Presence of Developmental Defects of Enamel in Cystic Fibrosis Patients

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ABSTRACT

Purposes: Cystic fibrosis (CF) is an autosomal recessive hereditary disease and is the frequently common lethal genetic pathology. The purposes of this study were to: (1) determine the presence of 3 different types of enamel defects: (a) demarcated opacities; (b) diffuse opacities; and (c) hypoplasia in the deciduous and permanent dentition of CF patients; and (2) compare with a control group.

Methods: The case group was defined as 13 patients who were diagnosed with CF and enrolled in a multiprofessional project of the Catholic University of Brasília (CUB), Brasilia, Brazil. All CF subjects were compared with control subjects selected from patients at the CUB. Each CF subject was individually paired with a control subject of similar sex and age. A full-mouth examination was carried out for the developmental defects of enamel (DDE) index.

Results: The most prevalent enamel defect in deciduous teeth was demarcated opacities present in 16% of the case group and in 7% of the control group. Although the defects were more prevalent in the case group, the difference was not statistically significant (P=0.57). The frequency of demarcated opacities was more prevalent in permanent teeth of the case group: 39% compared to 11% in the control group. For the control group, diffuse opacities were the more prevalent defects: 17% compared to 15% in the case group. The case group had more enamel defects in permanent teeth compared to the control (P=0.0003).

Conclusions: In this study, enamel defects were frequently found in the permanent teeth of CF patients. Therefore, professionals who treat children should be alerted to promoting oral health among these patients. (J Dent Child 2006;73:159-163)

KEYWORDS: CYSTIC FIBROSIS, DEVELOPMENTAL DEFECTS OF ENAMEL

Cystic fibrosis (CF) is the frequently common life-shortening autosomal recessive disease among Caucasians.[1] An epidemiological survey in Brazil showed an incidence of 1:10,000 newborns.[2] In the Federal District, the region where the present research was conducted, 32 children were diagnosed as having CF. This number is lower than expected for this population, but can be explained by factors such as:

1. low genetic frequency in the Brazilian population;
2. high infant mortality rates, whose primary causes of death would be pulmonary and gastrointestinal diseases (the most frequent symptoms of CF);
3. death without diagnosis of a large number of those affected;
4. difficulty of access to diagnostic tests; and
5. the intrinsic conditions of the disease (eg, the variability of expression of the clinical forms).[1,2]

CF is caused by defects in a single gene on the long arm of chromosome 7 encoding a protein, the CF transmembrane regulator, which functions as a cyclic adenosine monophosphate-regulated chloride channel.[3]

Homozygous individuals have defective exocrine gland secretions due to abnormal water and electrolyte transport across epithelial cells, resulting in: (1) chronic disease of the

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respiratory and gastrointestinal systems; (2) elevated sweat electrolytes; and (3) impaired reproductive function.[4]

Respiratory problems are the most critical, because of tachy-dispnea, sibilation, and recurrent bacterial infections with viscous secretion. These problems make the disease severe and lethal. These patients also have maldigestion and insufficient absorption of protein and fat because of the lack of pancreatic enzymes.[5] Poor growth can also be observed as the result of nutritional deficiencies.[6]

Improved therapies have markedly increased the longevity of CF patients, but only occasionally do they live beyond the third decade.[4]

Regarding dental aspects, a delay in dental maturation can be observed and the calcium content in saliva, as well as the mean pH and buffering capacity of whole saliva, is found to be elevated.[4]

Caries prevalence has been reported to be lower when compared with an age-matched healthy population.[7,8] Less dental plaque and gingivitis has also been observed in CF patients,[4] and several patients also had a slight amount of calculus.[9] In earlier decades, staining of the clinical crowns related to tetracycline ingestion was observed.[8,9] Enamel defects were also observed in 5% of the CF group and in 1% of their siblings.[7] A 14% prevalence of hypoplasia and 16% prevalence of enamel opacities was found.[8]

In Brazilian 10-year-old children without CF, a prevalence of enamel defects of approximately 13% was reported.[13] No data were found on the prevalence of these defects in 10-year-old CF children in this country.

To study the cause of enamel defects in CF, the mouse model was used. In this model, the CF gene was isolated and CF was induced in the animals. Wright et al[6] studied the incisor enamel of the CF mouse, which showed a lack of pigmentation and had a distinct chalky-white hypomineralized appearance. Ameloblasts in the CF mice appeared as well-differentiated tall columnar cells, with a polarized nucleus in the early secretory stage. The CF ameloblasts appeared not to retain a normal morphology during the late secretory and maturation phases of their life cycles and showed evidence of premature degeneration to a reduced epithelium. The CF teeth surfaces looked porous, with the prism ends visible, while the normal enamel had a relatively smooth appearance. More detailed examination with TEM showed that CF crystallites appeared to be porous and frequently had a granular surface topography, in contrast to that of normal enamel.

It was noticed that the enamel abnormalities seen in CF were related to amelogenin retention and crystallite defects. The enamel showed a: (1) normal thickness; (2) a normal prism structure; and (3) crystallite orientation. The crystallite defects were associated with the retention of matrix proteins. These findings suggest that retention of only small amounts of amelogenin may be sufficient to alter crystallite formation and enamel mineralization.[6]

Normal mouse and CF mouse enamel had a mean mineral content of 81% and 52%, respectively. The magnesium content was also altered: 2,280 ppm in the normal mouse and 3,560 ppm in the CF mouse. It may also indicate that enamel maturation ceased prematurely.[6]

Mineral analysis of the mature enamel of human CF teeth indicated that CF children had equivalent levels of zinc and phosphorus and decreased calcium levels compared with healthy control subjects, regardless of their tetracycline history.[11]

In the mouse model, it seems likely that abnormal expression of the CF gene in developing teeth was responsible for the dental phenotype. In these models, however, the possibility of the enamel defects being nutritionally related was stated, since the CF mouse exhibited major gastrointestinal abnormalities.

The pH regulation during enamel mineralization is considered to be essential for normal apatite deposition and crystallite growth. In the secretory stage, the pH is neutral. In the maturation stage, the enamel matrix alternates between a neutral and acidic pH.[12] Using the mouse model, it was observed that the altered enamel mineralization present in mice with cystic fibrosis results in an abnormal extracellular pH in the enamel mineralization. The normal mouse enamel matrix pH was generally higher and differently modulated compared with the CF mouse enamel. Therefore, it can be concluded that a reduced pH results in a lack of calcium reflux during enamel maturation and hypomineralization of the CF incisor enamel.[14]

As aforementioned, CF is a disease that interferes with dental aspects. Reports on the prevalence of enamel defects as a consequence of CF are scarce in the literature. The investigations were accomplished in earlier decades when tetracycline was recommended as the therapy of choice and was associated with these defects.[8] Now that alternative antibiotic regimens are available, there has been no investigation on these aspects and the prevalence of enamel defects in CF patients is unknown. To contribute to this knowledge, this study's purposes were to:

1. evaluate the presence of the 3 different types of enamel defects:
   a. demarcated opacities;
   b. diffuse opacities; and
   c. hypoplasia in deciduous and permanent dentition of CF patients; and
2. compare them with a control group.

METHODS

The case group was defined as patients diagnosed with CF confirmed by 2 sweat tests and clinical evidence of disease. The patients were enrolled in a multiprofessional project of CUB and treated at the dental clinic at the CUB School of Dentistry. During the study period, all patients were evaluated consecutively as they presented for treatment. This cross-sectional study was conducted after approval by the Ethics Committee of CUB.

All CF subjects were compared with control subjects selected from patients at the CUB School of Dentistry. Each CF subject was individually paired with a control subject of similar sex and age.

After the parents gave consent and the patients brushed their teeth, a single examiner carried out clinical examinations. Each patient was examined in a dental chair under natural and artificial lighting. The investigator was positioned in front of the patient during examination. All tooth surfaces were inspected visually for defects in a wet environment situation. If there were doubts in any areas, the probe was used to determine abnormalities in the surface contour.

The tooth was considered present in the mouth when any part of it was visible. If more than two thirds of a tooth surface was extensively restored, badly decayed, or fractured, it was excluded for study purposes. A full-mouth examination was carried out, and the buccal and lingual surfaces of anterior teeth and buccal, lingual, and occlusal surfaces of posterior teeth were examined and scored using the DDE index.[10] According to this index, the 3 basic types of defects were recorded:

1. demarcated opacities (a defect involving an alteration in the translucency of the enamel, which has a distinct and clear boundary with the adjacent normal enamel);
2. diffuse opacities (defect involving an alteration in the translucency of the enamel, which can have a linear, patchy, or confluent distribution); and
3. hypoplastic defects (defect involving enamel surfaces and associated with a reduced localized thickness of enamel).[10]

The defects were recorded for both permanent and deciduous teeth. If an abnormality was present, it was recorded on a specific dental chart. Single defects of less than 1 mm in diameter were not recorded.

Statistical analysis included both descriptive and analytical tests. Discrete and categorical data were presented as frequency/percent distribution. The chi-square analytical test was used. This test analyzed whether the cystic fibrosis group was different from the control group for the presence of dental abnormalities. To verify whether there was a difference between the groups relative to the type of dental abnormalities—as well as the analysis of the link between the clinical signs and the presence of abnormalities—was done by the contingency table, using the Mantel-Haenszel nonparametric test. The significance level was set at 5%. The database was processed by EPIINFO 6.04 (Centers for Disease Control and Prevention) and SPSS for Windows (SPSS Science, Inc., Chicago, Il).

RESULTS

The final sample comprised 13 CF patients (case group) with a mean age of 10.3 years—54% being boys and 46% girls. This group was paired with children of the same age and sex who did not have CF (control group).

In the case group, 9 of the 13 patients examined had deciduous teeth; in the control group, 10 of the 13 had deciduous teeth (Table 1).

The distribution of deciduous teeth according to the type of enamel defect is shown in Table 2. The difference between the prevalence of enamel alterations in the 2 groups was not statistically significant (P=.57).

Table 1. Characterization of Groups With Deciduous Teeth

	Case	Control
No. of individuals with deciduous teeth	9	10
No. of individuals with at least 1 tooth with enamel defect	6 (67%)	5 (50%)
Mean no. of deciduous teeth present per child	13.8	10.7
Mean no. of deciduous teeth affected by enamel defect per child	2.9	1

Table 2. Number and Percentage of Deciduous Teeth Affected According to Enamel Defect Type*

	Case	Control
No. of examined teeth	124	107
Demarcated opacities	20 (16%)	7 (7%)
Diffuse opacities	0 (0%)	3 (3%)
Hypoplasia	6 (5%)	0 (0%)

*P=.57.

All subjects from both groups had permanent teeth (Table 3). Demarcated opacities were the most prevalent enamel defects among the CF cases. In the control group, diffuse opacities were more frequent, as shown in Table 4. The prevalence of enamel defects was statistically different in the 2 groups (P=.0003).

DISCUSSION

Of the 32 CF children in the Federal District, 25 were enrolled in CUB's multiprofessional project and 19 were patients from the dental clinic at CUB's School of Dentistry. The study sample comprised 13 of these patients, which was a sufficient sample size to represent the target population.

In this study, 67% of individuals in the case group had at least 1 deciduous tooth with an enamel defect compared with 50% of the control group (Table 1).

The most prevalent enamel defect present in deciduous teeth was demarcated opacity, present in 16% of the cases and 7% of the controls (Table 2). Primosh[8] found a 2% prevalence of hypoplasia in deciduous teeth in CF patients, but there was no comparison with the control group. In the present study, although the defects were more prevalent in the case group, the difference was not statistically significant (P=.57).

Little is known regarding the effect of the CF gene in amelogenesis of deciduous teeth. From the results obtained, it may be speculated that:

1. CF patients' teeth are susceptible to the formation of enamel defects only during the first years of life; and
2. teeth formed during the embryonic period are not compromised.

Further research is necessary, however, to prove this

Table 3. Characterization of Group With Permanent Teeth

	Case	Control
Individuals with permanent teeth	13	13
Individuals with at least 1 permanent tooth with enamel defect	12 (92%)	10 (77%)
Mean no. of permanent teeth present per child	14.8	14.5
Mean no. of permanent teeth affected by enamel defect per child	8.4	4.3

Table 4. Number and Percentage of Permanent Teeth Affected According to Enamel Defect Type*

	Case	Control
No. of examined teeth	193	189
Demarcated opacities	75 (39%)	20 (11%)
Diffuse opacities	29 (15%)	32 (17%)
Hypoplasia	5 (3%)	4 (2%)

*$P=.0003$.

relationship (eg, an attempt to induce CF in animals with 2 dentitions) in order to study the effect of the CF gene in the amelogenesis of deciduous teeth.

Ninety-two percent of CF group individuals had at least 1 permanent tooth with an enamel defect compared with 77% of the control group (Table 3). Two previous studies examining enamel defects reported lower results: Primosch[8] found 30% of enamel defects in CF individuals and 13% in the control group. Jagels and Sweeney,[7] meanwhile, reported 5% in the CF group and 1% in the control group. This may be explained by the fact that, during the 1970s and 1980s, tetracycline therapy was recommended for treating CF patients. Permanent staining of the teeth was a side effect, making it difficult to diagnose enamel opacities. Therefore, enamel defects could have been underestimated. Furthermore, Jagels and Sweeney[7] only considered hypoplasic defects, making the prevalence lower. Direct comparison of the present findings with these studies would be of little value due to methodological differences.

In the present investigation, the frequency of teeth with demarcated opacities was more prevalent in the case group: 39% vs 11% in the control group. For the control group, diffuse opacities were the more prevalent defects: 17% vs 15% in the case group (Table 4). Primosch[8] found nearly 5% of teeth with hypoplasia and over 5% with opacities in CF patients. It is important to note that the index used to record enamel defects in these 2 studies was different. Primosch[8] used the Weinman index, which excludes opacities that could be associated with fluorosis. In the present work, the epidemiological index proposed by FDI was used. This methodological difference makes comparison difficult.

The case group had more enamel defects in permanent teeth when compared to the control. This difference was statistically significant ($P=.0003$). Jagels and Sweeney[7] and Primosch[8] also found higher prevalence in the CF group when compared with the control group.

All CF individuals that reported having diseases during the formation of their permanent teeth had recurrent crises of pneumonia, requiring various periods of hospitalization, which may also have contributed to the development of alterations in the enamel.

Therefore, it can be speculated that enamel defects in the permanent dentition of CF individuals result directly from either the expression of the CF gene or from secondary effects of the disease, such as infections and metabolic disturbances. Accordingly, Sui et al[14] reported that the CF gene plays a role in pH regulation during enamel development and that a reduced pH results in a lack of calcium influx during enamel maturation and hypomineralization of the CF incisor enamel. It was also noticed that respiratory acidosis can affect pH and could result in enamel hypomineralization caused by an acidic environment.

CONCLUSIONS

Based on this study's results, the following conclusions can be made:

1. This study suggests that enamel defects are more frequent in the permanent teeth of CF patients, when compared with control patients.
2. Professionals that deal with children should be alerted to promoting oral health in these patients.
3. To obtain more information about these enamel changes during the course of the disease, further studies are suggested, such as an epidemiological study with more detailed information based on defect location, number, demarcation, and coloration of the defects, which could also contribute to the role of abnormal enamel formation.

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