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Dental Enamel Defects in Italian Children with Cystic Fibrosis: an observational study

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***Objective*:** The relationship between cystic fibrosis (CF) and caries experience has already been explored, but relatively little information is available on dental enamel defects prevalence among children affected by cystic fibrosis. The aim of this study was to investigate this issue in deciduous and permanent teeth of children with CF resident in southern Italy. ***Basic research design*:** This cross sectional observational study was undertaken between October 2009 and March 2010. ***Participants*:** 88 CF patients and 101 healthy age-matched participated in this study. ***Methods*:** The prevalence of dental enamel defects was calculated using a modified Developmental Defects of Enamel (DDE) index. The comparison of dental enamel defects prevalence among groups was carried out using regression binary logistic analysis. ***Results*:** In the CF subjects there was a higher prevalence (56%) of enamel defects in comparison to the healthy group (22%). The most prevalent enamel defect was hypoplasia with loss of enamel (23% of CF patients vs 1½% of control group) in permanent teeth. ***Conclusion*:** This study confirms that children with cystic fibrosis are at increased risk of developing hypoplastic defects on their permanent teeth.

Key words: enamel defects, cystic fibrosis, enamel hypoplasia.

Introduction

Cystic fibrosis (CF) is one of the most common life-shortening hereditary diseases in European countries (1 in 3500 children) (Southern *et al.*, 2007). In Italy, the median birth incidence of CF is 1 in 3700 children and it seems to be slightly higher in northern Italy than in southern Italy (Castellani *et al.*, 2009).

It is caused by mutations in a gene on chromosome 7 encoding the CFTR (cystic fibrosis trans-membrane conductance regulator protein), which functions as a chloride channel within a number of epithelial tissues (Castellani *et al.*, 2009; Damas *et al.*, 2008). Mutations of the *CFTR* gene reduce the channel function of the CFTR protein leading to an altered fluid and electrolyte composition of secretions, thereby resulting in their increased viscosity, which is responsible for progressive obstruction and fibrosis of various organs. Thus, CFTR mutations affect respiratory, gastrointestinal, hepatobiliary, and reproductive systems, as well as exocrine glands, including the salivary glands (Aps *et al.*, 2004; Weiner *et al.*, 2008).

CF patients need many between-meal snacks and sugar-rich drinks to provide themselves the necessary body energy. This diet is highly cariogenic and the frequent use of antibiotics, as well as the disease itself, may impose upon the oral environment of CF patients certain changes which could affect their dental health (Jagels and Sweeney, 1975).

Despite the cariogenic diet the CF patients have a lower caries experience than healthy controls (Aps *et al.*, 2001, 2004; Kinirons, 1992; Martens *et al.*, 2001). Subjects affected by cystic fibrosis have a high percentage of dental anomalies and reduced plaque levels, with little gingivitis compared to healthy controls of the same age (Aps *et al.*, 2002a., 2002b; Dabrowska *et al.*, 2006).

In explaining this high percentage of dental anomalies it should be remembered that dental enamel often acts as a biological marker of systemic insults received during the growth period because the developing tooth germ is sensitive to a wide range of systemic disturbances and is unable to recover once damaged. In many cases, knowledge of the timing of tooth development permits estimates about the timing of the disturbance. Enamel defects, in fact, might be useful as biological markers of the timing and, in some cases, of the nature of insults during second half of pregnancy or during infantile life (Crombie *et al.*, 2009).

Enamel defects are many and of different typology, therefore the Commission on Oral Health Research and Epidemiology of the Federation Dentaire International (FDI, 1982) suggested the DDE (Developmental Defects of Enamel) index based on clinical appearance, providing a standardized classification (Table 1). Dental enamel defects were classified as opacity and hypoplasia. Enamel opacity was defined as a qualitative defect, characterized by white or discoloured enamel with a smooth surface and normal thickness. Enamel hypoplasia was defined as a quantitative defect with pits or rows of pits, grooves, or partial or complete absence of enamel (Clarkson and O'Mullane, 1989).

Factors associated with developmental enamel defects in teeth are many and often unknown. Among the known factors is necessary to remember: ingestion of chemicals such as fluorides, tetracyclines, and thalidomides; prematurity/low birth weight; severe malnutrition; neonatal hypocalcemia; vitamin D deficiency; deprivation of sunlight;

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Table 1. Classification of dental enamel defects.

Modified DDE Index
0 - Normal
1 - Demarcated opacities white/cream
2 – Demarcated opacities yellow/brown
3 – Diffuse lines opacities
4 – Diffuse patchy opacities
5 – Diffuse confluent opacities
6 – Diffuse confluent/patchy opacities with hypoplasia missing enamel
7 – Hypoplasia pits
8 – Hypoplasia missing enamel
9 – Any other defects

hyperbilirubinemia; thyroid and parathyroid disturbances; maternal diabetes; neonatal asphyxia; certain viral infections; genetic disorders such as amelogenesis imperfecta; tuberous sclerosis and cystic fibrosis (Commission on oral health research and oral epidemiology, 1992).

The high prevalence of enamel defects in CF subjects would be attributable to the metabolic illness and to the long term pharmacological therapies (antibiotics and pancreatic enzymes) to which they are subjected (Primosch, 1980; Laisi *et al.,* 2009).

The aim of the present study was to describe the prevalence of the enamel defects (modified DDE index) of CF patients compared with healthy controls in Campania region, Italy.

Method

Eighty-eight children affected by cystic fibrosis (age range 4-12 years; 46 males and 42 females) were recruited from volunteer patients at the Cystic Fibrosis Centre of the University of Naples "Federico II", Italy, and compared to 101 age-matched healthy children (54 males and 47 females) randomly selected from 10 public schools of the Regional Campanian district.

The ethical principles expressed in the World Medical Association Declaration of Helsinki were followed in this study and all the parents of the children, after they received oral and written explanations of the experimental protocol and the study aims, gave written informed consent. The approval for this study was obtained from the ethical committee of the University of Naples "Federico II", Italy.

Inclusion criteria for the CF group only required that children had cystic fibrosis with or without a history of therapeutic dental care. Inclusion criteria for the control group required that children were from single live births, in good health (ASA I-II) (American Society of Anesthesiologists classification I-II) with or without history of therapeutic dental care. In order to avoid the influence of other factors associated with developmental enamel defects, exclusion criteria for both groups required that children were not preterm born, they did not have malnutrition or neonatal hypocalcemia, they did not report a dental history of trauma in deciduous dentition and they were not exposed to fluoridated water and fluoride supplements (only the use of fluoride toothpaste was accepted).

Parents or guardians were approached by a trained interviewer who explained the aim of the study, its procedure and benefits.

A panel of three dentists with experience in the care of patients with enamel defects was convened and trained in the procedures to be followed. Clinical examinations were carried out by the three calibrated professionals, in the same room and using the same dental unit (so that all patients were examined under the same lighting conditions) using a plane buccal mirror and air drying when necessary.

Before beginning the study, the examiners were calibrated for DDE index recorded. The kappa statistic was used to compare each of the three examiners to one examiner used as gold standard with respect to DDE index measured on 40 teeth. Then, each examiner was compared against the other two. The teeth were dried before evaluation of the DDE. Enamel defects were evaluated using modified Developmental Defects of Enamel (DDE) index, in which the type (opacity, hypoplasia, discoloration), number (single and multiple), demarcation (demarcated and diffuse), and location of defects on the buccal and lingual surface of teeth were recorded (Clarkson and O'Mullane, 1989) (Table 1).

All statistical procedures were performed using the Statistical Package for the Social Sciences (SPSS for Windows). The comparison of the enamel defects presence among groups was carried out using regression binary logistic analysis. A confidence interval of 95% was selected to determine when the difference was statistically significant ($p<0.05$).

Results

The kappa statistic, comparing DDE measured by each of the three examiners to DDE measured by an examiner who was used as a gold standard. This comparison yielded scores of 0.83, 0.78, and 0.87 for the examiners. The kappa score for DDE index was 0.76 when comparing examiners 1 and 2, 0.73 when comparing examiners 2 and 3, and 0.81 when comparing examiners 1 and 3.

For subjects' permanent teeth 56% of the subjects affected by CF had enamel defects in comparison to 22% of the healthy subjects. The breakdown of defects by type and group are given in Table 2. Considering deciduous

Table 2. Prevalence of enamel defects for permanent and deciduous teeth in CF and healthy groups

	Permanent Teeth		*Deciduous Teeth*	
	Cystic fibrosis group	*Healthy group*	*Cystic fibrosis group*	*Healthy group*
Number of subjects	29	15	12	9
Prevalence of Enamel Defect (%)	56	23	33	20
Hypoplasia with loss of enamel (%)	23	2	3	0
White/cream coloured opacity (%)	17	9	14	10
Yellow/brown coloured opacity (%)	10	5	6	5
Irregular diffuse opacity (%)	2	8	11	7
Hypoplasia pits (%)	4	0	0	0

teeth, 33% of the CF children had enamel defects in comparison to 20% of the control group (Table 2). The most prevalent defects in deciduous dentition were white/cream and irregular diffuse opacities in the CF group.

Discussion

In the present study, the prevalence of DDEs was found to be higher among the examined CF subjects than in the healthy group. In particular, concerning the presence of enamel defects in permanent teeth, a significant difference was found among the two groups (OR=4.37; CI 95% 1.97-9.66). In deciduous teeth, no statistically significant difference was found. Furthermore, the type of dental defects was different between groups. In fact, regarding permanent teeth, the CF subjects showed a higher incidence of hypoplasia with loss of enamel, yellow/brown opacities and hypoplasia consisting in pits respect to healthy group (Table 2). For deciduous teeth the types of enamel defects were the same for both groups. Our findings are in agreement with those of another group of authors who observed an increased prevalence of dental enamel defects in CF patients, compared both with healthy children and with children affected by other chronic respiratory disorders (Ferrazzano *et al.*, 2009; Narang *et al*., 2003).

Calcification of human primary teeth begins at about 13-16 weeks of pregnancy for incisors, 15-18 weeks for canines and 14-24 weeks for molars (Lunt and Law, 1974). For permanent teeth, calcification of the first permanent molar occurs just before birth (Christensen and Kraus, 1965). For these reasons, it might be hypothesised that any pathogenic effect due to the cystic fibrosis could contribute to alterations in the enamel development.

As suggested by Suckling and Thurley (1984) demarcated enamel opacities resulted from either an acute severe insult, during the ameloblasts maturation stage, or from a less severe, but longer lasting, disturbance during the secretory stage. In addition, diffuse opacities were the result of a chronic, less severe insult, causing a delay in the completion of the ameloblasts maturation process (Suckling and Thurley, 1984). Finally, enamel hypoplasia has great potential as an indicator of stress during the prenatal to childhood periods (Crombie *et al.*, 2009).

It is possible that the gene deletion that causes cystic fibrosis could be responsible for the high incidence of enamel defects. In fact, molecular studies show that the CFTR gene is expressed in developing teeth and other mineralized tissues (Sui *et al.*, 2003). The CFTR gene's deletion causes pH alteration during enamel development which results in a lack of calcium influx during enamel maturation, hypomineralization, alteration of the normal crystal growth and of the protein processing functions necessary for optimal enamel formation (Arquitt *et al.*, 2002; Wright *et al.*, 1996). In particular, iron and potassium are significantly increased, and calcium is significantly decreased in the CF mature enamel. Abnormal enamel mineralization, ion concentrations, and molecular evidence of CFTR mRNA expression by odontogenic cells strongly suggest that CFTR plays an important role in enamel formation (Arquitt *et al.*, 2002).

It is also reasonable to consider that the drug therapies to which CF children are subjected and the metabolic illness may be both responsible for the high incidence of enamel defects. (Azevedo *et al.*, 2006). It should be emphasized that CF patients (since birth) often consume a lot of antibiotics which could influence their dental development (Narang *et al.*, 2003).

According to these considerations, early and regular dental visits may prevent the damages that could be caused by developmental enamel defects. In fact, developmental defects in the enamel present important clinical significance since they are responsible for aesthetic problems, with subsequent psychological discomfort for the patients, dental sensitivity, dentofacial anomalies, as well as for a predisposition to dental caries.

This emphasises the need for a paediatric dentist to be a member of the multi-professional team involved in the care of children with CF with the aim of establishing appropriate dental treatment programs to improve their health-related quality of life. In particular, treatment options may depend on the severity of dental enamel defects and could comprise: dental restoration for anterior aesthetically compromised teeth, management of dental sensitivity through use of desensitizing agents, application of pit and fissure sealant on the occlusal surface of hypoplastic molars and/or topical fluoride treatment.

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