ORAL MANIFESTATIONS IN PATIENTS WITH CYSTIC FIBROSIS

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ABSTRACT: Objective: The purpose of this paper is to review literature data related to oral manifestations in patients with cystic fibrosis and to emphasize the importance of prevention and early identification, as much as possible, of these manifestations in order to increase the patients' quality of life. Materials and method: Articles published in international indexed databases were evaluated, mostly from PubMed, using the following search terms: cystic fibrosis, oral manifestations, dental, periodontal, enamel, caries, in combination with several synonyms such as teeth, oral cavity, oral mucosa, periodontitis, carious lesions. Results: Patients with cystic fibrosis have numerous modifications in the composition and proprieties of saliva which lower resistance to microorganisms. Studies showed higher prevalence of enamel disorders in permanent dentition, and enamel hypoplasia was the most frequent defect. On the other hand, data regarding carious lesions showed a lower risk of occurrence at patients with cystic fibrosis compared to control group. Conclusions: Stomatologists should be part of cystic fibrosis multidisciplinary team, as the oral modifications are frequent at the patients diagnosed with this disorder.

Keywords: cystic fibrosis, oral manifestations, dental caries, enamel defects, periodontal disorders

INTRODUCTION

Cystic fibrosis (CF) is a multisystem autosomal recessive genetic disease, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene localized on the long arm of chromosome 7. CF affects 1 in 2500 individuals in Europe and 1 in 25 European individuals is a healthy carrier of a CTFR gene mutation. CFTR is a protein which functions as a transmembrane cAMP-activated chloride channel and transports ions across the apical membrane of epithelial cells. (1, 2)

CTFR mutations lead to a defective electrolyte transport in epithelial cells resulting viscous secretions which predispose to microbial proliferation and infections. This disorder involves mainly the lungs and the pancreas, but also salivary glands, gut, kidney, cervix, uterus. CTFR can be also expressed in non-epithelial tissues, such as ventricular cardiomyocytes and aortic smooth muscle cells, neurons, corneal cells, endothelial cells, lymphocytes, but this situation is rare. (1, 3)

In addition to the typical symptoms of this condition, there are oral manifestations that can occur, such as dental caries, mineralization defects, periodontal disorders, gingivitis and changes in the biochemical and biophysical proprieties of saliva. (1, 4) The oral manifestations in cystic fibrosis have been studied since 1960 by Zegarelli who studied tooth discoloration due to tetracycline. (5)

One particularity of this disease is the high phenotypic variability. There are several factors that influence the phenotype of patients with cystic fibrosis, such as the variety of mutations (over 2000), the gene modifiers, the treatment and patients' adherence to therapy and numerous environmental factors. (1, 4) Oral cavity manifestations can also be determined by comorbidities, such as diabetes and osteoporosis which are risk factors for periodontal disorders, or by

gastroesophageal reflux, which promotes dental erosions and caries. (6, 7, 8, 9)

MATERIAL AND METHODS

This paper is a review of literature. Articles published in international indexed databases were evaluated, mostly from PubMed, using the following search terms: cystic fibrosis, oral manifestations, dental, periodontal, enamel, caries, in combination with several synonyms such as teeth, oral cavity, oral mucosa, periodontitis, carious lesions. Articles included in this review were full-text available online and available in English. We also had searched the bibliography from the included published articles in order to identify potentially relevant articles.

RESULTS AND DISCUSSIONS

SALIVA MODIFICATIONS

Patients with cystic fibrosis have an increased risk of developing oral disorders. These manifestations are explained by the involvement of exocrine glands, cariogenic, carbohydrate-rich diet, use of sweetened drugs, food supplements and antibiotics. (10) CF patients have numerous modifications in the composition and proprieties of saliva caused by the affected exocrine glands and also by the adverse effects of the medication. The primary secretion in glandular acinus is characterized by an ion concentration similar to that found on plasma. After the primary secretion, along the ductus, there are absorption and secretion processes which will determine the final saliva composition, characterized by reduced levels of sodium and chloride and increased levels of bicarbonate and potassium. (11)

As far as CF patients are concerned, their saliva has higher concentrations of chloride, sodium and potassium, as a result of CTFR disfunction. (11, 12, 13) In addition, saliva contains insoluble calcium-protein complexes as a consequence of increased levels of calcium and proteins, interfering with local enzymatic activity. (10, 14) The study conducted by Modesto et al showed that CF patients have a significant diminished salivary flow rate ($p \leq 0.05$), pH, sialic acid and salivary amylase and peroxidase activities. (10, 11) The sialic acid is part of glycoproteins and forms a protective layer on the surface of the oral mucosa, preventing dryness and penetration of microorganisms. Modesto et al explained the decrease of sialic acid level by the fact that the patients use mucolytics. Mucolytics have the role to clear the mucus, but also, they impair glycoprotein formation. (12) A slow salivary flow rate and an acidic pH contribute to a lower microbial resistance, being a favorable environment for the development of caries and periodontal disorders. (15, 16) Furthermore, reduced flow rate of saliva can lead to inflammation, modified taste perception, eating difficulties, predisposition to fungal infections, and biofilm stagnation with vicious oral cleansing. (17) However, literature data is inconclusive as far as the pH and the flow rate of the saliva are concerned. There are studies that have not found modifications of flow rate, while others have found increased pH or no difference between CF patients and the control group. (18, 19)

Another mechanism, which in physiological conditions prevents the microbial penetration, consists on secretory immunoglobulins, such as sIgA, decreased in saliva of CF patient, and IgA, IgM, IgG, IgE, increased at these patients. SIgA plays an important antimicrobial role and its decrease can be clinically objectified by the occurrence of oral infections and inflammation. Nazaryan et al have proven that sIgA level is decreased at CF patients and they supposed that the sIgA deficiency is due to the action of bacterial hydrolases. Furthermore, the lysozyme activity is decreased, additionally altering the barrier function of the oral mucosa. The reduction in local resistance is emphasized by the degree of oral dysbiosis. Nazaryan et al found in their study that dysbiosis is 3.7

times higher in CF group in comparison with the control group. (4)

These observations are of particular importance, as the CF patients are at risk of lung infections, frequently serious, with drug resistance. The relationship between oral dysbiosis and lung infections or colonization are often ignored, but taking into account the patients' susceptibility to respiratory infections, it may be useful to prevent oral infections or chronic inflammation. Oral cavity is considered a reservoir of commensal and pathogenic microorganism and the development of the latter is favored by the presence of deep carious lesions, chronic pulpitis, necrotic teeth, periodontal infections. The microorganisms found in saliva of CF patients was also found in their sputum, mainly due to micro-aspirations. (20) Caldas et al suggested that oral cavity is a reservoir of Pseudomonas aeruginosa for subsequent respiratory infections or colonization with the same microorganism, based on their findings that the same bacterial clonal type was found in saliva and also in sputum. (17, 21)

ENAMEL DEFECTS

Researchers showed that enamel defects in permanent dentition appear at least at an equal percentage or even higher when compared with healthy controls. Furthermore, the enamel defects seem to be more severe in CF patients. (22) Tooth enamel is the hardest, the most mineralized tissue and one of the most architecturally complex biological tissues. It forms a protective layer and its alterations during development are irreversible. Dental enamel is influenced by environmental factors, but also by the CTFR defect which interferes with transepithelial ion transport in amelogenesis. Ameloblasts formation and development are influenced by temperature variability, hypocalcemia, bicarbonate level, pH modifications, traumatic or infectious events, toxic and nutritional factors. (23, 25)

Data from the literature suggest that in the past CF patients experienced more often enamel hypoplasia and teeth discoloration as a result of the use of tetracycline for treating pulmonary infections. (25) Nowadays, tetracycline is rarely used, as there are available other antibiotics.

Azevedo et al aimed to assess in their study the presence of developmental defects of enamel in CF patients. The researchers concluded that demarcated opacities were the most frequent enamel defects appeared in deciduous teeth and even if they were more prevalent in the case group compared to control group, the difference was not significant statistically. As far as the permanent teeth are concerned, the most frequent enamel defect was also demarcated opacities (39% compared to 11%). However, the enamel defects in permanent dentition were significant statistically more prevalent in the case group compared to control group ($P = 0.0003$). (26) Similar results were obtained by Ferazzano et al in their study, which aim was to asses enamel defects in deciduous and permanent teeth. Researchers concluded that in the case group, hypoplasia with loss of enamel was the most prevalent defect in permanent dentition and it was significant statistically compared to results from the control group (23% vs 1.5%). On the other hand, as far as deciduous dentition is concerned, there was not found differences between the two groups. (27) Tuggle et al showed in their study that rats with CF had some enamel modifications, such as discoloration and altered abrasion of incisors, but also malformed upper and lower incisors. (28)

As a summary, literature data show no statistically significant difference in enamel defects in primary dentition between patients with CF and healthy people, while, as far as permanent dentition is concerned, enamel defects are more prevalent in cystic fibrosis population. (22) The enamel defects can represent a compromised aesthetic for CF patients and

they induce tooth sensibility, interfering with patients' quality of life. Decreased enamel hardness and increased porosity represent the foundation of future dental caries, as a consequence of facilitating penetration of cariogenic microorganisms. (29, 30, 31)

DENTAL CARIES

After tooth eruption, there are several factors that influence the development of carious lesions. A particularity of CF patients consists on their diet, as they have to increase the calories and carbohydrates intake, to eat frequently snacks between meals and also, they need to use sweetened drugs. Cariogenic microorganisms, such as Streptococcus mutans and Lactobacillus acidophilus, use carbohydrates in order to develop dental caries. (12, 22, 32) Catalan et al showed in their study that carious lesions developed in rats with cystic fibrosis after only 5 weeks of exposure at cariogenic diet. (33) Taking into account all risk factors, it has been hypothesised that CF patients are at high risk of developing carious lesions. However, studies on this topic showed that CF patients have, surprisingly, a lower risk comparing with their healthy peers. (29) Chi et al conducted a systematic review and concluded that children with CF are at lower risk for carious lesions and adolescents with CF present the same risk as their healthy peers. (34) Another recent systematic review had similar results, there is no evidence that CF patients experience more dental caries compared to healthy people. (22)

There are several explanations for the lower or equal risk of carious lesions in CF patients. Aps et al studied oral hygiene of CF patients objectified by measuring plaque, calculus, and gingival bleeding. They observed a satisfactorily dental care among these patients. (35) Similar results obtained Peker et al and Martens et al in their studies. Other hypothesis put forward consists on the effects that antibiotics have on oral bacteria, offering protection against carious lesions. (18, 36) In addition, CF patients need pancreatic enzyme intake and there is evidence that this therapy decreases the plaque formation, and consequently dental caries. (29)

PERIODONTAL DISORDERS

Periodontal disorders consist on inflammatory conditions which involve the periodontium. Periodontium is a term that defines the supportive tissues surrounding the teeth, which includes the gingival tissue, alveolar bone, cementum, and periodontal ligament. (37) Initially, the first stage of this disorder consists on gingivitis. Untreated inflammation progresses to the supporting tissues and causes periodontitis, and finally will determine teeth loss. (38) At CF patients, who experience multiple respiratory infections, due to the fact that they use frequently oral respiration, malocclusion and misalignment of teeth can appear. These defects promote periodontitis. (29, 39)

As far as periodontal disorders are concerned, the findings are inconclusive as the publications have contradictory results. The studies assessed dental plaque, dental calculus and gingival bleedings. Dental plaque seems to be similar in both control and case groups. (40, 41) Only one study showed a higher incidence of gingivitis at CF patients, while others found no differences between CF patients and their healthy peers or found even a lower rate of gingivitis. (42, 43, 44, 45)

Regarding dental calculus, researchers did not observe differences between case groups and control ones. The mineralized dental deposits do not seem to be influenced by modifications specific for cystic fibrosis and they do not appear more frequently. (35, 45)

Cystic fibrosis-related diabetes is one of the most important extrapulmonary complication of cystic fibrosis, with a high prevalence. Data suggest that it appears at 2% of children, 19% of adolescents, and up to 50% of individuals 30 years of age and older. This multifactorial condition is

associated with more severe lung disease and increased mortality. It is the result of vicious glucose metabolism, objectified by insulin deficiency and insulin resistance. (46) Researchers have found in their studies that diabetic persons are more predispose to periodontal disorders compared to nondiabetic ones. (47)

The life expectancy of CF patients has improved in the last decades and the quality of life should be the on multidisciplinary team focus. According to the 2019 Cystic Fibrosis Foundation Patient Registry data, the life expectancy of children born between 2015 and 2019 is anticipated to be 46 years and data predict that 50 percent of children will reach the age of 46 years old. (1, 3)

Even if oral health is not yet a central point of the multidisciplinary CF team, dental check-ups should be done as soon as possible after the diagnosis, in order to prevent dental caries or enamel disorders and to improve the patients' quality of life. Pain decreases dramatically the quality of life, 59.8% of subjects included in a research studying the pain at CF patients claimed that pain is the main cause of distress. (3) Another important aspect consists on improving communication between health care professionals and patients and their parents, offering clear information, as they should know the complications that can occur during the evolution of the disease and how they can prevent it. According to the American Academy of Paediatric Dentistry (AAPD) and to the American Dental Association (ADA), the first visit to the dentist should be done when the first tooth erupted or before 1 year of age, and after this, at least at every 6 months. (16, 48, 49)

CONCLUSIONS

Studies analyzed emphasize a higher prevalence and severity of enamel disorders in permanent dentition of CF patients, while carious lesions seem to be less frequent, compared to healthy controls. Oral cavity should be considered a reservoir with different commensal or pathogenic microorganisms capable to colonize or infect the lungs through micro-aspirations. Oral health is extremely important at these patients who are predisposed to infections with multi drug resistance microorganisms.

In the past decades, CF patients had a short life expectancy and oral health was not a focus of the medical team. However, nowadays, as the diagnostic tools and the therapies have advanced, life expectancy is improved and one of the central purposes consists on a better quality of life. In order to obtain this desideratum, it is important to prevent dental and periodontal disorders. Dentists should be part of the cystic fibrosis multidisciplinary team, in the center of which is always the patient.

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