ORAL MANIFESTATIONS OF THE CELIAC DISEASE PART I. A SYSTEMATIC REVIEW OF CASE-CONTROLLED STUDIES

Roxana NEMȚEANU[1], Gheorghe G. BĂLAN[1], Eugeniu MIHALAŞ[2], Alina PLEŞA[1], Carmen SAVIN[2]

[1]M.D., PhD, "Grigore T. Popa" University of Medicine and Pharmacy of Iaşi, Romania
[2]D.M.D., PhD,"Grigore T. Popa" University of Medicine and Pharmacy of Iaşi, Romania

Corresponding author: Gheorghe G. Balan; e-mail: balan.gheo@me.com

Abstract

Celiac disease (CD) is responsible for digestive and systemic manifestations leading to moderate-to-severe health disparities and impaired quality of life for the affected patients. Several oral manifestations have been described, including mainly dental enamel defects (DEDs) and recurrent aphthous stomatitis (RAS). Nevertheless, publications on the topic reveal visible reporting discrepancies. Therefore, the aim of our study was to perform a systematic-review of case-controlled observational studies on CD oral manifestations. The searching protocol was applied to EMBASE, OVID and PubMed. Both pediatric and adult cohorts were included. The main oral manifestation in children was represented by DEDs, while RAS was rather reported in adults. Despite the relatively constant prevalence reported for such oral manifestations, publications are characterized by high publication and outcome bias. Moreover, oral manifestations are influenced by concurring the oral conditions possibly generated by diet and healthcare disparities. Thus, CD should be searched in patients with DEDs and aphthous ulcers or RAS, yet the concurring conditions should be ruled out, and a thorough CD diagnosis algorithm should be implemented.

Keywords: *dental enamel defects, aphthous ulcers, dental caries, malabsorption*.

1. INTRODUCTION

Celiac disease (CD) is a chronic, multiorgan autoimmune disease that affects the small bowel in genetically predisposed persons precipitated by the ingestion of gluten, affecting around 1% of the population [1,2]. A substantial increase in the number of new cases has also been documented, partly due to better diagnostic tools and thorough screening of individuals considered to be at high risk for this disorder. Nevertheless, CD still represents a statistical iceberg, with still more cases that need to be diagnosed [3].

The diagnosis is currently defined by 5 components: symptoms, the presence of HLA-DQ2/DQ8, celiac antibodies in serum, duodenal histology and response to the gluten-free diet [4,5]. Because CD is a multisystem disorder with protean clinical manifestations, a high index of suspicion is needed to make an appropriate diagnosis. Classic CD is the term used to describe patients with CD with features of a malabsorption syndrome; a combination of diarrhea, steatorrhea, weight loss, or growth failure is usually required. Non-classic CD is characterized by the predominance of extraintestinal features, often monosymptomatic (iron deficiency anemia, premature metabolic bone disease, infertility, elevated transaminase levels) in the absence of clinical malabsorption [5,6]. Interestingly, the frequency of classic CD among incident cases has decreased over time, while those presenting with non-classic features has increased [7,8].

Oral manifestations of CD refer to a distinct category of extraintestinal manifestations that include both lesions of the mineralized tissues, such as dental enamel defects (DED) and subtypes: enamel hypoplasia, erosions or tooth wear, soft tissues lesions like aphthous ulcers (AU), recurrent aphthous stomatitis (RAS), angular cheilitis, atrophic glossitis and, in some cases, squamous cell carcinoma of the oropharynx [9-11]. Subsequent findings consist in delayed eruption of teeth (DET) and dental caries (DC). Numerous publications have addressed the association between the lesions of the oral cavity and CD, and found out conflicting results. Although most reviews on the subject suggest a significantly higher prevalence of developing enamel defects and RAS among CD patients, implying that RAS and enamel hypoplasia are "risk indicators" that may suggest that an

individual has CD, others fail to find such a connection [12-18]. Aphthae, especially RAS, are observed particularly often among patients with CD, yet a true pathogenic link has not been established. Whether aphthous ulcers are a direct manifestation of the CD or whether they occur due to the indirect effects of malabsorption is still a matter of debate [19].

The versatility of clinical manifestations should warn physicians of different specialties to consider this disorder when a patient presents with extraintestinal signs and symptoms that might be related to CD [8]. Currently, active case-finding (serological testing for CD among individuals with only subtle or atypical symptoms, and in risk groups) is a favored strategy to increase detection [20]. DED and RAS are the most common and well-documented oral manifestations, and several studies have confirmed the occurrence of these lesions in both children and adults with CD.

The purpose of our study was to perform a systematic review of case-controlled observational studies and to compare the presence of oral manifestations, such as DED, AU, RAS, DC or DET, both among patients with CD and healthy subjects.

2. MATERIALS AND METHODS

The systematic review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, [21] following a protocol established by the authors. PRISMA checklist and flow diagrams have been used [22].

Search strategy

Publications covering the field of oral manifestations of CD were included in the systematic review protocol. The review was limited to peer-reviewed publications, journal articles, books or chapters, and abstracts presenting the oral conditions associated with celiac disease. Unpublished or additional materials containing older or complementary data have not been included. No limits were applied as to the language, and foreign papers were translated into English. Most of the cases were reported in English, several were also in Dutch, Spanish, French, German, Hebrew, Italian, Portuguese, Russian, and Polish languages.

Cases were identified by active keyword assessment within 3 biomedical databases: EMBASE, OVID and PubMed. Database screening was done during the 21st and the 28th of March 2020. Publication date limits have been set: 2000-2020. No supplementary approaches, such as hand searching of journals, checking reference lists, searching trials or court registries, contacting involved parties, or contacting authors, were performed. Search terms were selected from the Medical Subject Headings (MeSH) registry. Operator 'and' was used. The following keyword combination was searched for in all databases: 'oral manifestations and celiac disease'. No other search restrictions were applied.

Study selection

Study selection and eligibility assessment for systematic review were performed independently by all authors, according to an unblinded algorythm. Disagreements were resolved by consensus. The standard process for selection included first an assessment of relevance performed by the analysis of title, after which we assessed duplication and excluded duplicates. Duplication arise from the identification of the same study published in two different publications. Subsequently, the data items required for review were searched within the full-text versions of relevant publications. Studies published only in abstract and inaccessible full text versions due to unknown language or inaccessible journal archives were excluded. Within the eligible publications, inclusion and exclusion criteria for systematic review were applied. Inclusion criteria consisted in: (a) study design: case-controlled observational study; (b) assessment of oral lesions associated with CD; (c) publication consistent with peer-reviewed article; (d) quotation of clear numerical and/or categorical data for the analyzed groups. Exclusion criteria: (a) other types of observational and/or experimental study designs; (b) publication including only theoretical data (books, chapters, syllabuses); (c) case reports and case series; (d) letters to the editor; (e) partial disclosure of data; (f) systematic reviews and meta-analyses. The remaining publications were referred to for systematic review. The flowchart of study selection is presented in Figure 1.

Choice of outcomes, data abstraction and bias assessment

A data extraction sheet was developed for the selected moderators. Moderators consisted in bibliographic references (authors, date of publication and source), type of population (adults, pediatric, mixed) and screened outcomes. The outcomes included: (i) type of oral manifestations: DEDs, RAS, DC (quantified by DMF(dmf)/DMFT(dmft)/DMFS(dmfs)), AU, and DET; (ii) number of study cases (iii) number of controls; (iv) prevalence of oral manifestations within the observed groups (quoted in percent values). We performed data abstraction and included in the systematic review only the oral manifestations with significantly different prevalence reported between study groups and controls.

Some studies reported subtypes of DED, so that, in order to achieve uniformity and control bias, we reported the general prevalence of DED within the group. Outcomes were mainly numerical. Numerical data was presented in either absolute values (n) or percent ratios (%). Publication bias was minimized by implementing the study selection protocol. Publications selected for systematic review and qualitative assessment of data consist in a homogenous group of case-controlled observational studies. Further reporting bias has been minimized by excluding the studies presenting partial or non-specific data (multiple cohort designs, therapy biased trials, or mixed case-controlled and longitudinal studies). An important source of bias was driven by language, controlled by exclusion of publications in Dutch, Italian, Hebrew, Portugese, Polish and Russian.

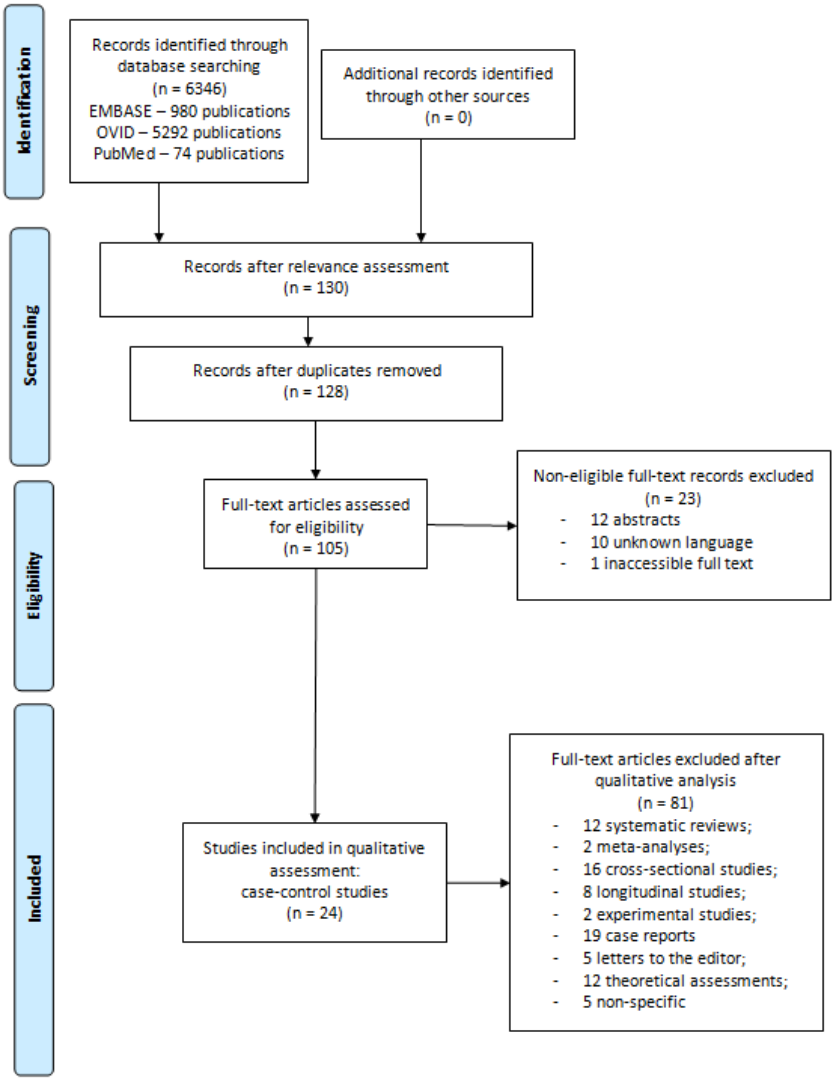

Fig. 1. Flowchart of selected publications

3. RESULTS

By implementing the search strategy, 6,346 publications were identified within the databases: original articles, books, chaperts, abstracts, posters, and letters - respectively 980 publications in EBSCO, 5292 in OVID and 74 publications in PUBMED. After assessing their relevance by screening of title, 130 publications were selected. After adjusting for duplicates, 128 publications remained for full-text analysis of the inclusion and exclusion criteria. Two articles with the same content were identified within two different publications. Out of the 128 remaining publications, 28 were excluded, due to absence of eligibility. The reasons for non-eligibility included mainly: publication is abstract only (12 publications) or the inaccessible language (10 publications). Studies published in Dutch, Italian, Hebrew, Portuguese, Polish and Russian have been excluded as non-eligible. One article was not accessible in full text and therefore excluded as non-eligible. Thus, 105 publications were included in the full-text assessment, choice of outcomes and data abstraction. Inclusion and exclusion criteria for the systematic review were applied. Hence, 76 publications had to be further discharged due to study design miss-match (as follows: 12 systematic reviews, 2 meta-analyses, 16 cross-sectional studies, 8 longitudinal studies, 2 experimental studies, 19 case reports, 5 letters to the editor, and 12 theoretical assessments), and 5 due to the non-specific presentation of outcomes. The remaining 24 publications – case-controlled observational studies reporting oral manifestations of CD – met all criteria for inclusion in meta-analysis. No unpublished relevant studies were selected.

The main characteristics of publications included in the systematic review are reported in Table 1. Most of them are case-controlled studies on pediatric populations reporting mainly DEDs as oral manifestations of CD [23-39]. The highest reported prevalence was 73.3% [24]. Particularly, some studies report specific subtypes of DEDs as opacities or enamel hypoplasia [26]. Other studies reported consequences of DEDs as dental caries, thus citing DMFT/S (dmft/s) scores [25,26,28,36,37,39]. Regarding the impact of CD on pediatric patients, two studies report DET as one of the main oral manifestations of the disease [33,39]. Moreover, only few studies report soft tissue manifestations, such as RAS in children [27,31,32,36-38]. When a diagnosis of RAS could not have been established, oral manifestations have been reported as aphthous ulcers [27,40]. The main oral manifestation in adults was the presence of RAS [40-43]. Nevertheless, DED was reported in aldults, as well [40,44,45]. Only one study designed mixed pediatric and adult subjects for both case and control groups [46].

Table 1. Main characteristics and findings of publications included in the systematic review

Authors, Year	Source	Population	Study group					Controls				
			n	DEDs (%)	RAS/AU (%)	DC (m.v.)	DET (%)	n	DEDs (%)	RAS (%)AU	DC (m.v.)	DET (%)
Bolguel et al., 2009 [23]	Turkiye Klinikleri J Med Sci 2009;29(3)	Pediatric	82	40.2	0	2.4*	-	110	7.2	0	6.9*	-
Ortega Paez et al., 2008 [24]	Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106(1)	Pediatric	30	73.3	-	-	-	40	23.3	-	-	-
Avsar et al., 2008 [25]	Turkish Journal of Pediatrics 2008;50(1)	Pediatric	64	42.2	-	3.6*	-	64	9.4	-	6.4*	-
Farmakis et al., 2005 [26]	Eur J Ped Dent 2005;3	Pediatric	19	47.3	-	0.13**	-	19	15.7	-	2.14**	-
Campisi et al., 2008 [27]	Dig Liver Dis 2008;40	Pediatric	269	-	22.7	-	-	575	-	7.1	-	-

Authors, Year	Source	Population	Study group					Controls				
			n	DEDs (%)	RAS/AU (%)	DC (m.v.)	DET (%)	n	DEDs (%)	RAS (%)AU	DC (m.v.)	DET (%)
Aydemir et al., 2004 [41]	Turk J Gastroenterol 2004;15(3)	Adult	41	-	4.8%	-	-	49	-	0	-	-
Priovolou et al., 2004 [28]	Eur J Pediatric Dent 2004;2	Pediatric	27	44.4	-	6.0**	-	27	11.1	-	11.5**	-
Rasmussen et al., 2001 [29]	Int J Ped Dent 2001;11	Pediatric	40	50.0	-	-	-	40	38.0	-	-	-
Shahraki et al., 2019 [30]	Iran J Pediatr 2019;29(1)	Pediatric	200	45	-	-	-	60	14	-	-	-
Bucci et al., 2006 [31]	Acta Pediatrica 2006;95	Pediatric	72	20	33	-	-	162	5.6	23.4	-	-
Campisi et al., 2007 [40]	Aliment Pharmacol Ther 2007;26	Adult	197	23	42	-	-	413	9	2	-	-
Cruz et al., 2018 [44]	Med Oral Patol Oral Cir Bucal 2018;23(6)	Adult	22	62.8	0	-	-	20	31.8	0	-	-
Amato et al., 2017 [45]	Nutrients 2017;9	Adult	49	32.6	-	-	-	51	5.9	-	-	-
Van Gils et al., 2017 [42]	Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2017;124(2)	Adult	740	-	35	-	-	270	-	23	-	-
Zoumpoulakis et al., 2019 [32]	J Clin Ped Dent 2019;43(4)	Pediatric	45	64.4	40	-	-	45	24.6	4.44	-	-
Aksit Bicak et al., 2018 [33]	Eur Oral Res 2018;52(3)	Pediatric	30	66.6	-	-	33.3	30	0	-	-	0
Dane et al., 2016 [34]	Eur J Ped Dent 2016;17(1)	Pediatric	35	54.3	31.4	-	-	35	20	0	-	-
Macho et al., 2019 [43]	J Int Oral Health 2019;11(6)	Adult	80	-	56.3	-	-	80	-	20	-	-
Cheng et al., 2010 [46]	J Clin Gastroenterol 2010;44(3)	Adult & Pediatric	67	57	-	-	-	69	30	-	-	-
Majorana et al., 2010 [35]	Int J Ped Dent 2010;20	Pediatric	250	46.4	-	-	-	125	5.6	-	-	-
Cantekin et al., 2015 [36]	Pak J Med Sci 2015;31(3)	Pediatric	25	48	44	3.25*	-	25	16	0	4.56*	-
De Carvalho et al., 2015 [37]	Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2015;119(6)	Pediatric	52	61.54	40.38	2.11*	-	52	21.15	17.31	3.9*	-
Acar et al., 2012 [38]	Med Princ Pract 2012;21	Pediatric	35	40	37.1	-	-	35	0	11.4	-	-
Costacurta et al., 2010 [39]	Oral & Implantology 2010;1	Pediatric	300	33	-	2.97*	20	300	11	-	1.74*	8

DEDs – dental enamel defects, RAS – recurrent aphthous stomatitis, AU – aphthous ulcers, DC, dental caries, m.v. – mean value, *DMFT(dmft), ** DMFS(dmfs), DET – delayed erruption of teeht, (-) – not specified

Given the results obtained, the risk of outcome and publication bias within the included publications was assessed. Publication bias control strategy has been presented within the methods section. An important source of outcome bias resides in the disparities in CD diagnosis protocols within the study groups, and subsequently in CD exclusion within the controls. Not all authors used the same criteria for CD diagnosis and exclusions. Minimizing such source of bias was facilitated by setting a twenty year time limit for the search (2000-2020). Before 2000, diagnosis of CD seems to have been even more non-homogenous. On the other hand, diagnosis of DEDs is not standardized, therefore lacking reproducibility and interoperator validation. Hence, we did not aim to present a detailed typology of DEDs but to consider them a group outcome. The same principle was also applied to RAS and AU, as there is no unanimously accepted definition of RAS. Given such additional outcome bias, the results of the review should be interpreted with caution.

4. DISCUSSION

The prevalence of CD has significantly increased over the past 50 years [20]. Nevertheless, most of the patients with CD remain undetected worldwide. Diagnosing-silent or non-classic CD is troublesome and challenging, because CD may present in extremely different ways. The pivotal place played by nutrients, shaping human physiology and pathology, not just only in the intestinal compartment, is increasingly appreciated. In fact, the nutritional effects are irradiated peripherally to remote organs, and even to the brain [15].

Malabsorption in CD, if present, results from damage to the small-bowel mucosa with loss of absorptive surface area, reduction of digestive enzymes (both luminal and also pancreatic enzymes) with consequent impaired absorption of micronutrients and fat-soluble vitamins, iron, vitamins D, B12, calcium and folic acid [5,6,20]. This may disrupt the process of amelogenesis and may enable the appearance of DED and hypoplasia, respectively. However, the true pathogenic pathway is still unknown [12]. Thus, our results show that oral lesions, such as DED or RAS, are more frequently identified among CD patients.

RAS is characterized by painful, recurrent, single or multiple ulcers of the oral mucosa, which are round or ovoid, and have an erythematous halo and a yellow or gray floor. It is one of the most common mouth diseases, affecting more than half of the population [14]. The exact cause of RAS is unknown, but stress, allergies, nutritional deficiencies, trauma, hormone imbalance or infectious agents have been incriminated.

The association of RAS with CD needs to be evaluated with caution, because a wide range of systemic or local conditions may be linked to this type of lesions. Ulcerations of the oral cavity can be similarly seen in cases of oral infections, immunodeficiency states and Crohn disease [11,12,23]. In most people, aphthous ulcers are benign and not associated with any underlying systemic condition. However, as CD is very common (although poorly recognized), it must remain part of the differential diagnosis in cases of aphthous ulcers and enamel defects [3,4,6,41,48].

Life-long strict adherence to a gluten-free diet is tough to maintain because, realistically, it is quite difficult to avoid exposure to small amounts of gluten, thus minute exposure to the ingested food might cause oral lesions [10].

Qualitative analysis of the case-controlled studies shows that DEDs, AUs and RAS are typical oral manifestations of CD in both children and adults. Such findings have been previously reported in similar reviews, but with a higher degree of bias, due to the inclusion of studies with multiple designs and variable reporting methodology [14]. Other reported conditions associated with CD include atrophic glossitis, oral lichen planus, oral lymphomas and periodontitis, all leading to feeding dificulties and aditional risk for malnutrition [14,15]. Furthermore, an important comorbidity of CD is xerostomia and Sjögren's syndrome, that have been incriminated as main cofactors in the development of DEDs [42,43].

Independently on their type, oral mucosal changes persist and can be diagnosed despite patient adherence to a gluten-free diet [17].

Therefore, an experimental study which used oral mucosa for immunological testing ebidenced the reaction to gliadin challenge, suggesting the same pattern for an abnormal immune response in CD patients, triggering oral manifestations [48]. Persistently increased infiltration of T cells into the oral mucosa even aflter a gluten-free diet may explain why oral manifestations tend to be refractory in treated CD patients [49]. However, adherence to a gluten-free diet has been reported to decrease the severity of oral soft tissue lesions [43].

To what extend such conditions should be regarded as extraintestinal manifestations of CD is still unknown. Similar oral findings have been also reported in patients with inflammatory bowel diseases [50]. Thus, as shown in a recent systematic review and meta-analysis, DEDs seem to be the only oral manifestations signifficantly associated to CD [13]. However, another relatively recent meta-analysis of controlled studies reports signifficant association with CD for both DEDs and RAS [12]. As both cited studies conclude, the presence of DEDs and/or RAS, especially in pediatric populations, should be a clear indication for further diagnostic exams and follow-up for high suspicion for CD [12,13].

5. CONCLUSIONS

The mouth is considered to be the entry hallway to the gut. Physicians need to examine the oral cavity of patients as part of the physical examination, but they seldom assess the teeth. Also, they may not be trained to recognize dental abnormalities. Increasing awareness among physicians is the key to quickly and accurately diagnose patients at risk for CD. A multidisciplinary approach is warranted, and family dentists and dental hygienists can play an important role in identifying patients who should be further evaluated for CD.

However, there is currently insufficient evidence to recommend routine screening for CD among patients with RAS or DED. Recurrent oral ulcerations can be a sign of CD and, as such, long-term studies are required in representative populations. More studies with low risk bias are needed to estimate with higher precision the relationship among CD, aphthous stomatitis and enamel defects in children and, more importantly, in adults.

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