell (33), which opens new pathways in the treatment of PCD.

Conflict of interest

Dr. Amparo Escribano declares no conflict of interests.

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