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Research paper

Oral manifestations of celiac disease in French children

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ABSTRACT

Celiac disease (CD) is an immune-mediated systemic disorder caused by ingestion of the gluten found in wheat, rye, and barley. The currently estimated prevalence in children is about 1%. CD is a chronic enteropathy with gastrointestinal manifestations including diarrhea, abdominal distension and weight loss, but extra-intestinal features are increasingly being reported. Dental and oral manifestations such as dental enamel defects (ED), delay in dental eruption, and recurrent aphthous stomatitis (RAS) are well-recognized manifestations of CD. The aim of this study was to compare the frequency of oral manifestations (ED, RAS and delay in dental eruption) on deciduous and permanent teeth between children with CD and a control population. An oral examination was performed on 28 CD children and 59 control children. All children were younger than 12 years old and had deciduous or mixed dentition. CD children had significantly more ED and RAS than the control group (67.9% vs. 33.9% $P = 0.004$ and 50.0% vs. 21.8% $P = 0.011$, respectively). No delay in dental eruption was observed in CD children. ED were mainly grade I and II of Aine's classification (color defects and slight structural defects). ED were more often seen on CD children's deciduous teeth than on permanent teeth (57.1% and 13.6%, respectively; $P < 0.001$). The main teeth affected by ED are the second molar and canines of the deciduous teeth, and the first molar, central incisor, and lateral incisors of the permanent teeth. RAS and ED that were symmetrical in all quadrants and occurred firstly in teeth that mineralize during the first year of life both seem to be signs of CD. Thus, more information for dentists and pediatricians on these oral manifestations should help improve detection of CD.

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1. Introduction

Celiac disease (CD) is an autoimmune disease caused by ingestion of gluten in genetically susceptible individuals: More than 95% of people with CD express the HLA DQ2 or HLA DQ8 haplotype [1]. The classic form is an enteropathy with villous atrophy caused by an unbalanced immune-mediated response of the small intestinal mucosa against the protein found in wheat, rye, and barley [1].

The prevalence of CD is approximately 1–2% and can reach 20% in high-risk groups. CD generally occurs in children under 3 years of age, some weeks after gluten introduction to the diet. Symptoms include chronic diarrhea with abundant and foul-smelling stool, digestive discomfort, abdominal distension and bloating, anorexia, and apathy. Clinical examination shows signs of undernutrition including muscle and fat loss. Failure to thrive confirms the nutritional impact [2].

The presentation of CD has changed over the years and monosymptomatic patients are more prevalent today. Epidemiological studies show that 75% of individuals with CD with non-classic symptoms are undiagnosed [3], exposing patients to complications and deterioration in their quality of life.

In 1986, Aine described enamel defects (ED) in children that were exclusively related to CD. These defects were symmetrically and chronologically detectable in all four quadrants of dentition [4]. Today it is widely acknowledged that the oral manifestations most frequently related to CD are ED, recurrent aphthous stomatitis (RAS), and delay in dental eruption [5].

Most studies have focused on the ED of permanent teeth in CD. However, mineralization of deciduous teeth starts during intra-uterine life and continues through the first year of life, a period when gluten is introduced into the infant diet.

The aim of this study was to compare the frequency of oral manifestations (ED, RAS, and delay in dental eruption) on

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deciduous and permanent teeth between CD children followed up at Toulouse Children University Hospital (France) and a control population.

2. Materials and Methods

2.1. Study population

A total of 28 children, who were being followed up at Toulouse Children University Hospital for CD, were included in the study between January and June 2017 (Fig. 1). The diagnosis of CD was made according to the 2012 ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology, and Nutrition) guidelines: symptoms of CD and positive serum immunoglobulin A (IgA) anti-transglutaminase 2 (TG2) levels $\geq$ 10 times upper limit of normal (ULN) and positive HLA-DQ2 or DQ8 genotyping and anti-endomysial antibody [6]. Before 2012, the diagnosis of CD was made following the previous guidelines: positive IgA anti-TG2 level in blood with clinical signs suggestive of CD and endoscopic biopsies with pathological evidence of intestinal villous atrophy, crypt hyperplasia, and increased number of intra-epithelial lymphocytes. In total, 14 children were excluded: 11 had incomplete criteria for CD diagnosis (HLA typing or biopsies are missing), two had poor dental hygiene conditions that did not allow us to discriminate specific lesions of CD, and one did not have CD.

A complete medical history was collected for each patient to ensure maximal information about the diagnosis (age at diagnosis, symptoms, family history of CD or auto-immune disease) and a complete physical examination was performed. A dental check-up was performed by two pediatric dentists using a scialytic light and after air-drying teeth. No information about eating sweets and tooth-brushing habits was collected. RAS was evaluated by asking the parents how many times their children had RAS during the last 12 months. Research data were collected either during consultations, or retrospectively from medical records, or via telephone with the parents if information was missing.

Overall, 59 non-CD children were included in the control group between May and November 2017 (Fig. 1). These children were under 12 years old and were followed up at the Pediatric Endocrinology Unit either for growth retardation, early puberty, obesity, or genital disorders. All of them were IgA anti-TG2 negative. Exclusion criteria for the control group were bone, thyroid, auto-immune, or digestive disorders. Control children were included on the day of their endocrinological consultation. Dental examinations were performed by our pediatric dentistry team, after obtaining parental consent. Clinical data were collected from the parents and the medical records.

ED on deciduous and permanent teeth were rated from grades I to IV, according to Aine's 1986 classification (defect in color, slight structural defects, evident structural defects, and severe structural defects) [7–9] (Fig. 2). These defects were assumed to be linked to CD when they showed a symmetrical distribution in at least two quadrants with chronological coherence. RAS was evaluated through clinical observation complemented by the parents' information. Usual eruption tables were used to evaluate delay in dental eruption. It was considered delayed if teeth were in arch later than 6 months after their normal age of eruption.

2.2. Ethics

No additional blood samples were taken for the purpose of the study. The dental examination was only observational and totally painless. After advice from the Ethics Committee of Toulouse University Hospital, the study did not require an ethics committee agreement but all parents were informed and provided written consent for enrolment in the study.

2.3. Statistical analysis

Statistical analyses were carried out by using STATA© version 11. Differences between CD children and the control group were tested using the chi-square test or Fisher's exact test for categorical variables and the Student test or Mann–Whitney test for continuous variables. A *P* value of less than 0.05 was considered as statistically significant.

3. Results

For 19 children, the diagnosis of CD was made after 2012, using ESPGHAN 2012 criteria, and no biopsy was carried out. For nine children, it was performed before 2012 and all of them had

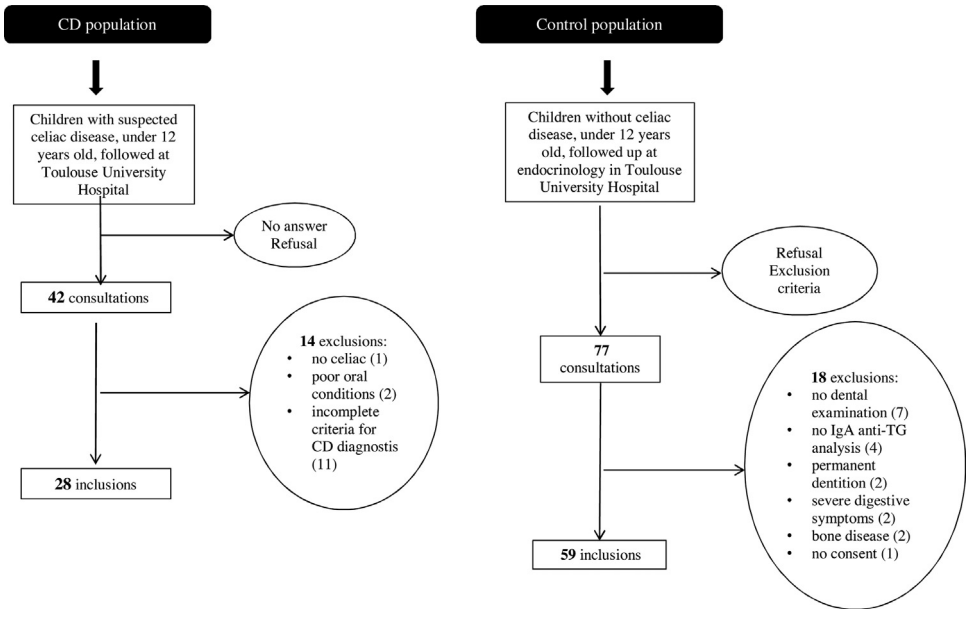

Fig. 1. Flowchart.

Grade 0	No defect	
Grade I	Defect in color of enamel	 [29]
Grade II	Slight structural defects	 [8]
Grade III	Evident structural defects	 [29]
Grade IV	Severe structural defects	 [30]

Fig. 2. Aine's classification.

duodenal biopsies. The data of 28 CD children, between 3 and 12 years old, with a mean age of 8 years (95% confidence interval [95% CI: 6.94–8.80], were analyzed. There were 19 female (67.86%) and nine male (32.14%) patients with a female–male ratio of 2.1. Overall, 20 patients (71.43%) were HLA DQ2 positive and 12 (42.86%) were HLA DQ8 positive. HLA typing was not performed for seven children (25%). The control group comprised 59 children, between 1 and 12 years old, with a mean age of 7.2 years (95% CI: 6.47–7.92). There were 29 female (49.15%) and 30 male (50.85%) patients. The study population was equally distributed for age and sex (Table 1).

Regarding oral manifestations, 19 (67.86%) of the CD children were affected by ED, 14 (50%) by RAS, and none by delay in dental eruption. In the control group, only 20 children (33.9%) were affected by ED, 12 (21.82%) by RAS, and two (3.57%) presented delay in dental eruption.

Significant differences between groups were observed for the prevalence of ED ($P = 0.004$) and RAS ($P = 0.01$), with a higher prevalence for CD children. No difference was noted for the prevalence of delay in dental eruption.

Table 1
Description of CD children and control group.

	CD children ($n = 28$)		Control group ($n = 59$)		P
	Mean (n)	Range (%)	Mean (n)	Range (%)	
Age (year)	8 [95% CI 6.9–9.2]	3–12	7.2 [95% CI 6.5–7.9]	1–12	0.177
Gender					
Female	19	67.86	29	49.15	0.11
Male	9	32.14	30	50.85	
ED					
Yes	19	67.86	20	33.9	0.004
No	9	32.14	39	66.1	
RAS					
Yes	14	50	12	21.82	0.01
No	14	50	47	78.18	
Delayed eruption					
Yes	0	0	2	3.57	NS
No	28	100	57	96.43	

CD: Celiac disease; ED: enamel defects; RAS: recurrent aphthous stomatitis; NS: nonsignificant; CI: confidence interval.

3.1. Enamel defects

ED in the CD children showed the following pattern: In the deciduous teeth they occurred more often in the second molars (85.71%), first molars (67.86%), and canines (39.29%) (Fig. 3) and had a symmetrical distribution in 2–4 quadrants. This prevalence was higher in CD children (57.14%) than in the control group (13.56%; $P < 0.001$). In the permanent teeth, they occurred more often in the first molars (64.28%) and central incisors (21.42) and also had a symmetrical distribution in 2–4 quadrants. The difference between the two groups was not significant (35.71% vs. 22.03%, respectively, $P = 0.18$) (Fig. 4). Of the children with CD, 16 (57%) had a symmetrical distribution of ED, three (11%) did not have a symmetrical distribution of ED, and nine (32%) did not have ED.

The extent of ED in CD children was assessed using Aine's classification: 67.86% had defects in the enamel color (Grade I), 7.14% had slight structural defects (Grade II), 3.57% had evident structural defects (Grade III), while no severe structural defects (Grade IV) were observed. In the control group, only defects in the enamel color (Grade I) were observed (32.14%) (Fig. 5). Thus, ED in the CD group were more severe than in the control group ($P = 0.04$).

3.2. Recurrence aphthous stomatitis

The mean number of RAS per year in CD children was 3.86 as opposed to 0.72 in the control group. The difference between the groups was significant ($P = 0.003$).

4. Discussion

We conducted an observational and monocentric study. The dental examinations were prospective and carried out specifically

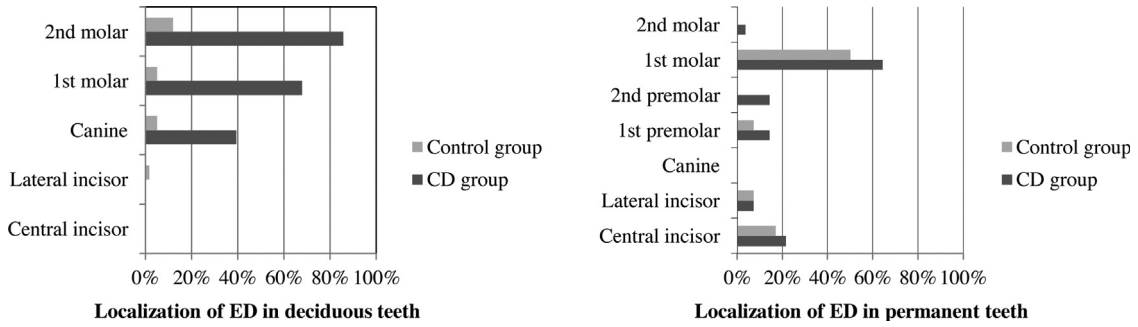

Fig. 3. Localization of enamel defects (ED) in deciduous and permanent teeth in CD children and control group. CD: Celiac disease.

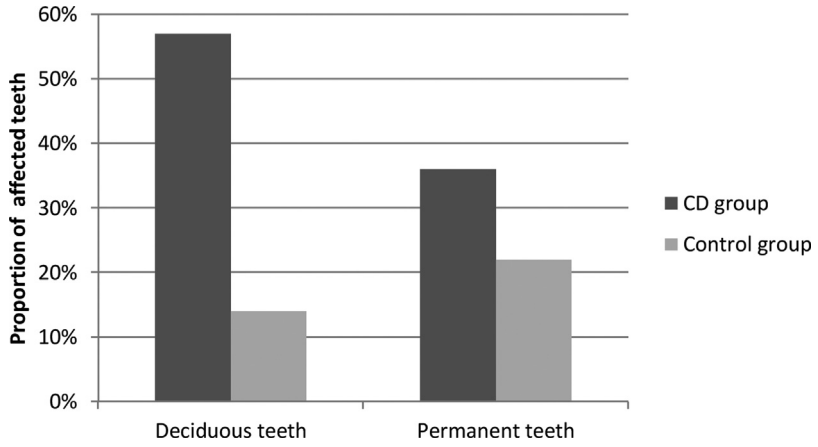

Fig. 4. Proportion of deciduous and permanent teeth affected in CD children and control group. CD: Celiac disease.

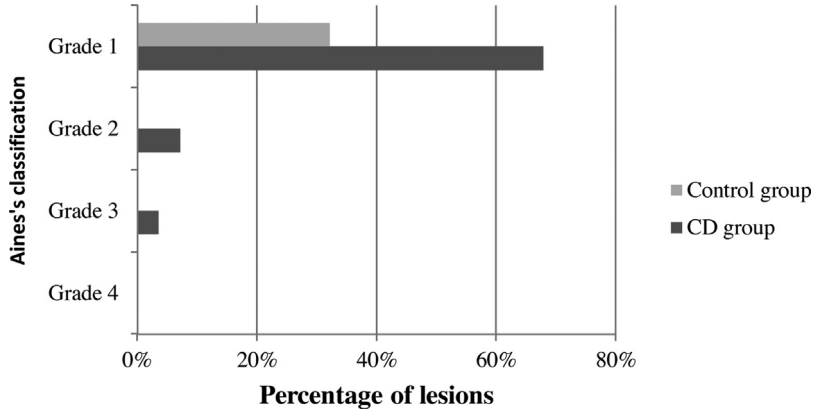

Fig. 5. Enamel defects according to Aine's classification in CD children and control group. CD: Celiac disease.

for the study, whereas CD data were collected retrospectively during consultations with parents or from medical records. Thus, some data may be missing.

Our population of CD children was representative of the classic form of CD, with typical gastrointestinal symptoms. A 2014 Italian study demonstrated that ED was more often observed in CD children with typical gastrointestinal symptoms, whereas RAS was more frequently observed in patients with atypical and silent CD [10]. Delay in dental eruption was more prevalent when the diagnosis was performed after 8 years of age [11], which would explain the lack of association between CD and delay in dental eruption in our study, as the mean age of the population was under 8 years.

As in other studies, CD was more prevalent in female than male patients (67.86% vs. 32.14%, respectively, in our CD sample). For example, the Danish nationwide cohort study of CD epidemiology used data from 1977 to 2016 and showed an increase in the female–male ratio from 1.3 in 1986 to 2 in 2016 [12].

Our control group was not completely representative of the general population. These children were followed up at the Endocrinology Unit of our hospital for benign and frequent pathologies in the general population. We excluded pathologies that could have interfered with CD and tooth mineralization. For ethical reasons, we chose children who previously had a blood sample for serological study of CD and whose levels of IgA anti-TG2 antibodies were negative.

Of the 59 children in the control group, 31 were followed up at the Endocrinology Unit for short stature or delayed growth. A resistance to growth hormone in CD has been reported, with normal or elevated levels of GH and low IGF1 levels, usually corrected by introducing a gluten-free diet [13].

Three of the children without CD were followed up for obesity. According to the literature, the prevalence of obesity among CD patients varies from 8 to 20% either at diagnosis or after starting the gluten-free diet [14]. In this population, the oral manifestations are usually poor oral–dental status with caries and inflammation of the periodontium that are clinically different from CD.

In total, 22 children were followed up for early or advanced puberty. In untreated CD, puberty may be delayed in girls and boys. However, this is generally not the case when a gluten-free diet is correctly followed [15].

The pathophysiological mechanisms responsible for oral manifestations in CD are probably multiple. The immune system could be especially involved because there are similar sequences between gliadin and dental enamel proteins, which may be recognized by CD antibodies [16]. Genetics factors are also probably a cause. The HLA DQB1*02 allele seems to have a protective role for ED and RAS in CD, whereas the HLA DR52-53 alleles are more often associated with ED in CD [17]. Due to its direct contact with teeth, the salivary composition has also been studied. For example, it has been demonstrated that salivary glutenase activities were higher in CD patients compared with controls and that salivary levels of lactobacilli were also higher [18].

In the literature, the link between ED and CD in children is now widely acknowledged. However, the prevalence of these abnormalities is highly variable from one study to another [19]. A recent meta-analysis of 45 studies – including 2840 patients – found a prevalence of 50% ED in CD patients [20].

In our study, the percentage of ED was high in both populations (67.86% vs. 33.9%, respectively). A Brazilian meta-analysis published in 2018 showed that only the defects affecting deciduous teeth were associated with CD [20]. Similarly, a study performed in 2010 comparing ED in children and adults only found a significant link with CD in children [21]. However, other studies have shown a greater impairment of the permanent teeth [10]. The deciduous teeth were significantly more affected in CD children in our study. One explanation is that we included children $\leq$ 12 years old in order to primarily study deciduous and mixed dentition. None of our patients had all their permanent teeth.

As in the literature, we found the preferential impairment of the first molars and the central and lateral incisors for the permanent teeth and the second molars and canines for the deciduous teeth [4]. The preferential damage to these teeth follows the chronology of their mineralization: The first molar and the incisors are the first of the permanent teeth to be mineralized (in the first 4 months of life) and the second molar and the canines are the last of the deciduous teeth to complete their mineralization (between 9 and 12 months of life). It is important to note that this period of life corresponds to the introduction of gluten into infant feeding. Our study also showed the high rate of damage of the lower left deciduous first molar, which – although less frequent–follows the same logic: It completes its mineralization between 6 and 9 months of life.

In our study, like in the literature, the major ED was the color defect (grade I, Aine's classification) [22]. Structural defects were not found in the control group, and they may indicate the specific involvement of CD, with the teeth affected symmetrically in several quadrants. However, the comparison of symmetrical defects in the CD group and in the control group did not show significant differences, probably due to an insufficient number of patients.

The pathophysiological mechanisms responsible for the RAS in CD are poorly understood. Disturbances in autoimmunity and genetic factors are likely to be involved, since mouth sores are also common in Crohn's disease and Behcet's disease, as well as in cases with a family history [23]. The prevalence of RAS in CD varies widely from one study to another [20,24]. A 2015 study compared 35 CD children with 25 controls and showed a 44% prevalence [25]. In our study, the prevalence of RAS in CD children was similar to that of the literature, approximately 50%.

The presence of RAS in CD could also be explained by its high frequency in the general population (approximately 20%) [26]. It has no clinical specificity that would point to an association with CD. In our survey, the collection of data on RAS was purely declarative, with a questionnaire completed by the children's parents, and this may have decreased the reliability of the results.

The clinical peculiarity of RAS in CD is its regression after the introduction of a strict and well-followed gluten-free diet [27]. In our study, the parents noted a decrease in the frequency of recurrences after introducing the diet, but we were unable to study this parameter statistically.

The evaluation of the delay in dental eruption is very difficult, and reliable evaluation requires frequent dental follow-ups. In our study, the children were only examined once by a dentist at the hospital. Delayed eruption was therefore assessed primarily on the basis of parental reports and the evaluation at the time of consultation. Thus, it is understandable that our results did not show a significant difference between the two populations.

In the literature, delay in dental eruption is less often studied than ED and RAS. The mean prevalence is 20–27% [28] but it is debated. It is more important in the case of late diagnosis after 8 years of age [29], and it decreases after the introduction of a well-conducted gluten-free diet [30].

Our investigation is the first French case study confirming that both ED and RAS are symptoms associated with childhood CD. ED are symmetrical, follow the chronology of dental mineralization, and usually comprise slight color or structural defects.

We were unable to identify a risk factor for these defects in CD. A large-scale prospective study should evaluate the relationship between these dental abnormalities and the severity of the pathological lesions or the IgA anti-TG2 levels at the time of diagnosis, in order to detect them more systematically.

The reversibility of ED in CD with the introduction of a gluten-free diet should also be further investigated in order to improve awareness of the importance of their screening and management among patients, their families, and pediatricians. If they are reversible, it might be useful to perform a systematic dental check-up after diagnosis of CD.

5. Conclusion

Dentists and general pediatricians should be aware of the presence of oral lesions in CD and about their specificities. This knowledge should improve CD screening and enhance the diagnosis of paucisymptomatic children.

Disclosure of interest

The authors declare that they have no competing interest.

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