Research Article **RJPP 2017 1:10**

Research Journal of Pharmacology and Pharmacy (ISSN:2572-8377)

PRIMARY CILIARY DYSKINESIA

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ABSTRACT

Primary Ciliary Dyskinesia (PCD) is a heterogeneous recessive autosomal disorder that affects mainly the motile cilia. The objective of the present review is to enlighten the ciliary ultrastructure, activity and biogenesis to understand the clinical symptoms of the disease; describe the limitations of the currently available diagnostic tests and therapies; and present the future perspectives about the illness, based on ongoing studies. This systematic literature review was built from a bibliography research of scientific papers, publications and materials available on the Internet in English and Portuguese. From this research, five essential themes were identified: ciliary structure and biogenesis, genetic determination, physiopathology, diagnostic and therapeutic approaches. In the end, it was possible to notice that advances on the molecular and genetic biology studies contribute significantly to the construction of a clinical phenotype from a multidisciplinary approach, which facilitates the diagnosis and the treatment.

Keywords: primary ciliary dyskinesia; kartagener syndrome; cilia; dynein; genes.

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How to cite this article:
LEMOS et al.,. PRIMARY CILIARY DYSKINESIA. Research Journal of Pharmacology and Pharmacy, 2017, 1:10

eSciencePublisher
eSciPub LLC, Houston, TX USA.
Website: http://escipub.com/

INTRODUCTION

Primary Ciliary Dyskinesia (PCD) is a heterogeneous recessive autosomal disorder, with estimate incidence of 1 at every 10000-20000 births[1], characterized by the impairment of the structure and/or cilia functions[2,3,4,5] – structures similar to hair on the apical surface of the cells and involved in cell motility and sensitivity[2,5]- due to mutations in a great number of genes, which characterizes it as heterogeneous and that codify proteins involved in the process of ciliary biogenesis, as well as its structuring and regulation[1,3].

Manes Kartagener initially described this disease in the decade of 1930, when it received the name of Kartagener Syndrome and it was based on the triad: bronchiectasis, chronic sinusitis and *situs inversus.* In 1976, Afzelius affirmed that the individuals pointed by Kartagener were carriers of defects on the ciliary ultrastructure, which would imply on its immobility and functional compromise, changing the denomination for Syndrome of Immotile Cilia[1,4]. More recently, advances on the knowledge of the physiopathology of the disease enabled the identification of the immobility as only one of the ways of ciliary compromise, so it was then renamed to Primary Ciliary Dyskinesia. The term “primary” was adopted to differentiate the structural and functional defects, secondary or acquired, commonly associated to infections and inflammations[1]. Nowadays, the term Kartagener Syndrome is applied only to the cases of PCD where there is no change on the ciliary ultrastructure, which corresponds to around 30% of the cases of the disease[1,3].

The symptomatology of the PCD involves neonatal respiratory distress in around 80% of the cases[1], daily nasal congestion and humid cough, with a possibility of developing bronchiectasis, more common in adults, and progressing with a picture of recurrent superior and inferior chronic respiratory infections, which may lead to a severe pulmonary compromise. However, it may occur the development of chronic diseases in the middle ear, changes on the establishment of symmetry in the embryonic development and a decrease in the feminine and masculine fertility[1,4].

The diagnostic approaches are complicated by the variety of phenotypes of individuals with PCD[1], so the transmission electron microscopy (TEM) and the study of the ciliary beat will give place to measurements of nasal concentration of nitric oxide (NO), usually low in PCD individuals, and genetic tracking and sequencing of reduced subjectivity[1,4]. The difficulty is also present on the treatment of PCD due to the inexistence of specific therapies for the disorder. So, there is the use of procedures recommended to other disorders where there is the compromise of the mucociliary transport, such as Cystic Fibrosis[1], and only to control the symptoms[3], emphasizing the clearance of the airways, the use of antibiotics to control infections and the non-exposure to inflammatory triggers, for example: smoking and dust[1,4]. In this context, it is possible to notice the need of a multidisciplinary team and an expensive infrastructure to support the complex investigations and the impasses faced on the treatment and monitoring of an individual with PCD[5].

Thus, the present review brings structure, activity and process of ciliary assembly, associated to the genetic basis that permeates the biosynthesis of this structure as a substrate to understand the clinical manifestations of the PCD, as well as the difficulties and limitations of the diagnostic and therapeutic approaches of such disorder, associating them to the future perspectives revealed by ongoing studies.

METHODS

This is a study of systematic review of scientific literature. The choice of this method is to create opportunities for a scientific basis that allows, through previous studies, a more complete comprehension of the topic of interest. The study was conducted as a literature review, which used the following databases of scientific papers, publications and Internet materials as tools: PORTAL CAPES, SCIELO, LILACs, PubMed and MEDLINE. The describers used to search the articles were: “primary ciliary dyskinesia”; “kartagener syndrome”; “cilia”; “dynein”; “neonatal respiratory distress”; “genes”. In order to organize the material, there were stages and procedures of preliminary bibliographic research and identification, book reports and summaries, analysis and interpretation of the material, bibliography, review and final report. Six people were actively engaged during this proves, being 31 scientific papers pre-selected. However, 16 of them were excluded to build the present review, once there

was no new information on them when compared to the other references. Also, many were based on a clinical mutation phenotype of a specific gene, when the objective of the work was to offer a more generalized approach of the Primary Ciliary Dyskinesia.

RESULTS

Data from 15 scientific papers that fitted the criteria established on the methodology were collected, which involved, in a general way, the themes: ciliary structure and biogenesis (6); relations between genetics and Primary Ciliary Dyskinesia (4); physiopathology of the disease, diagnostic and therapeutic approaches of the PCD (2 as a central theme and others as a secondary theme); prevalence of respiratory diseases related to cilia in congenital cardiac patients with heterotaxy (1) and evaluation of the ultrastructure and ciliary movement in children with chronic and repetition pneumonias (1). This way, the articles reviewed provided a more complete comprehension of the topic of interest and were guiding tools for the development of this text, which had as a substrate the previously presented topics of greater incidence.

DISCUSSION

CILIARY STRUCTURE AND BIOGENESIS

The cilia are structures that protrude on the apical surface of cells, similar to fingers[6]. With its continuous membranes, the cellular membrane[7] plays a fundamental role on the cellular motility and sensibility, as well as on the regulation of cellular growing and differentiation[8]. They are constituted mainly by the polymerization of tubulin α and β in microtubule structures, the axoneme, which stands in a centriole basal body[1,11]. Based on the evolutionary history of the eukaryotic cell, cilia emerged early and were maintained in its protein constitution, structure and function[5]. The ciliary axoneme, extends from the centriole inherited from the mitosis to the cell membrane, since the process of ciliary biogenesis depends on the release of cell division centriole, after the cytokinesis[6,8].

The advances on the studies of the ciliary biogenesis, ultrastructure and activity, assured the discovery of a group of disorders that result on the compromise of the function of this organelle, as the case of PCD[8]. In order to understand the physiology of the PCD, it is fundamental to understand the genesis of the ciliary outline and how this process determines its functioning.

The motile cilia are responsible for transporting fluids and cells and are present on the respiratory tract, where they constitute a mechanism of innate defense of the lung by obstructing the passage of bacteria, dust particles and toxic substances through the conduction airways; in the auditory tube of the middle ear, with the role of protecting the middle year on its communication with the nasopharynx; in the uterine tubes, where they hit towards the uterus and mainly intend to transport the oocyte; and in ependymal cells of the brain ventricles, where they are fundamental to produce the cerebrospinal fluid (CSF). The scourge of the sperm, whose beat is responsible for the transportation of this cell, has a similar structure[1,3,6].

The motile cilia usually have 9 pairs of peripheral microtubules, in a cylindrical shape, and two centrals, an organization known as 9+2. Associated to the peripheral pairs of MT there is a protein, dynein, containing an external and an internal arm and a site to hydrolyze the ATP, which is involved in the ciliary beating and intracellular transport; nexin connections, that link the peripheral MT; radial spicules, which extend from the periphery to the central pairs of MT and, with the nexin connections, are responsible for the stability of the microtubule structure[1-3,6,7]. The result of this structure is a ciliary beat of around 8-20 Hz under normal conditions. The deregulation of the ciliary movement may generate acquired ciliopathies, which may have as causes alterations on the microenvironment, viscosity of the fluid involved, infections and polluters[3].

Sensorial or primary cilia are important on the interaction of the cell with the environment, performing the transduction of environmental stimuli (mechanical, chemical, thermal, luminous) and regulating the signaling pathways fundamental for the development, growth and repairmen, through surface receptors, among which we can highlight Sonic Hedgehog, Human Epidermal and Platelet-Derived Growth Factors[3,6,7,11]. Since most of our cells have at least one primary cilium, they are present on kidney tubes, astrocytes, chondrocytes, bile duct and other sensory

epithelia in the body, such as retinal and olfactory. Defects on these structures may lead to polycystic kidneys, retinal degeneration, liver and pancreas diseases for many reasons[7]. Mutations on the genes that codify these sensorial cilia are known by causing the Bardet-Biedl Syndrome, nephroptosis, retinitis pigmentosa, Joubert syndrome and dominant autosomal polycystic kidney disease[1]. Sensorial cilia have a differentiated structure from the motile cilia, since they do not have the two central MTs, presenting, then, a 9+0 conformation[1,3].

The motile cilia may also be sensorial, being called nodal cilia, transitorily present on the Gastrula phase of the embryo development and, fundamental, through the activation of a biochemical cascade of transcription of growth factors to the establishment of the laterality of the embryo, that is, the symmetry between the left and right sides. The cilia do not have a central pair and present a 9+0 configuration, however, there is dynein to guarantee the motility. In the absence of the normal nodal ciliary function, there is the issue on the positioning of organs, as the case of *situs inversus* and *situs ambigus*[1,3,6].

The formation of the ciliary axoneme and other accessory proteins depends on the coordination of the intraflagellar transport, since the cilia do not have mechanisms to synthetize proteins, once all its protein content must be synthetized in the cellular cytoplasm and then transported, with proper regulation, to the cilium under formation[5-7,9]. The molecules necessary for construction and maintenance of cilia travel through kinesins, anterograde (from base to apex), and retrograde dyneins (from base to apex), which use the energy of the ATP hydrolysis[6-8].

At the distal extremity of the basal body, the plasma membrane of the cell gives place to the ciliary membrane, different and essentially lipid composition, being rich in sterols, glycolipids and sphingolipids, made in the Golgi complex[8]. Y-shaped links connecting the peripheral microtubules to the ciliary membrane and organize rows of protein molecules attached to the membrane, called ciliary collar[7]. The ciliary membrane is anchored to the basal body by the transitional fibers. Next to this attachment point, there are areas to the entrance of molecules from the intraflagellar transport[6-8]. The regulation of the ciliary entrance and exit of protein may depend on other proteins on the ciliary basis as a barrier of diffusion or gate, which prevents the unspecified movement of the protein, from inside and outside of the cilium, at the zone of ciliary transition, near region of the cilium, where the 9 trios of centriole microtubules will build he 9+2 axonemal[6,7,9]. The components of the cilium structure are incorporated in the distal extremity of the axoneme, that is, the ciliary axoneme and its associated elements are not prolonged through the addition to the base, but through extension from the extremity growing[8]. Once built, the cilium remains in dynamic balance, with successive polymerizations and depolymerizations[7].

GENETICS AND PCD

PCD is the only genetic disorder of motile cilia. Despite being a heterogeneous recessive autosomal disorder, some cases of dominant autosomal transmission have been described and linked to the X chromosome. The first mutation that caused the disorder was described around 10 years ago[3] and ever since, the rhythm of gene discovery has speeded up rapidly, allowing the comprehension of the foundations of this disorder. Nowadays, it is being said that almost 30 genes, when modified, may cause PCD, which can consider it very heterogeneous[1-3,12,13]. However, it is believed that the known genes represent around 60% of the PCD cases already registered[3], revealing the need for more advances on the genetic tracking and sequencing to identify other genes that codify the great variety of proteins related to biogenesis and the ciliary activity, as well as its regulation[1-3,12,13].

The identification of genes associated to the PCD involves experimental models, proteomic analysis and sequencing of candidate genes. More recently, the parallel sequencing to analyze the regions of interest of the genome allowed a faster identification of other mutations in individuals with PCD without previous knowledge of candidate genes. Moreover, the sequencing of all the exome is being recently used to identify new candidate genes related to PCD[3,13]. These are promising technologies when it comes to genetically heterogeneous diseases[13].

The highlights are the genes DNAI1, DNAI2 and DNAH5, associated to defects on the external arm of dynein and together are responsible

for more than 30% of the PCD cases; SPAG1, LRRC6, HEATR2 and DNAAF3, related to cytoplasmic proteins, involved direct or indirectly on the ciliary biogenesis, and participations on the external e internal arm of dynein; CCDC40 and CCDC39 involved with the microtubule disorganization and loss of the internal arm of dynein, only at part of the motile cilia present on the organism; and DNAH11 that, despite codifying protein of the external arm of the dynein, it is not related to ultrastructural defects, but it may cause the hyperkinesia and the decrease of amplitude of the ciliary beat[2,3,12].

Due to genetic heterogeneity, it is difficult to determine a phenotype that is characteristic for individuals with PCD, compromising the diagnostic and therapeutic approach of the disorder[1,11].

PHYSIOPATHOLOGY

The motile cilia are responsible for the transport of fluids and cells at the most diverse areas of the body. Symptoms of PCD are closely related to the organs where the ciliary motility is fundamental for the local homeostasis[14]. The compromise of this motility, due to the defective ciliary functioning on PCD, may affect the upper and lower airways, paranasal sinuses, middle ear (auditory tube), male and female reproductive tract, as well as the embryonic development, by reaching the nodal cilia during the Gastrula phase[1-4,14].

In healthy individuals, the airway mucus retains bacteria, debris and toxic substances through the ciliary activity. In the person with PCD, the prejudice of the ciliary activity promotes the appearance of recurring and chronic infections of the respiratory tract, which show the symptoms right after the birth, so that about 80% of the newborns with PCD present respiratory distress[1,4,5]. Furthermore, it can be associated to productive cough (it ay temporarily compensate the transportation of defective mucus, but it does not prevents the occurrence of infections[1]), hypoxia, pneumonia, chronic bronchitis, tachypnea (commonly identified as transient pneumonia neonatal or tachypnea of the newborn[1,14]), and may require supplemental oxygen for prolonged periods, and changes in imaging tests, such as atelectasis, air trapping, peribronchial thickening and ground-glass opacity, which may lead to one bronchiectasis[1,4,14].

However, bronchiectasis is not very common in children, appearing in adult patients and mainly the inferior and middle lobes[5]. Progression and gravity of the disorder vary among the carriers of PCD, however, bronchiectasis usually leads to lung damages and respiratory insufficiency[14].

The spectrum of microorganisms in PCD, responsible for the previously mentioned chronic infections, one of the main causes of lethality in the disease, involves *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, oropharyngeal flora. *Pseudomonas aeruginosa* and non-tubercular mycobacteria, despite presenting low prevalence in children, are present in great part of the adults with PCD[1,4,14]. It has been verified that some patients may present more than one type of bacteria in the same sample[4].

The ciliated epithelium that lines the middle ear, auditory tube, nasal cavity and paranasal sinuses are also affected in the PCD, so that the carrier of the disease also has clinical manifestations including middle otitis with effusion, affecting about 85% of children with the disease, leading to conductive hearing loss, which usually oscillates, but it can be permanent[5]; delay in language development; atelectasis of the tympanic membrane and cholesteatoma[1,2,4,14]. Chronic rhinitis and sinusitis are also present in the PCD, with the presence of nasal polyps in about 15% of the patients[1,2,14].

The laterality defects, as *situs inversus* and *situs ambigus*, which are present in about 50% and 6% of the PCD carriers, respectively, and heterotaxy, reflect the abnormal activity of the nodal cilia in the embryogenesis[1-4,14]. Studies with rats verified that the mutation of the gene DNAHC5, responsible for the PCD, would lead to a high prevalence of congenital heart diseases, revealing the importance of the cilia on the normal development of the heart[1,14,15].

The decrease of fertility or the infertility is present in men and women carrying PCD. In men, it occurs because of changes in sperm motility, of which plagues have a similar constitution to cilia, compromised by the disorder above mentioned. There have been reports, however, of male carriers of PCD with some motile sperms and who have already had children. In women, the function of cilia in the fallopian tube, with the

beat towards the uterus, is damaged and it may reduce fertility and promote the appearance of ectopic pregnancy by discouraging the traffic of the oocyte towards the uterine cavity[1,2,4].

Clinical manifestations may also involve hallowed chest and scoliosis, present in around 5-10 %, respectively, of the PCD cases, as well as retinitis pigmentosa and hydrocephalus[1,4].

DIAGNOSTIC APPROACHES

It is necessary a high degree of suspicion to diagnose and start the treatment, this way, patients with suspicion of PCD must be sent to Specialized Centers, with proper infrastructure and experienced staff[1,2,4]. There are many methods to support the diagnosis, however, there is no “gold standard”[2].

The patient should be sent to diagnostic test if there is *situs inversus* related to symptoms of the airways; unexplained neonatal respiratory distress; sibling with PCD, mainly in symptomatic; productive cough on a daily basis and persistent nasal congestion; bronchiectasis of unknown origins; middle otitis associated to airway symptoms; congenital heat diseases associated to heterotaxy, if there are symptoms of airways or ear symptoms; men and women with low fertility of infertility, if they present respiratory symptoms[1,2]. Difficulties on the diagnosis may be present in cases of overlapping phenotypes, especially cystic fibrosis[4].

Retinitis pigmentosa, hydrocephalus, hallowed chest and scoliosis are major indicators of the disorder if combined with other characteristic symptoms[1,2]. The relation of PCD with the Bardet-Biedl and Alstrom syndromes, which affect the primary or sensorial cilia, is not a consensus yet[1].

It is necessary to give special attention to patients of populations where consanguinity is common, since it may increase the incidence of the disease in 1 at every 10000-20000 to 1 at every 2000 births[1,2].

TRANSMISSION ELECTRON MICROSCOPY

The identification of defects on the structure of the cilia has the transmission electronic microscopy (TEM) as its base, a test traditionally used to confirm the diagnosis of PCD and that was already considered a gold standard[2,4]. However, this approach presents strong limitations, once it is not able to diagnose patients with an intact ciliary ultrastructure, which correspond to 30 % of the individuals with PCD. Other limitations of the TEM involve the difficulty of obtaining and handling proper samples and the correct interpretation of images, which makes the diagnostic of false positive PCD, present in 15-20 % of the individuals sent to diagnostic centers[1,3,4]. A very common impasse is the difficult to differentiate secondary causes, resultant of infections and environmental polluters and from PCD, revealing the need of a posterior repetition of the process[1,3].

Abnormalities on the external and/or internal arms of dynein, microtubule disorganization, which may contain transposition or agenesis of the central pair, and changes on the nexin connections and radial spiculesmay be verified through the transmission electronic microscopy[1-4]. Some patients do not present cilia on the biopsied cells, but there are no conclusions about it, once it has not being discovered any genetic etiology for this possible ciliary aplasia[1].

Samples must be collected from the nasal epithelium or from the bronchia, a process that may create some discomfort[2], when there are no infections or inflammations, since this secondary causes may change the ciliary ultrastructure. The acquisition of samples in children is less viable than in adults, because of the difficulty offered by the narrow airways[1]. The processing is highly specialized, once it is common that te microscopy does not allow the visualization of some components of the ciliary structure, then, a quantitative approach is fundamental for the proper interpretation[1,3,4].

IMMUNOFLUORESCENCE

This technique is present only in part of the labs and uses marked antibodies to identify structural abnormalities of the cilia, changes on the process of ciliary biogenesis and in cytoplasmic proteins[1,2,4].

HIGH SPEED VIDEO MICROSCOPY

The pattern (analysis of the characteristic waving movement) and frequency of the ciliary beat may be seen through the analysis of epithelial

cells from the airways in a high speed video microscopy. Cilia may appear static, slow and hyperkinetic or in a rotatory movement, which may configure a PCD. The ciliary function may be classified, in a considerably subjective way, as normal, dyskinetic or immotile.

There also may be confusion with the etiology of the ciliary function, that is, if the cause is primary or secondary, which makes it fundamental to perform a posterior evaluation[2-4]. This diagnostic approach requires experienced analysts and it is also present in a limited number of diagnostic centers[3].

Besides the limitations generated by the lack of technical precision when identifying or handling samples, PCD may not present itself with changes on the frequency and the pattern of ciliary beating, so that this approach does not allow the diagnosis of the variety of phenotypes of the Primary Ciliary Dyskinesia[1].

NASAL NITRIC OXIDE MEASUREMENT

Patients with Primary Ciliary Dyskinesia usually have the levels of nitric oxide low, around 10-20 % of the normal value[1,4], which allows its measurement to be an excellent diagnostic approach; it is one of the most important advances in the context of investigative techniques related to PCD[1-4]. Nitric oxide (NO) is produced in the epithelium of the paranasal sinuses through the NO-synthases enzyme[4].

In the PCD there is the compromise of this region, also verified in cases of cystic fibrosis, acute and chronic sinusitis and nasal polyposis, which results in the decrease of the production of this gas. High or normal levels may occasionally appear in patients with PCD[2]. This way, it is fundamental to repeat the measurement when there are no infections in the respiratory treat and when the values are incoherent with the clinical chart, and other tests to affirm that the individual is carrying PCD[1-4].

The measurement consists in the aspiration of nasal air through a nostril, while the other is patent and will be then led to a measurer. The non-contamination of the nasal air with air from the inferior airways, which contains greater amount of NO, is fundamental. This way, it is necessary to maneuver to close the soft palate while the patient holds the breath. However, this maneuver is not successful in younger children, so that is necessary to use other approaches, which are not proven to be effective in the diagnosis of PCD[1,2].

The analysis of the nasal nitric oxide has been made in a restrict number of diagnostic centers so far. With the future standardization of the technique and the establishment of the proper cut values, the measurement of the nasal NO tends to expands itself and be consolidated as the diagnostic test of the PCD[1,4].

GENETIC TESTS

In spite of not being present on the routine of the diagnostic centers, genetic tests are future alternatives of complementation for the other tests. With the ability of identifying around 65% of the cases of patients with PCD, they present magnified importance in cases of greater complexity, due to the uncommon phenotype or the confusions with other diseases, such as cystic fibrosis. Moreover, advances in molecular genetics tend to reveal a series of information about the physiopathology of the disorder, which would facilitate the consolidation of diagnostic and therapeutic approaches in cases of Primary Ciliary Dyskinesia[2,4].

OTHER DIAGNOSTIC METHODS

The saccharine test has been used as a screening test for this disease. The hindsight of a saccharine particle placed in the inferior turbinate could indicate changes in ciliary activity. However, several limitations in testing and interpretation of results diminished the credibility of the disease and the test is no longer recommended[1,2].

THERAPEUTIC APPROACHES AND MONITORING

As a result of the lack of randomized and long-term studies and medicine based on evidence about therapies for the Primary Ciliary Dyskinesia, there is no specific treatment. Many features of the therapeutic approaches have their basis on other diseases characterized by defect on the ciliary activity and that present similar clinical manifestations, such as cystic fibrosis[1,2], especially when it comes to the use of macrolide an-

tibiotic and anti-inflammatory medicines[1], since the therapies focus on the control of symptoms.

The procedures recommended to treat the PCD involve the monitoring of the airways, use of antibiotics to control the infection and the elimination of the exposure to inflammatory triggers, such as smoke and dust, which makes it essential to support to the end of smoking[1,2,4]. The regular clinical surveillance, supported in image tests periodically performed, is essential for the evaluation of the pulmonary function, to estimate the extension of the disorder and guarantee that the patient is following the therapy properly[4]. Preventive measures include routine immunizations, associated to pneumococci and influenza vaccines[1,4].

AIRWAY CLEARING

Periodical visitations to evaluate the airways and spirometry are important to monitor the clinical manifestations of the PCD in the respiratory treat[1]. If obstructed, the process of clearing is fundamental to limit the progression of the disease, which may include the hypertonic saline nebulization, which aims to increase the hydration of the net periciliary layer, leaving more fluid secretions and facilitating posterior elimination. These clearance techniques are proven positive in PCD, improving pulmonary function and quality of life, reducing the need for antibiotics[5]. Among the various techniques, none has proved to be superior and the physical therapy plan should be facing each patient[2].

Stimulation of chloride secretion by inhalation of a P2Y2 receptor agonist improved airway clearance by cough, particles labeled evidenced by radiation in case of PCD[1]. The deoxyribonuclease enzyme that is proposed to catalyze eukaryotic DNA, despite being used in the treatment of cystic fibrosis to degrade the genetic material of neutrophils that did not survive to recurrent infections, thus reducing the viscosity of mucus and facilitating cleaning of airways, is not recommended in patients with primary ciliary dyskinesia due to presenting controversies[2,4].

Physical exercises are highly recommended, once they can facilitate the airway clearance, increasing the secretion release and, since they are bronchodilators, such as the mucolytics and the mechanical assistance to cough[1,2,4]. The regular inhalation of salbutamol, a bronchodilator, pre-physiotherapy, is not proven to be beneficial, as well as nebulizing mucolytics, including N-acetylcysteine, which can be a time consuming and expensive process[2].

ANTIBIOTIC TREATMENT

Infections should be treated immediately after the diagnosis of PCD and in an aggressive way. High doses of prolonged use can be prescribed when there is aggravation of the respiratory symptoms, compromise of the pulmonary function or positive culture that, in cases of PCD, is usually abundant and varied[1,2]. Antibiotics should be chosen based on data of the culture and as a response to previous therapies[1,4]. If there is no answer to the oral antibiotics, the intravenous can be given to limit the progression of the disease. Chronic infections are, many times, treated with nebulizing antibiotics for a long time[1,2,4]. Individuals with PCD who develop infection with *pseudomonas aeruginosas*, usually present high indexes of eradication[1,4].

ANTI-INFLAMATORY TREATMENT

It is being used in diseases with similar physiopathology, such as cystic fibrosis and it may include oral prednisone, inhaled corticosteroids and macrolides. However, there are no studies that prove the efficacy of prednisone in a population with PCD; the benefits of inhaled corticoids in such diseases are questionable and the macrolides are proving to be efficient in the control of the disease, but it is still not clear if by an anti-inflammatory or antibiotic effect. In order to use macrolides, it is fundamental that the patients are tested and do not host nontuberculous bacteria to avoid the development of a resistance[1,4].

PULMONARY RESECTION AND TRANSPLANTATION

Surgical intervention is always the last option. In cases of severe and local compromises, processes of resection – withdrawal of the compromised area and part of the healthy tissue around it – and lobectomy – excision of a lobe – can be considered[1,2,4] and the preference is given to patients with located bronchiectasis, recurring fever and/or severe hemoptysis[1]. Patients at the final stage of the pulmonary disease, bilateral transplantation is an option[1,2,4].

MANAGEMENT OF THE EXTRA-PULMONARY MANIFESTATIONS

As an attempt to eliminate the possibility of conductional hearing loss in cases of middle otitis with effusion, the role of the ventilation tubes is controversial. Hearing losses should be managed through hearing aids and speech therapy, with the objective of overcoming problems of language development[2,4].

Antibiotics help minimizing rhinosinusitis characteristic of the PCD, which makes surgery on the nasal sinuses unnecessary. There are no studies that prove the benefits of antihistamines or steroids, but they are useful on random additional episodes of allergy[2,4].

The role of the adenotonsillectomy was not yet proved. Obstructive sleep apnea and other respiratory disturbs are magnified in the PCD, but also there are no studies that affirm there is any relation with the adenotonsillar hypertrophy[2].

Male and female infertility can be overcome through techniques of assisted technology, such as injections and artificial insemination[4].

MONITORING

Patients with PCD must be regularly monitored by a varied team of experienced professionals with multiple techniques of monitoring to evaluate the progression of the disease. Spirometry, a mechanism of analysis of the pulmonary function, is one of the main monitoring tools, along with the evaluation of the pulmonary clearance rate and the high-resolution computerized tomography that, in spite of being useful, is unfeasible, so that is necessary to develop low cost and easy access tests, that optimize this monitoring of Primary Ciliary Dyskinesia patients[2].

CONCLUSIONS

Primary Ciliary Dyskinesia (PCD), a heterogeneous recessive autosomal disorder involving mutations in almost 30 genes, with the advances on the studies of molecular and genetic biology is being slowly unraveled, which contributes significantly to the construction of a clinical phenotype that makes the diagnostic and therapeutic approaches easier, since both lack precision and specificity when it comes to PCD. A multi-professional approach since the early age is fundamental for an early diagnosis and consequent contention on the advance of the disease, considering these impasses offered by the lack of standardization of procedures and the common care of regular monitoring of the disease carriers.

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