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Diagnosing celiac disease in children using oral manifestations

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Abstract

Purpose Celiac disease (CD) may be frequently undiagnosed due to the absence of characteristic gastroenterologic symptoms in many CD patients. Our objective was to diagnose CD by utilizing documented oral manifestations such as Recurrent Aphthous Stomatitis (RAS) and Molar-Incisor Hypomineralization (MIH).

Methods The study comprised sixty children who presented with complaints of RAS lesions. The MIH group consisted of 40 children, while the control group comprised 20 children without MIH lesions, ranging in age from 7 to 13 years. After the dental examination, all children were given a questionnaire to assess whether they had any previous history of general symptoms related to CD. Following that, diagnostic testing for celiac disease were conducted, including serological tests such as Tissue transglutaminase IgA (tTG-IgA), Endomysium Antibody (EMA), and Total IgA, as well as genetic tests for HLA-DQ2 and HLA-DQ8.

Results The statistical analysis, conducted using Fisher's Exact, Yates' Continuity Correction, Fisher Freeman Halton, and Student's t tests, revealed no significant differences between the groups ($p < 0.05$). Within the MIH group, 3 children exhibited border tTG-IgA values, while another 3 had positive tTG-IgA results. Two of these 6 children had also positive EMA and HLA results. Following a biopsy procedure, these two children were ultimately diagnosed with celiac disease (CD).

Conclusions In this study, while children initially presented to the clinic with complaints of recurrent aphthous stomatitis (RAS), 2 children (5% of the MIH group) were diagnosed with CD shortly after the onset of MIH lesions. CD enhanced the likelihood of observing some oral manifestations particularly recurrent aphtous stomatitis and developmental enamel defects. We recommend that dentists be cautious about diagnosing CD when RAS lesions and DEDs and/or MIH lesions are present, whether or not other indications of this systemic disease exist.

Keywords Celiac disease, Children, Developmental enamel defects, Molar incisor hypomineralization

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Background

Celiac Disease (CD) is an enteropathy that affects genetically sensitive people. It develops following gluten intake, which causes an autoimmune condition due to the existence of autoantibodies. This causes histopathologic harm in the small bowel mucosa, including crypt hyperplasia, villous atrophy, and an inflammatory infiltration in the neighboring connective tissue. Celiac disease is characterized by a wide range of gastrointestinal and/or extraintestinal symptoms including diarrhea/constipation, abdominal pain, vomiting, weight loss, fatigue, delayed puberty, dermatitis, iron deficiency anemia, dental enamel defects, recurrent aphtous stomatitis [1, 2]. However, CD can often go undiagnosed because many CD patients have no classic gastroenterologic symptoms and may be completely asymptomatic. Additionally, the risk of developing other autoimmune diseases was found 3 to 10 times higher in CD patients than the general population [2, 3]. This emphasizes the significance of a multidisciplinary approach to early diagnosis of CD, particularly for patients/children who exhibit/describe none of the gastroenterologic CD signs and symptoms.

Some publications suggest that oral symptoms in celiac patients may provide diagnostic clues for difficult-to-identify celiac types [4, 5]. With respect to oral soft lesions, it has been suggested that CD patients are likely to suffer from Recurrent Apthous Stomatitis (RAS) compared with healthy controls, especially before the gluten-free diet [6]. The prevalence of RAS in CD varies significantly between studies [7, 8]. A 2015 study comparing 35 CD children to 25 controls revealed a 44% prevalence [9]. In another investigation, the prevalence of RAS in CD children was similar to the literature, at around 50% [1].

CD has also been explored as the cause of developmental enamel defects (DEDs), which can be quantitative or qualitative [10, 11]. DED can be characterized as either enamel hypoplasia or hypomineralization. Enamel hypoplasia is caused by a disruption in ameloblast function during the secretory stage of enamel production, whereas hypomineralisation is caused by a disruption in the maturation stage. CD can be linked to these enamel lesions via hypocalcemia caused by malabsorption during enamel formation and/or gluten-induced immunological response during enamel formation.

To our knowledge, the existence of DEDs has been studied as an indicator for CD patients since the early 1900s, but Molar-Incisor Hypomineralization (MIH) lesions, which are clinically comparable to DEDs, have not been evaluated to diagnose CD patients [10, 12]. In recent years, Elbek-Cubukcu et al. discovered a positive link between the duration of celiac disease and the severity of MIH lesions, implying that there was an inverse relationship between the duration of celiac diagnosis and the presence of MIH [13].

Weerheijm et al. (2001) introduced Molar Incisor Hypomineralization known as MIH [14]. MIH, defined by discolored areas or patches of porous dental enamel ("demarcated opacities") in one or more permanent first molars (PFM), can also occur in the incisors and primary molars. These children are at great risk for toothache and extremely quick decay, which frequently necessitates costly management (e.g., continuous restorations, extractions, and orthodontics). Recent research has highlighted the impact of MIH on children's quality of life, emphasizing the importance of early detection, assessment, and intervention [15, 16].

Causation and pathogenesis of MIH remain unknown, with research focusing on a variety of environmental factors acting systemically, including genetic, prenatal (maternal illness or infection, nutrition, etc.), perinatal (infant hypoxia, low birth weight, calcium deficiency, etc.), and postnatal conditions (dioxins and polychlorinated bisphenols, otitis media, fevers, antibiotics, etc.) that may affect the developing enamel [17].

The objective of this study was to diagnose CD by utilizing documented oral manifestations such as Recurrent Aphthous Stomatitis (RAS) and Molar-Incisor Hypomineralization (MIH). Because previous research collected data on RAS solely through a questionnaire filled by the children's parents, which may have reduced the dependability of the results [18], to gain a better understanding of the importance of oral symptoms in identifying CD, we sought to examine CD in children who presented to our dental clinic with a RAS complaint.

Methods

The Ethics Committee of Bezmialem Vakif University authorized the research procedure (procedure number 71306642-050.01.04). Written informed consent to participate was obtained from both the children and their parents who applied with RAS concerns to the Department of Pediatric Dentistry Clinic between January 2020 and January 2021.

To include in the study, the inclusion and exclusion criteria of children were given in Table 1.

Experimental design

The included 60 children were separated into two subgroups following their oral examinations:

During the oral examination; the DMFT; decayed-missed-filled teeth values were recorded and MIH lesions were diagnosed by two pediatric dentists.

1) MIH group; children with MIH lesions
2) Control group; children without MIH lesions

Table 1 The inclusion and exclusion criteria

Inclusion criteria:
1) Children diagnosed with an acute apthous lesion and a history of RAS in terms of the number of recurrences,
2) Children aged 7 to13 years old,
3) Children who are healthy,
4) Children who do not follow a special diet for nutrition,
5) Children who volunteered and collaborated.
Exclusion criteria:
1) Children who indicated injection phobia during blood collection so as not to generate anxiety,
2) Children who have taken any drugs in the last three months.

Table 2 The structured questionnaire for testing CD with signs and symptoms

	Yes	No
1- Has any of your first degree relatives diagnosed with CD?		
2- Has your child had ever diagnosed any of the following medical conditions?		
recurrent aphthous stomatitis		
chronic iron-deficiency anaemia		
arthritis/arthralgia		
decreased bone mineralization (osteopenia/ osteoporosis)		
dermatitis herpetiformis		
chronic fatigue		
abnormal liver biochemistry		
weight loss/failure-to-thrive/ delayed puberty		
recurrent nausea and/or vomiting		
chronic diarrhea/ constipation /abdominal pain		
3- Has your child had any of the following clinical conditions in the last 2 weeks?		
abdominal pain		
diarrhea		
constipation		
nausea/vomiting		
distended abdomen		

The diagnostic criteria and clinical appearance of MIH lesions were agreed upon by the 'European Academy of Paediatric Dentistry (EAPD) Clinical Practice Guidance for practitioners dealing with children presenting with Molar-Incisor-Hypomineralization (MIH)' (Weerheijm, 2003). According to the MIH severity rating system (MIH-SSS), the study group includes Codes 1–6. The codes were: code 0, no enamel opacity; code 1, the presence of white/creamy enamel opacity without post-eruptive breakdown (PEB); code 2, the presence of yellow/brown opacity without PEB; code 3, PEB restricted to the enamel with white/creamy opacity; code 4, PEB restricted to the enamel with yellow/brown opacity; code 5, PEB exposing dentin (hard when probed); code 6, PEB exposing dentin (soft when probed); code 7, atypical restoration without marginal defect; code 8, atypical restoration with marginal defect; and code 9, tooth extracted due to MIH [19]. To assess the repeatability of diagnosing MIH lesions, two pediatric dentists examined all children again one week later. The intraclass correlation coefficient (ICC) was used to assess the agreement between the first and second examinations. Furthermore, the oral examinations in ten cases were repeated by each of two pediatric dentists to assess inter-rater reliability.

Subsequent to oral examination; all parents were asked to complete a structured questionnaire on behalf of their children, which assesses the presence any medical history of general manifestations of 'CD' described by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [20] (The questionnaire were presented in Table 2).

Finally, the blood samples were taken from all children to conduct;

1) The serology tests; which are total immunglobulin A (Total IgA) by using spectrophotometric method, tissue transglutaminase IgA (tTG-IgA) by using Enzyme-linked immunosorbent assay (ELISA), anti-endomysium antibody IgA (EMA-IgA) by using indirect fluorescence assay (IFA).
2) Genetic analysis of human leukocyte antigens; including HLA-DQ2 and HLA-DQ8 was performed using a Celiac real-time PCR kit (Real-time Polymerase Chain Reaction kit, SNP Biotecnology R&D Ltd., Ankara, Turkey).

Statistical analysis

Statistical analysis was carried out with SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented as the mean, standard deviation (SD), and/or median. Fisher's Exact test, Yates Continuity Correction test, Fisher Freeman Halton test, and Student's t test were employed to determine significant differences between the study and control groups. A p-value of <0.05 indicated statistical significance.

Kappa statistics were used to measure interexaminer reliability on ten independent cases from the sample. Interexaminer reliability Kappa scores and intraclass correlation coefficients were both 1, indicating complete agreement between two pediatric dentists.

Results

The study included 60 children; the control group had 20 children without MIH lesions and the MIH group had 20 children. Sandstrom et al. were studied the hypothetical screening strategies in 12-year old Swedish Celiac children to evaluate a serological screening strategy based on determination of serum IgA, tTG-IgA, tTG-IgG, EMA and HLA risk allles [21]. Based on this sstudy, to detect a significant difference, the minimum subject size should be at least 9, given type I error (alpha) of 0.05, power

Table 3 Demographic data and DMFT values of the groups

		MIH group	Control group
Age (mean ± SD)		8.2 ± 1.28	9.4 ± 1.31
Gender (n%)	Female	26 (65%)	10 (50%)
	Male	14 (35%)	10 (50%)
DMFT mean ± SD (median)		3.35 ± 1.07 (4)	3.35 ± 1.78 (4)

Yates Continuity Correction test ($p<0.05$)

Table 4 The intensity and distribution of MIH lesions

36 children had MIH lesions on both PFMs and permanent incisors

4 children had MIH lesions only on PFMs.

33 children had all four PFMs affected simultaneously.

According to MIH severity scoring system (MIH-SSS) [19]; 22 children had Code 6 MIH lesions, 12 children had Code 3–5 and 6 children had Code 1,2.

Table 5 Serological and genetic test results of groups

		MIH group	Control group	*p*
Total IgA (mg/dL) (mean ± SD)		113.3 ± 47.5	111.1 ± 28.2	[1]0.848
		n (%)	n (%)	
tTG IgA (IU/mL)	Negative	34 (85%)	20 (100%)	[2]0.327
	Border	3 (7.5%)	0	
	Positive	3 (7.5%)	0	
EMA IgA (titer)	Negative	38 (95%)	20 (100%)	[2]0.548
	Positive	2 (5%)	0	
HLA-DQ2	Negative	17 (42.5%)	7 (35%)	[3]0.780
	Positive	23 (57.5%)	13 (65%)	
HLA-DQ8	Negative	9 (22.5%)	5 (25%)	[4]1.000
	Positive	31 (77.5%)	15 (75%)	

[1]Student's t test. [2]Fisher Freeman Halton test. [3]Yates Continuity Correction test. [4]Fisher's Exact test

($p>0.05$)

The reference values of serological tests which are as follows;

• Total IgA (mg/dL): 21–282 mg/dL

• tTG IgA (IU/mL): negative < 12, border = 12–18, positve > 18

• EMA IgA (titer): negative < 1:10

(1-beta) of 0.8, effect size of 2.79, and two-sided alternative hypothesis (H1).

Table 3 shows the demographic data and DMFT levels for each group. All children had all four permanent first molars fully erupted, which is required to diagnose MIH. The average age was 8.2±1.28 in the MIH group and 9.4±1.31 in the control group. The gender distribution did not differ significantly between the MIH and control groups ($p=0.402$), and both groups had homogeneous DMFT values (Table 3).

The intensity and distribution of MIH lesions in the MIH group were given in Table 4.

The data obtained from the questionnaire were not statistically analyzed, as all responses to the first and second questions were 'no'. For the third question, the responses indicated 1 case of diarrhea and 1 case of constipation with abdominal pain in the control group.

Table 6 The serological and genetic test results of children suspected with CD

Suspected subjects	Total IgA (mg/dL)	tTG-IgA (IU/mL)	EMA-IgA (titer)	HLA-DQ2	HLA-DQ8
Child 1	246	Border	Negative	Positive	Positive
Child 2	247	Border	Negative	Positive	Negative
Child 3	98	Border	Negative	Negative	Positive
Child 4	**137**	**Positive**	**Positive**	**Positive**	**Positive**
Child 5	**114**	**Positive**	**Positive**	**Positive**	**Positive**
Child 6	144	Positive	Negative	Positive	Positive

mg/dL; milligrams (mg) per deciliter (dL). IU/mL; International Units Per Milliliter

The serologic and genetic test findings are shown in Table 5. There was no significant difference between the groups. Because the current guidelines advocate the tTG-IgA antibody as the most cost-effective and reliable test for identifying CD patients [22–24], we invited our 6 children with borderline (n:3) or positive (n:3) tTG-IgA results to a clinical follow-up with their pediatrician.

The pediatrician instructed these 6 children to repeat tTG-IgA and EMA-IgA assays to confirm the earlier results and the second results were given in Table 6. Two of these 6 children (Child 4 and Child 5 in Table 6) who met the serologic criteria to diagnosis CD underwent small intestine biopsy and both of them were eventually identified as Type 3b in Marsh–Oberhuber classification of CD.

Discussion

In the light of the 50% prevalance of DED in the CD population, dentists can play an important role in the diagnosis of CD [7]. CD-related DEDs are most commonly affect the incisors and molars, followed by the canines and premolars [4]. It should be noted, however, that the incisors and molars are also the impacted teeth in MIH cases. This distribution likely correlates with the chronology of permanent tooth formation, as the calcification of incisors and first molars begins around the same time, between the ages of 0 and 3 years. In CD patients, these early years are generally spent without a specific CD diagnosis, which could explain why the teeth are predominantly damaged. Symptoms usually occur in children after ingestion of gluten containing grains between 4 and 24 months, but there may be a delay or latent period between gluten intake and the onset of symptoms which masks the diagnose CD [25].

The clinical appearance of enamel abnormalities on MIH is quite similar to DED lesions found in CD patients. Notably, DEDs specific to CD are typically symmetrical and present in all four quadrants [23. 31. 32]. Our findings revealed that a total of 40 children had MIH lesions with 33 of them having all 4 molars affected simultaneously. Among these, two children who were later diagnosed with CD after biopsy also had all 4 molars affected.

These findings suggest that MIH lesions can be studied further using CD diagnostic testing. This is particularly important because CD can go undiagnosed, and early diagnosis is crucial to prevent the long-term complications of the disease such as osteopenia, infertility, hyposplenism, refractory celiac disease, intestinal lymphoma, small bowel adenocarcinoma, and ulcerative jejunoileitis [2].

Classical symptoms of CD have been reported to include failure to thrive, weight loss, and chronic diarrhea caused by malabsorption. Additionally, studies have shown that the chronic constipation prevalence which is a common problem in childhood is three times higher in children with CD than in the general population [26]. Nevertheless, many CD patients do not exhibit these classic gastrointestinal symptoms and may be completely asymptomatic, as was observed in our study results.

Gastrointestinal and extra-intestinal symptoms are clinical manifestations of CD. Additionally, some celiac associated disease have also been reported in literature. Because we included only healthy children to our study, the questionnaire does not include a question asking any of the high risk specific conditions for CD, such as type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, William's-Beuren syndrome, immunoglobulin (Ig)A deficiency [2]. We also excluded the children who have a specific nutritional diets. This exclusion was necessary because, before performing a serological test for CD, it should be advised to patients should take gluten-containing foods for 2–8 weeks before serological tests [27]. Otherwise, the serological tests may yield negative results, complicating the diagnosis of CD.

CD laboratory serum indicators are detected using antibodies (AGA) and anti-endomysial (EMA) antibodies, which have been available since the early 1980s. Today, Enzyme-linked immunosorbent assay (ELISA) testing of IgA antibodies directed against the CD autoantigen tTG are most typically and highly suggestive in pediatric populations [28]. The tTG test was created in the 1990s, and its sensitivity and specificity were shown to be similar to EMA [24]. Our findings support the notion that positive tTG-IgA results, when combined with positive EMA-IgA results (Child 4 and Child 5 in Table 6), provide a robust and reliable approach for detecting CD. In several studies, positive results for these serological tests (tTG-IgA and EMA-IgA) have been considered sufficient to diagnose CD [29–31]. For many years, an intestinal biopsy was accepted as the gold standard for diagnosing CD. In our study, two children who had both positive autoantibodies to tTG and EMA IgA with positive CD-associated HLA-DQ haplotypes, were sent to a biopsy and were subsequently diagnosed with CD for the first time in their lives.

However, recent guidelines from the ESPGHAN recommend a no-biopsy approach if very high TGA-IgA titres and EMA-IgA positivity are found with positive HLA-DQ2 and DQ8 results. In such cases, the decision to perform biopsies should involve a shared decision making process between the paediatric gastroenterologist or CD specialist, the parents, and, if appropriate, the child [20].

While testing for polymorphisms within HLA-DQ2/DQ8 locus for CD diagnosis [32] has been suggested in previous literature [24, 33], it is now understood that a negative result for HLA-DQ2 and/or -DQ8 indicates a very low risk of CD, while a positive result does not confirm the diagnosis [20]. Therefore, HLA-testing is not required in patients with positive TGA-IgA, if they meet the criteria for CD diagnosis with biopsies or have high serum TGA-IgA and EMA-IgA positivity.

In our study, we performed HLA testing, and the two children diagnosed with CD showed positive results. However, HLA typing is not universally available and can be quite costly in many countries. Since it does not add to the certainty of the diagnosis, the suggestion is that HLA testing should be omitted, if it does not improve the accuracy of a no-biopsy diagnosis.

The study observed that children with recurrent aphthous stomatitis (RAS) visited the clinic, and two of the children (5% of the MIH group) were later diagnosed with celiac disease (CD) following the appearance of molar incisor hypomineralization (MIH) lesions. The findings suggest that while the sample size is small, it points to a potential connection between oral manifestations and systemic diseases like CD. The study emphasizes the critical role of dentists in recognizing these oral signs and the need for larger, long-term studies to validate these observations and address the study's limitations.

Conclusions

The study highlights the importance of a multidisciplinary approach to diagnosing celiac disease (CD), especially in patients who may not display typical signs and symptoms of the condition. It underscores the role that dentists can play in detecting CD through oral manifestations such as recurrent aphthous stomatitis (RAS) and developmental enamel defects (DED), including molar incisor hypomineralization (MIH). The findings suggest that dentists should be vigilant when examining patients with these oral conditions, as they could be indicators of a systemic disease like CD. Ultimately, thorough dental examinations can help identify oral lesions that may reflect underlying health issues.

Abbreviations

CD	Celiac Disease
DED	Developmental enamel defects
DMFT	Decayed-missed-filled teeth

EAPD	European Academy of Paediatric Dentistry
ELISA	Enzyme-linked immunosorbent assay
EMA	Endomysium Antibody
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
ICC	Intraclass correlation coefficient
IU/mL	International Units Per Milliliter
mg/dL	Milligrams (mg) per deciliter (dL)
MIH	Molar Incisor Hypomineralization
PEB	Post-eruptive breakdown
PFM	Permanent first molar
tTG-IgA	Tissue transglutaminase IgA

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Author contributions
MB, ADD and AVC designed the research study. AVC performed the research. ADD provided help and advice on analysis. MB, ADD and AVC analyzed the data. MB wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research protocol was approved by the Ethics Committee of Bezmialem Vakif University (Protocol number; 71306642-050.01.04). Written informed consent to participate was obtained from both the children and their parents (all parents of participing children who were under 16).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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