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Research article

Oral health in individuals with cystic fibrosis: A cross-sectional study

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A B S T R A C T

Cystic Fibrosis (CF) is an autosomal recessive disease characterized by the production of thick and viscous mucus progressively affecting various organs and systems, with recurrent respiratory infections. The aim of this study was to learn about the oral health characteristics in CF patients. Methodology: Data, such as sociodemographic, general and oral health, were collected from the medical records of CF patients aged 0 to 18 years old. The number of patients with tooth decay, prevalence of developmental defects of enamel (DDE), classification of dental occlusion, sialometry, salivary pH and oral microbial profile and respiratory secretions evaluations were recorded. Results: Most patients had pancreatic insufficiency (84.2%), malnutrition (60%), respiratory problems (75.4%) and genotyping of the F508del (66.7%). Regarding the medications used, 96.5% used vitamins and electrolyte replacement, 84,02% used pancreatic enzymes, 64.9% used dornase alfa and 47% were using antibiotics. The percentage of patients with tooth decay was 19.3%, 47% had DDE, low salivary flow and basic salivary pH. The most prevalent microorganisms found on tongue biofilm and respiratory secretions were *SA* and PA. There was a positive association between the presence of bacteria and fungi found on both the tongue and respiratory secretions. The presence of fungi on the tongue biofilm was significantly associated with the use of antibiotics. Conclusions: These findings underscore the importance of dentists focusing on prevention and on the specific needs of the patient as well.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease mainly caused by the presence of two variants of the gene that produces the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which regulates the transport of sodium-chloride and bicarbonate across epithelial membranes [1]. Consequently, alterations in the transport of such ions across cell membranes make it difficult to eliminate mucus, which is thick and viscous, in addition to sweat and pancreatic enzymes by the exocrine glands and lining tissues [1]. Among rare diseases, it is considered the most common, reaching 1:2,500 live births, with a higher incidence in white people [2]. Although the worldwide incidence has been more precisely determined after the implementation of neonatal screening tests, it may still be underreported in South American countries [2], such as Brazil, reaching 1:8,400 to 1:10,000 live births [3,4]. Despite the severity of the disease, patient survival has been increased due to the care provided by multidisciplinary teams in reference centers [2]. Still, the use of antibiotics is frequent in order to reduce the occurrence of pulmonary infections, as well as the use of pancreatic enzymes during meals along with the prescription of a hypercaloric diet, are part of the treatment.

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The lung is one of the most affected organs [1]. Due to the thickening of the mucus produced by the ciliary cells, there is often colonization of the respiratory tree by *Pseudomonas aeruginosa (PA)*, associated with a high rate of morbidity and mortality [5]. Colonization initially occurs in the nose, paranasal sinuses and mouth and later in the lung; and after becoming chronic, its eradication is quite difficult [6]. Therefore, studies have shown that the mouth and the nose can be reservoirs of respiratory pathogens in CF patients, favoring transmission to the lower airways [7]. The eradication of such microorganisms from the upper airways and mouth can prevent pulmonary infection [7]. Considering that the colonization of the mouth by pathogens associated with respiratory infections [8] is a risk factor for respiratory diseases in CF patients, oral health care can prevent such occurrence.

In this context, knowledge of changes in oral health and the dental treatment given to patients have played an important role as they increase understanding about the disease and integrate adequate treatment, which significantly improves quality of life [9]. In addition, studies have shown contradictory results regarding the impairment of oral health in CF patients, such as caries, periodontal disease and changes in both salivary and dental enamel formation [10]. Given the above, the aim of this study was to learn about the oral health characteristics in CF patients.

2. Methodology

2.1. Study design, place and period

This is a cross-sectional study carried out at the Pediatric Reference Center for CF at Brasilia's José Alencar Children Hospital (HCB, in Portuguese) between 2018 and 2021. The study was approved by the Research Ethics Committee involving Human Beings at HCB.

2.2. Data collection

Data were collected from the medical records of patients aged 0 to 18 years old diagnosed with CF according to the Brazilian Guidelines for the Diagnosis and Treatment of CF [11] in outpatient follow-up at HCB.

2.3. Participants

All patients with a confirmed diagnosis of the disease, who wanted to participate in the study, were included in the research, and patients with another associated limiting disease were excluded. Informed consent was obtained from all patients who participated in the research.

2.4. Data collected

Sociodemographic and general health data, such as prematurity at birth, comorbidities, CF complications, namely the use of a nasogastric tube or gastrostomy, pancreatic insufficiency, nutritional profile, hypovitaminosis D, respiratory symptoms, in addition to the genetic profile and medications for continuous use, were collected. Regarding oral health, data were collected from routine dental examinations performed on all patients under follow-up at the time, aiming at identifying microbiological evaluation of the tongue biofilm and respiratory secretions, developmental defects of enamel (DDE), pattern of dental occlusion, sialometry and salivary pH, in addition to presence of caries. The DMF-t or dmf-t index distribution was calculated as a function of deciduous and permanent teeth to identify the most affected teeth by caries. The physical examination was performed on a dental chair, under adequate lighting and all biosafety norms, after dental prophylaxis. Mouth mirror and the *"ball point"* probe were used.

The number of teeth with caries should be divided according to the DMF-t index – number of teeth with caries, number of teeth missing due to caries, and number of teeth with fillings due to caries. DDEs are changes resulting from disturbances in the amelogenesis process and can be classified as qualitative (diffuse or demarcated opacities) and/or quantitative (hypoplasia). The assessment of the presence of DDE was verified by oral clinical examination and no index was used.

Data related to occlusion classification and sialometry and pH measurement were only available for patients aged 7 years or older. In order to measure saliva volume, the patient chewed the mechanical sialagogue for one minute. Then, he spat out all the saliva produced into a disposable cup. This saliva was aspirated using a 5 ml disposable millimeter syringe and we were able to visual verify the total volume. From then on, the salivary flow in mL/min was established. A volume <1.0 mL indicated low flow and >1.0 mL a normal quantity of stimulated saliva.

For pH assessment, the patient discarded about 1 mL of saliva into a disposable plastic container and was transferred directly to a pHmeter previously calibrated. All patients underwent microbiological evaluation of the tongue biofilm (through the collection of the tongue coating with a swab) and respiratory secretions (through the collection of tongue coating with a swab) in order to identify the most prevalent bacteria and fungi in CF cases. The collection of respiratory secretion and lingual biofilm was carried out by interexaminer agreement, always following the same routine in care.

At the study site, patients are seen every 3 months in a multidisciplinary consultation and at the time of care, the patient's routine was not changed for salivary analysis, that is, the patient ate normally before the consultation, took his morning medications and supplemental medications were provided. Routine medications for patients diagnosed with fibrosis are prescribed in accordance with international protocols. The patients were in good general condition at the time of collection.

Microbiological culture was performed to identify common microorganisms in the respiratory tree, such as *PA, Staphylococcus aureus (SA)*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, mycobacteria, *Achromobacter xylosoxidans*, *Serratia marcescens*, *Rothia mucilaginosa*.

Table 1
Sociodemographic and general health data of patients with CF treated at HCB. Data presented as absolute numbers and percentages.

		n	%
Gender	feminine	25	43,9
	masculine	32	56,1
Age	0 to 6 months		
	7 months-6 years		
	7 at 18 years		
Prematurity		6	11,3
Pancreatic sufficiency	Pancreatic sufficiency	9	15,8
	Pancreatic insufficiency	48	84,2
Nutritional classification	malnutrition	33	60,0
	good	20	35
	Overweight/obesity	3	5,5
	No data	1	
Hypovitaminosis D		26	45,6
Diabetes		8	14,3
Respiratory symptoms		43	75,4
Gastrostomy/nasogastric tube		10	17,9
Genetic sequencing	F508del	38	66,7
	Outros	19	33,3
Total		57	100

In order to collect tongue biofilm, the dorsum of the tongue was scraped with a wooden spatula and a swab was rubbed over the obtained material. In order to collect respiratory secretions, a swab was rubbed in the oropharynx or on sputum material in patients able to expectorate. The swabs were immersed into Stuart medium and transported up to 1 hour after collection to the laboratory, which processed the samples for the characterization of bacteria and fungi. For the culture and identification of bacteria, the material was sown on non-selective media (chocolate agar and blood agar) for broad-range bacterial growth and selective media (MacConkey agar) for specific microorganisms growth. These media allowed growth for gram positive and gram-negative bacteria, fungi and yeast. For bacteria the media were kept in an oven at 37°C and for yeasts and filamentous fungi at 30°C for up to 72 hours. Identification and antibiogram were performed by automation with the Vitek System (bioMérieux Vitek Inc., St. Louis, MO).

2.5. Risk of bias

Use of a convenience sample from a reference service. In addition, sialometry and pH measurement were carried out at different times, and without standardization of oral hygiene foods due to the logistics of the outpatient clinic, as noted in the medical record.

2.6. Sample size

Considering that this is not a hypothesis test, a convenience sample was used, consisting of the patients medical records who attended the HCB outpatient clinic during the research development period.

2.7. Statistical analysis

Data were presented according to descriptive statistics and association analysis. Data analyzes were performed using the IBM SPSS program (*Statistical Package for the Social Sciences*) 23, 2015. The results are presented by means of frequency (n) and percentage (%). Association analyses were performed using Pearson's chi-squared test. Quantitative variables were initially evaluated regarding their distribution using the Kolmogorov Smirnov test. For quantitative variables, the null hypothesis of normality was rejected, therefore using non-parametric tests.

2.8. Results

Initially, 58 medical records of patients seen between October 2019 and September 2021 were examined. One was excluded due to the patient having severe autism and not allowing the dental examination. Thus, a total of 57 records were included. The patients' sociodemographic and general health data are described in Table 1. The patients came from the Federal District, Brazil. Malnutrition, respiratory problems and pancreatic insufficiency were the health problems presented by most patients.

Of the total of 1228 teeth evaluated, among the patients aged 6 months or more, the number of caries disease was 31. 25 patients had primary dentition and 32 had mixed or permanent dentition. The number of teeth with caries should be divided according to the DMF-t index – number of teeth with caries: 27, number of teeth with missing due to caries: 4, and number of teeth with feelings due to caries: 9.

Table 2
Characteristics of oral health indicators of patients with CF treated at HCB. Data presented as median or absolute Number and percentage.

		n	%
DMF-t /dmf-t	Teeth with caries	27	2,2
	Teeth with missing due to caries	4	0,32
	Teeth with feelings due to caries	9	0,73
	Teeth without caries	1197	97,4
Saliva flow	Low (<1 mL/min)	22	53,7
	Normal (>1 mL/min)	19	46,3
	Not measured	16	
pH	Basic (ph >7,0)	31	75,6
	Neutral (ph = 7,0)	10	24,4
	Not measured	16	
Enamel defects	HMI*/HSPM**	22	81,5
	Fluorosis	4	14,8
	Hypoplasia	1	3,7
	Not measured	30	
Occlusion	Class 1	28	68,3
	Class 2	1	2,4
	Class 3	12	29,3
	Not applicable	16	
Total		57	100,0

*Molar-incisor hypomineralization ** Deciduous second molar hypomineralization.

Table 3
Association between the presence of fungi in respiratory secretions (SR) and in the tongue biofilm (TB) of patients with CF treated at HCB.

			SR fungi		Total	*P**	RC	I.C.95%
			No	Yes				
TB fungi	No	n	35	2	37	0,01	9,4	1,7 - 51,4
		%	72,9	22,2	64,9			
	Yes	n	13	7	20			
		%	27,1	77,8	35,1			
Total	n	36	5	41				
		%	100,0	100,0	100,0			

*Pearson's chi-squared test.

Table 4
Association between the presence of bacteria in respiratory secretions (SR) and in the tongue biofilm (TB) of patients with CF treated at HCB.

			SR bacteria		Total	*P**	RC	I.C.95%
			No	Yes				
TB bacteria	No	n	11	19	30	0,02	7,2	1,4 - 36,6
		%	84,6	43,2	52,6			
	Sim	n	2	25	27			
		%	15,4	56,8	47,4			
Total		n	9	32	41			
		%	100,0	100,0	100,0			

* Pearson's chi-squared test.

About 47% of the patients had some type of development defects of enamel. Most had class I occlusion, low salivary flow and basic salivary pH (Table 2).

The work shows the prevalence of patients colonized by the microorganisms identified in the tongue biofilm (TB) and respiratory secretion (RS). The most

prevalent microorganisms found in both sites (tongue and oropharynx) were *SA* and *PA*.

Table 3 shows the significant association between the presence of fungi in the RS and TB. Patients with the presence of fungus in respiratory secretions were 9.4 times more likely to have fungus in the TB compared to patients without this microorganism.

Table 4 shows the significant association between the presence of bacteria in the RS and the TB. Patients with the presence of bacteria in the oropharynx were 7.2 times more likely to have bacteria in the TB compared to patients without these microorganisms.

It is observed that the presence of fungi in the LB was significantly associated with the use of antibiotics. Patients who used antibiotics were 6.3 times more likely to have fungus in the TB.

3. Discussion

Our study showed low prevalence of caries in CF patients assisted at HCB according to the DMFT index. However, patients are monitored by the dentistry service and this factor may contribute to the reduced rate. Some studies indicate a stable oral biofilm ecology for patients diagnosed with CF, associated with pharmacologically conditions [12].

In fact, although there is controversy in the literature, there are several studies that have shown a lower frequency of caries among CF patients when compared to healthy patients [13,14].

Despite the adopted diet being rich in carbohydrates and fats [13], the frequent use of penicillin due to respiratory tract infections may be one of the explanations for the reduction of gram-positive cocci involved in acidogenesis from fermentation of cariogenic foods [15].

Pawlaczyk-Kamieńska et al. (2019), showed that CF patients, in comparison with the healthy people, had a significantly higher value of the DMF-S index, a higher number of tooth surfaces with active caries, and a higher number of teeth extracted due to caries [16].

In addition, the salivary composition deserves special attention, since there is an increase in the concentration of chlorine, sodium and potassium ions [13,17], which could, in theory, reduce the bacterial proliferation. In our study, half of the patients, in whom it was possible to perform sialometry, had reduced salivary flow and most had basic salivary pH. Despite the limitations, our data are in line with the results of studies that also showed a reduction in salivary flow in CF patients [17,18] and neutral to basic salivary pH [18]. DDE were found in almost half of dentate patients; and of this total, 38% were cases of molar-incisor hypomineralization, about 2.7 times higher than the global prevalence [19]. Studies have shown a higher prevalence of DDE in CF patients when compared to patients without the disease[20–22]. There are several hypotheses that try to explain this finding; as possible drug interference [21]. Studies carried out in animal models showed that ameloblasts are sensitive to ionic changes resulting from the defect related to the CFTR gene, causing damage to the enamel [23,24].

Regarding the microbiological profile, non-oral bacteria and fungi present in CF patients were screened in two different sites: the tongue and respiratory secretions. In our study, the most prevalent bacteria identified in the oral environment were *PA* and *SA*, in addition to the fungus *CA*. It is known that these bacteria are not common in the oral cavity, so they are considered transitory and may remain in the mouth for a longer or shorter time, depending on the conditions of the host [25], in addition to having a high pathogenic potential. *SA* is the most prevalent microorganism in CF children with infection in up to 80% of patients in this age group. Major virulence factors include toxins associated with necrotizing lung infections. Furthermore, small colony variants may contribute to increased antimicrobial resistance and accelerate lung disease. Although the pathogenicity of methicillin-sensitive (MSSA) has been questioned, co-infection with other pathogens, such as *PA*, may be associated with worse clinical outcomes, including more severe lung disease. MRSA infection tends to occur more commonly in young adults than in children and has been associated with accelerated decline in lung function, increased hospitalization, and early mortality.

PA, on the other hand, has several virulence factors associated with host infection, including flagella that make it a mobile organism, as well as structures that facilitate attachment to epithelial cells of the respiratory tract. *PA* is resistant to some beta-lactam antibiotics and can acquire antimicrobial resistance through chromosomal mutation or horizontal gene transfer. Chronic infection has been associated with progressive decline in lung function and early mortality [26].

In addition, an association between the presence of bacteria and fungi in the mouth and respiratory secretions was found, which suggests the pattern of colonization of the upper airways and mouth as a function of anatomical proximity. The presence of fungus on the tongue was significantly associated with the use of antibiotics, a fact that can be explained by the dysbiosis caused by the drug [27].

Currently, there are at least 2000 identified variants of the CFTR gene, although not all of them are associated with the clinical picture of CF. The mutations fall into different classes (I to VI), with the most common in the Caucasian population being class II F508del. The F508del variant is the most frequent among Brazilian individuals with CF, identified in almost 60% of the alleles [11]. Our research showed in our sample universe 66.7% of patients with the F508del variant. Most patients had pancreatic insufficiency (84.2%), that is, they had difficulty absorbing nutrients, requiring nutritional supplementation and enzymatic [28]. We also showed that 60% of the evaluated patients had malnutrition and 45.6% had hypovitaminosis D at the time of the evaluation. These findings related to malnutrition and hypovitaminosis D are associated with the severity of the disease, which is chronic and progressive, leading to a loss of lung function and increased energy expenditure. The patient's nutritional status is a constant concern of the CF team, since, even though it is a characteristic of this patient profile, the worsening of the general status is associated with patients with low weight. Although most patients had malnutrition, 17.9% of patients were using a nasogastric tube or gastrostomy. This finding may be an indication that, despite the prescription of a hypercaloric diet associated with oral supplements by a nutritionist at the reference center of our study, many patients were unable to recover from malnutrition, needing the adoption of a more invasive nutritional therapy. It is important to highlight that, despite the hypercaloric diet, the tooth decay index was low.

Early diagnosis of CF can facilitate the rapid initiation of treatments, increasing the quality and life expectancy of patients [29]. In our study, only 11.3% of the patients were born prematurely, and dental follow-up started from birth. In Brazil, there are 51 CF treatment centers [30], however there is a scarcity of data on oral health from the Brazilian public system.

CF has no cure so far, so the treatment of the disease includes taking care of related complications. For respiratory involvement, mucolytics, inhaled or systemic antibiotics, mucus thinners and respiratory physiotherapy are used. In the gastrointestinal treatment,

nutritional intervention is carried out based on hypercaloric diets, pancreatic enzymes, administration of vitamins, macro and micro elements to prevent and treat malnutrition and bone mineralization disorders [13]. Treatment with CFTR modulates mas not net being made available in the Brazilian health system and, therefore, it was not a reality at the reference center during the Study period.

Despite CF having a progressive and lethal characteristic, patient survival has increased with the advent of new therapies and multidisciplinary treatment. The presence of the dental surgeon in the multidisciplinary teams is extremely important for the prevention of respiratory diseases in CF patients, seeking a better quality of life [31]. Patients with poor quality of oral health may have a worsening of their respiratory condition, due to the interrelationship between the oral microbiota and the occurrence of respiratory diseases [32]. Therefore, individualized dental care is imperative, in a multidisciplinary context, prevention-oriented and patient-centered, with a focus on risk and its specific needs [33].

4. Conclusion

Despite the low salivary flow, presence of DDE and hypercaloric diet, a low prevalence of patients affected by tooth decay was found. In addition, the presence of fungi was associated with the use of antibiotics. Etiological agents of diseases with great potential for mobi-mortality were found in both the tongue and oropharynx. These findings underscore the importance of dentists focusing on prevention and on the specific needs of the patient.

CRediT authorship contribution statement

Daniela Abreu de Moraes: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Érica Negrini Lia:** Writing – review & editing, Methodology, Formal analysis. **Letícia Maria Tenório Jácome:** Methodology, Investigation, Formal analysis, Data curation. **Carolina de Azevedo Pedrosa Cunha:** Writing – review & editing, Investigation, Formal analysis. **Luciana de Freitas Velloso Monte:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data associated with this study has not been deposited into any publicly available repository. It will however be made available upon request.

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Appendix A. Supplementary material

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25241.

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