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Letter to Editor Open Access

Oral Pathology in Celiac Disease: What's New?

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The first description of dental enamel defects in celiac disease (CD) dates back to 1990 [1]. Since then several authors have reported an association between oral pathology and CD. In recent years, two literature reviews have shown recurrent aphthous stomatitis (mouth ulcers) and dental enamel defects in a wide range of 4-41% and 10-96% of patients with CD [2,3]. In 2012 were published the new pediatric guidelines on CD [4]. CD is currently defined as an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies (against transglutaminase, endomysium and deamidated forms of gliadin peptides), HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy [4]. CD has thus shifted from a gluten-sensitive small bowel disorder with only gastrointestinal symptoms, to a multisystem disease with a very broad spectrum of intestinal and/or (just) extra intestinal symptoms, including oral manifestations. For the first time a combination of suggestive symptoms, (high levels of) specific antibodies and genetic findings may be sufficient, in children, to make the diagnosis of CD, regardless the histology features. Furthermore, a specific HLA profile may be useful as a first-line test for at-risk population such as relatives of CD patients, or children with autoimmune (especially type 1 diabetes and thyroiditis) or chromosomal aberrant (Down, Turner, Williams) disorders. Currently CD has a worldwide prevalence of 0.7-2% in the general population, and 0.4-1.3% in the pediatric population [5]. However, many cases are still undiagnosed. At any age, CD may be difficult to recognize because of the variability of the symptoms and signs, and the possibility of silent forms.

Enamel defects include pitting, grooving and sometimes complete loss of enamel may occur in CD, even in the absence of gastrointestinal symptoms, and have greater sensitivity and specificity for CD in more severe injuries [1]. In children with deciduous teeth, the prevalence of dental enamel defects is reported in 5.8-13.3% (mean of 9.6%) of patients with CD [6]. In 2012 El-Hodhod has evaluated 140 Egyptian children (aged 4-12 years) with enamel defects: CD was diagnosed in 18% of these patients compared to 0.97% of 720 healthy children and was associated with a greater severity of the defect of the enamel [7].

Enamel defects are seen most commonly in the permanent dentition and tend to appear symmetrically and chronologically in all four quadrants, with more defects in the maxillary and mandibular incisors and molars. Both hypoplasia and hypomineralization of the enamel can occur and a band of hypoplastic enamel, often with intact cusps, is common [1,3]. The exact pathogenesis of enamel defects related to CD related is not clear, but is suspected that the immune-mediated damageis the leading cause [6].

Recurrent aphthous stomatitis has been (less) associated with CD. Both nutritional and immune-inflammatory mechanisms have been suggested. Severe or recurrent aphtous ulcers may represent an early (and possible only) sign of other disorders involving gastrointestinal system such as Crohn's disease (even in young children), Behcet disease, infections or different immune deficiencies (as IgA deficiency commonly associated with CD). In 2012 Yaşar et al. did not confirm an increased prevalence of CD in a cohort of Turkish patients with recurrent aphthous stomatitis [8]. The etiopathogenesis of recurrent aphthous stomatitis has yet to be fully understood. The potential trigger factors include: genetic predisposition, viral and bacterial infections, food allergies, vitamin and microelement deficiencies, systemic immune diseases, increased oxidative stress, hormonal defects, mechanical injuries and anxiety [9].

The principal determinants of genetic susceptibility for CD are the major histocompatibility class II HLA DQA and DQB genes. More than 95% of patients with CD share the HLA-DQ2 heterodimer, either in the cis (encoded by HLA-DR3-DQA1*0501-DQB1*0201) or in the trans configuration (encoded by HLA-DR11-DQA1*0505 DQB1 0301/DR7-DQA1*0201 DQB1 0202), and most of the remainder have the HLA-DQ8 heterodimer (encoded by DQA1*0301-DQB1*0302) [4].

CD is a multigenetic disorder, which means that the expression of these HLA-DQ2 or HLA-DQ8 molecules is necessary but not sufficient to cause the disease because approximately 30% to 40% of the white population holds the HLA-DQ2 haplotype and only 1% develops CD. HLA testing may be offered to asymptomatic individuals with CD-associated conditions. The absence of DQ2 and DQ8 make CD highly unlikely and not necessary to perform any further antibody tests [4].

In 2011 Erriu et al. related the distribution of recurrent aphthous stomatitis and dental enamel defects in the oral cavity, in celiac patients, to the presence of the HLA-DQB1*02 allele, obtained by a rapid sample method of oral brushing, DNA extraction and polymerase chain reaction [10]. More recently, our group has reported recurrent aphthous stomatitis in 18%, dental enamel defects in 39% and one or more oral signs in 52% out of 44 children with CD (11). The percentage of patients carrying two copies of the HLA alleles was 39%, whereas 41% showed heterozygosis, and only 20% of children did not carry the specific allele. Dental enamel defect, but not recurrent aphthous stomatitis, was significantly related to HLA-DQB1*02 haplotype (*P* value=0.042 and *P* value=0.084, respectively) [11].

In recent years, non celiac gluten hypersensitivity has increasingly been reported. Intestinal and extra intestinal symptoms partially overlapping CD, response to gluten (or wheat or other fermentable carbohydrates) free diet, HLA-DQ2 (in 50% of patients) and IgG antigliadin antibodies positivity may be present [12]. Differences in immune and histological features between these two entities have been showed [13,14]. The exact prevalence, natural history and the presence of oral pathology in children with non celiac gluten hypersensitivity are currently unknown.

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The awareness of hallmarks of CD is still poor. Diagnostic delay is frequently reported especially in extra intestinal symptoms, increasing the rate of related complications including persistent gastrointestinal problems, nutritional deficiency, impaired growth, delayed puberty, reproductive and autoimmune disorders, and possible malignancy [15]. The practical implication of emphasizing the role of dentists in identifying oral pathology related to CD is in increasing early diagnosis and in selecting patients for CDscreening.

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