Otorhinolaryngologic Manifestations of Cystic Fibrosis: Literature Review

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SUMMARY

Introduction: Cystic Fibrosis is the most common recessive autosomic genetic disease among Caucasians. It's caused by mutations in the gene that decodes regulatory protein for transmembrane conductance, resulting in defective transport of chlorine.

Objective: Review the literature about Cystic Fibrosis, with emphasis on otorhinolaryngologic manifestations.

Method: The online Pub Med databases were researched and we applied the following search terms Fibrosis Cystic and Sinusitis, and Mucoviscidosis and Sinusitis.

Conclusions: Although it is not the main cause of death, the otorhinolaryngologic manifestations of the Cystic Fibrosis bring important morbidity to these patients.

Keywords: cystic fibrosis, sinusitis, nasal polyps.

INTRODUCTION

The cystic fibrosis is a severe exocrinopathy that affects mainly Caucasian patients. It is the most lethal recessive autosomal disease that affects this population (1,2), and occurs in the frequency of 1 per each 2.000 to 2.500 born alive in Europe (3). In the United States, approximately 30.000 people are affected, with the frequency of one gene per each 20 to 25 people. It's less frequent in African and Asian patients, and occur in 1 per 15.300 and 1 per 32.100, respectively (4).

In order to study this disease better, we decided to make a literature review and analyze articles found in Pub Med. The research was made by using the terms "Cystic Fibrosis and Sinusitis", with 304 articles found and 214 articles with the term "Mucoviscidosis and Sinusitis", which were contained in the first group. A pre-selection was made by excluding articles that were not in Portuguese, Spanish or English which decreased them to 102. These had their summaries studied and those which did not approach the Cystic Fibrosis otorhinolaryngologic manifestations were removed. Therefore, 63 articles were requested through Capes, Bireme and Ovid, and a total of 34 were researched within the years of 1981 through 2007.

LITERATURE REVIEW

Mutation

The Cystic Fibrosis mutation was located in a gene found in chromosome 7 (7q31) that decodes the Cystic Fibrosis transmembrane conductance regulator (CFTR). This protein is the pump of chlorine depending on cyclic adenosine-monophosphate (AMPc), whose mutation leads to a failure on the thal ion transport (1,4)

There are more than 1.000 mutations identified, and the most common is the deletion of three pairs of bases that decodes the phenylalanine in position 508, known as delta F508 or ΔF508 (4,5).

The CFTR mutation may be divided into five categories: 1) Absence of CFTR production; 2)Production of CFTR, but failure in the intracellular processing and transport; 3)Normal intracellular transport, but deregulation in the cellular membrane; 4)Normal expression of the cellular membrane, but change in the chlorine conductance and 5)Diminished synthesis. Classes 1 to 3 are associated with a more severe disease (4).

Clinical Manifestations

Also called Mucoviscidosis, the Cystic Fibrosis is characterized by an abnormal mechanism of systemic ionic transport, which generates a diminished permeability to the chlorine (6), and causes recurrent pulmonary infections; chronic pulmonary obstructive disease; rhinosinusitis; nasosinusal polyposis; bad gastrointestinal absorption resulting from pancreatic dysfunction; spastic ileus of the newborn; retal prolapse and infertility for obstruction of the deferent ducts (5,7).

In the sweat glands epithelium, it leads to low absorption of chlorine and sodium of the glandular lumen, which results in sweating with a strong concentration of these (1,8).

In the respiratory epithelium, there is a failure in the chlorine secretion, which causes an excessive absorption of sodium, results in a higher water inflow to the cells and therefore increases the mucus viscosity (1,8). The mucus becomes from 30 to 60 times thicker than the normal. It does not affect the mucociliary beating directly, but it becomes inefficient in the clearance of such a viscous substance and generates stasis, that allows the ostia obstruction and increase of bacterial colonization (6,9,10,11).

The most frequent otorhinolaryngological manifestations are chronic rhinosinusitis and nasosinusal polyposis (2,4). The presence of the disease in the paranasal sinuses is observed in 100% of the patient (4,12). The symptoms include nasal obstruction, rhinorrhea, cough, headache, facial pain and post nasal drip (2,4,12) and these are rarely the first ones to be observed (13). (The pulmonary disease, with repetition infection is the 1st Cystic fibrosis manifestation in 40% of the patients) (14).

The age range of major occurrence of nasosinusal symptoms is from about 5 to 14 years (15), but the symptoms incidence is low even in this range. These are underestimated due to the priority of more severe manifestation of the disease, such as pulmonary and gastrointestinal infection, as well as the adaptation the patients present to the nasosinusal symptoms and the lack of knowledge as for such otorhinolaryngological manifestations interfere with the life quality and progression of the pulmonary picture (15).

The incidence of polyposis in patients with Cystic Fibrosis ranges in the literature from 6 to 67% (1), with peak between 4 and 12 years of age (8), is uncommon below 4 years and its appearing becomes rare again after 20 years of age (16). At the first otorhinolaryngological evaluation, 75% of the children with Cystic Fibrosis present with bilateral polyposis (17).

One of the hypothesis to explain the formation of the polyps is that the releasing of growth factors by the chronic infection leads to submucous tissue proliferation, edema and mucosa prolapse which is taken as nasal polyposis (9,18). There is also hyperplasia of caliciform cells, squamous cells metaplasia and loss of ciliated cells, which increase the mucus thickness and contributes for the chicken-and-egg situation (4,18).

Studies describe a histological difference between the polyps found in patients with Mucoviscidosis and those without this disease. The first ones have a fine basal membrane, do not present with submucous hyalinization, present with abundant acid mucine in the mucous glands and a predominance of neutrophils. The polyps of patients without Cystic Fibrosis have a thick basal membrane, eosinophilic infiltration and neutral mucine (2,4,19). Rowe-Jones et al did not find any statistically significant difference in the number of patients with polyposis and eosinophilia upon comparison of patients with and without Cystic Fibrosis, in spite of having found more eosinophils in the group without this disease and neutrophils in those with mucoviscidosis (18).

It's no surprise that patients with Cystic Fibrosis presented a stronger incidence of otitis media, since they have a thick mucus, difficulty in the mucociliary clearance and an increase of sinusitis frequency. However, such patients have a wide mastoid pneumatization, which indicates they have some episodes of otitis (20,21). Todd et al suggest the Eustachian tube of good conformity is bound to the Cystic Fibrosis gene, which enables a suitable aeration and draining of the middle ear (20).

Mucoceles are rarely found in adults and even less commonly in children. Before the diagnosis of mucocele, we must raise the hypothesis of a Cystic Fibrosis affected patient. Its manifestation occurs through painless orbital edema and may still present epiphora, diplopia and chemosis. Despite such signs and symptoms, the mucocele is generally asymptomatic, probably due to its slow and progressive growth (5).

Microbiology

The patients with Cystic Fibrosis are frequently infected. The most frequently found organisms are Pseudomonas aeruginosa, *Haemophilus influenzae, α-streptococci* and anaerobes. We also found *Staphilococcus aureus, Escherichia coli, Burkholderia cepacia, Acinetobacter sp* and *Stenotrophomonas maltophilia* (2). There is not much information of the bacteriology in younger children. Muhlebach et al. found a large number of *Staphilococcus* aureus as the cause of sinusitis in children with Cystic Fibrosis and *Pseudomonas* only in older patients.

Patients who were diagnosed with Cystic Fibrosis at adult age presented with lower frequency of colonization by *P. aeruginosa* than those diagnosed in the childhood. The germs mostly found in patients with late diagnosis are S. aureus followed of *Burkholderia cepacia,* as well as *Mycobacterium* and not *tuberculosis* (7).

Candida albicans is the most isolated fungus in patients with Cystic Fibrosis, with incidence from 60 to 75%, followed of *Aspergillus fumigatus*, from 6 to 57%, according to Wise et al. (2).

There is great controversy as for the agreement among microorganisms found in the upper and lower airways. Wise et al. believe 80% of the cases are the same microorganisms (2). However, for Muhlebach and col only the minority of patients have the same germs. They compared cultures of oropharynx and of broncoalveolar lavage in the identification of sinusal microbiote. There was no difference among the bacteria identification exams, but their sensitivity was very low (40 to 50%) (22).

Radiology

Radiologic changes are found very early in patients with Cystic Fibrosis, even in the asymptomatic ones (8). Approximately 90 to 100% of the patients older than eight months already confirmed the radiologic evidence of the disease (19). This is so important that the absence of such changes excludes the diagnosis of Mucoviscidosis (23).

Kennedy classifies the tomographic changes of chronic sinusitis in four stages: 1) Anatomic changes, disease in one unilateral sinus or bilateral disease limited to the ethmoid sinus; 2) Ethmoid bilateral disease with involvement of one more paranasal sinus; 3) Ethmoid bilateral disease with involvement of two or more sinuses on each side and 4) Diffuse polyposis. Krzesky et al found predominance of stages 3 and 4 in patients with Cystic Fibrosis. Such findings are compatible with those of other authors (3).

There are several tomographic changes commonly found in patients with Mucoviscidosis, and the triad described by Nishioka is composed by an extensive nasosinusal polyposis, frontal agenesis and medial convexity of the nose lateral wall (3,23).

The incidence of frontal agenesis in healthy patients

is of 5 to 9%, in a contrast with 63% of the patients with Cystic Fibrosis (3). The occurrence of agenesis and/or hypoplasy of other paranasal sinuses, such as maxillary and sphenoidal sinuses are also common in the Cystic Fibrosis (3), as well as the absence of agger nasi pneumatization, Haller cells, middle infundibulum etc. (23). This is probably explained by the infection that occurs since the first months of life in these patients, and results in changes of the development of these structures. For some reason still unknown, these patients' mastoid develops very well and they have a minor incidence of otitis media as mentioned above (24).

The nasal lateral wall medialization widely found in the Mucoviscidosis occurs due to the extensive polyposis and in some cases reaches the nasal septum. Such findings occur in a frequency from 60 to 80% of the cases, depending on the authors (3,9). Such change is generally associated with the uncinate process demineralization (13,24), caused by the pressure the polyps exert on the osseous structures, in addition to the chronic ostitis and periostitis. Other authors suggest this osteopeny results from the frequent sinusitis exacerbations (3).

The occurrence of hydroaereal levels in these patients is uncommon probably due to the disease's extension and the high mucus viscosity that occupies the face sinuses (9).

Diagnosis

The Cystic Fibrosis diagnosis is made in the presence of one or more of the aforesaid clinical manifestations, associated with the presence of two gene mutations of the Cystic Fibrosis or two positive results in the sweat test (4), (up to 30 mmol/L it's normal, from 30 to 60 mmol/L it's dubious and above 60 it's altered) (25,26), or change in the nasal potential difference (4).

According to the level of the mutation found in the patients there are several phenotypes of the disease (23,27). The classical one includes pancreatic and sweating glands dysfunction (exocrine dysfunction), respiratory tract disease and deferent ducts malformation. These patients normally have their diagnosis in the first six months of life (7). Some of the diagnosis criteria, such as the sweat test, may fail in certain patients, which makes their identification difficult and may be taken for granted in the childhood (7,27).

There is also the presence of patients carriers of Cystic Fibrosis transmembrane conductance gene mutation, who present with a higher proneness to the chronic sinusitis, recurrent pancreatitis or deferent duct obstruction without other features of the disease, which may confuse the diagnosis (25,27,28,29).

Treatment

The objective of the treatment is to reduce the patient's symptoms through the re-establishing of nasosinusal ventilation and draining (30), to control infections, eliminate the pulmonary infection reservoir and improve the patient's nutritional state (9,26).

Despite the use of medications or even surgery, the patients with Cystic Fibrosis are not cured (10,31). However, the patients without this disease present and index of rhinosinusitis spontaneous cure that may reach 64.8% (32). The treatment in the Mucoviscidosis is basically to improve the quality of life (30).

The nasal treatment consists of washing with saline solution, intranasal corticosteroids, antimicrobial therapy and functional endoscopic surgery of the paranasal sinuses (FESS) (26).

The saline solution is aimed at fluidifying the secretion and providing nasal hygiene. It may be used in isotonic or hypertonic irrigations with the advantage of decongesting the nose (4).

The nasal topic corticosteroids' function is to diminish the polyposis, which helps improve the symptoms. The oral corticosteroids must not be used due to the increased number of collateral effects (4).

The antibiotics are the most important medications in the Cystic Fibrosis treatment. They must cover *Pseudomonas, Staphylococcus*, as well as the anaerobe germs (4,22). The mostly used are the aminosidine and quinolone antibiotics, despite these are not released for children by the FDA. Other antibiotics used are piperacillin, ceftazidime and imipenem (4).

Studies confirm the use of macrolides, such as azithromycin, in small dosages, and for a long period it has an immunomodulatory effect that diminishes IL-8 and the size of the polyps, without reaching the sufficient plasmatic concentration to be bactericide (4,15).

The Dornase α, a human recombining deoxyribonuclease, is a new drug that acts by destroying the DNAs released by leucocytes during inflammation. Such released DNAs increase the mucus viscosity and diminish the mucociliary clearance. Patients treated with Dornase α have an improvement in the mucous edema, a smaller polyps recurrence and a lesser need for new

surgery (4,6). Such drug may be a helpful tool for improvement of the symptoms and the extension of the surgical effects (6,30).

When all these measures fail to control the sinusitis, surgery should be considered (4). About 15 to 20% of the patients will need FESS (1,31).

The surgical indications consist of nasal obstruction, rhinorrhea, cough, facial pain, headache, mucocele and pulmonary function deterioration, as opposite to the medication treatment (1,6,31).

The FESS does not change the facial growth, as shown by SENIOR et al and BOTHWELL et al, and is very safe, with a complication index lower than 1% (32).

The surgery range from a simple polypectomy and a pansinusectomy (4). This is preferred by some due to the high level of infection of patients with Cystic Fibrosis and as an attempt to offer more time free from disease. Those who indicate polypectomy choose it due to less surgical time (33).

It's known the patients with Mucoviscidosis present with a higher surgical risk because of their advanced pulmonary disorder, extensive sinusal disease, anatomic changes caused by prior surgeries, coagulopathy for vitamin K deficiency, pancreatic and hepatic diseases, as well as nutritional deficiency (1,4).

However, SCHULTE et al did not present higher rates of complications and showed the general anesthesia, during more than one hour, was safe in all 42 cases studied (31).

The main surgical complication is epistaxis, which may occur due to the level of nasal polyposis, use of medications by the patient and vitamin K deficiency that ranges in frequency from 6 to 55% of the patients with Cystic Fibrosis. Some authors suggest this vitamin replacement prior to the surgery. There is controversy as for the use of nasal splint after sinusectomy. Some use it in the routine (1).

Another significant complication is the orbitary one, with violation of the papyraceous lamina. Patients with Cystic Fibrosis present with a higher risk of lesion (12.2%), when compared to the normal population, due to anatomic abnormalities (1,4). They run an even higher risk of liquoric fistula (4).

Faced with the highest surgical risk, some indicate previous hospital internment for intravenous antibiotic therapy and respiratory physiotherapy (17,31).

The postoperative cares are large nasal washings, use of antibiotics, periodical debridement of crusts and topic corticosteroid (4,8,33).

In spite of rigorous treatment, the recurrence is a rule (2,6), and the average of free time from symptoms ranges from 1 to 4 years (13,31,33)

WEBER et al made a study on the eosinophilic cationic protein as a marker of nasal inflammation in patients with Cystic Fibrosis. They observed patients with extensive polyposis and those with more recurrences presented with higher levels of such protein. It may be used in the future as a marker of the Cystic Fibrosis activity and then guide the therapy for this disease (34).

Prognosis

The Cystic Fibrosis is a lethal disease, whose life expectation is of approximately 40 years (4). Before the advent of antibiotic therapy, death occurred in the childhood, due to severe pulmonary infections that led to bronchiectasy and respiratory failure within a short period of time (33).

The life expectation ranges according to the patient's sex and age of diagnosis. We observed that women live an average of 3 to 5 years less than men and patients who were diagnosed older than 36 months have a reduction in the mortality risk of 50% when compared to those diagnosed before the 6 months of age. This occurs probably for it's a lighter mutation, does not present all the stigmas of the disease and the patient may achieve the age of 60 years (7).

The main cause of death is still the respiratory complication (7,14,22) or cor pulmonale (31).

DISCUSSION

The genetic changes found in the Cystic Fibrosis are well established and the authors agree the mostly found mutation is the deletion of three pairs of bases that decode the phenylalanine in the position of 508 of chromosome 7 (4,5). Such mutation changes the systemic ionic transport with a consequent increase of the mucus viscosity and several clinical manifestations, such as, chronic airways infections; changes in the gastrointestinal tract and infertility (2,5,7).

According to RAYNOR and col, EGGSBØ and col, MADONNA and col and MCSHANE and col, there is no change to the mucociliary beating, and the mucus is very thick, about 30 to 60 times the normal, and is responsible for the inefficient clearance and increase of infections (6,9,10,11).

Most authors reviewed found symptoms of nasal obstruction, rhinorrhea, cough, headache, facial pain and post nasal drip as the main otorhinolaryngological symptoms of the Mucoviscidosis, compatible with their picture of chronic rhinosinusitis and nasal polyposis (2,4,12). Despite their high frequency, the nasosinusal manifestations are the first ones in the diagnosis. Damas et al note in their study that in 40% of the patients the first manifestation is a recurrent pulmonary infection (13,14). The age range of more symptoms occurrence was from 5 to 14 years, like the polyposis peak of incidence (8,15).

For Wise et al, Tandon et al and Sobol et al, there's histopathological difference found in carriers of Cystic Fibrosis and other nasal polyps. However, Rowe-Jones et al didn't find statistically significant difference (2,4,18,19).

The patients with Mucoviscidosis are chronically infected by *Pseudomonas* and *Staphylococcus*, the germs mostly found in adults and children, respectively. It's still unknown whether the microorganisms found in the upper airway are the same as in the lower. Wise et al found in their study 80% of concordance among these germs, as Muhleback and col believe in an individual flora (2,22).

Faced with Cystic Fibrosis suspicion, a negative radiologic exam excludes the diagnosis due to the high index of changes found in these patients, even in the childhood (8,23).

The treatment is aimed at improving the patients life quality since the cure is not possible (30). In cases opposite to clinical treatment, FESS is used, for it's very safe, as shown by Schulte et al, Senior et al and Bothwell et al, even in these patients with Mucoviscidosis who present with more surgical risks (31,32).

In spite of suitable treatment, the recurrence is a rule (2,6) and patients evolve to death mainly for respiratory complication according to most authors (7,14,22) or cor pulmonale, according to Schulte et al (31).

Final Considerations

Despite they are not the main cause of death in the Cystic Fibrosis patients, the otorhinolaryngological manifestations of this disease bring them significant morbidity. With the advent of antibiotic therapy and the improvement of surgical techniques, there has been an increase in the life expectation, but with poor quality of life due to the intense symptomatology. We hope, with new drugs, with Dornase α and the appearing of other ones, we may promote the improvement in the conditions of the life of these patients.

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