Journal of Dental Applications

Open Access

Austin Publishing Group

Special Article - Celiac Diseases

Celiac Disease in Dentistry

Nasr IH[1], Nasr IH[2], Al Wahshi HA[3] and Nasr IH[4]*

[1]Department of Immunology and Allergy, Royal Hospital, Oman

[2]Department of Orthodontics, Princess Royal Hospital, UK

[3]Department of Rheumatology, Royal Hospital, Oman

[4]Department of Gastroenterology, Guy's and St Thomas' Hospital, NHS Trust, London, UK

***Corresponding author:** Nasr IH, Department of Gastroenterology, Guy's and St Thomas' Hospital, NHS Trust, 1st Floor North Wing, College House, Westminister Bridge Road, London, UK

Received: December 25, 2017; **Accepted:** January 18, 2018; **Published:** January 25, 2018

Abstract

Celiac disease (CD), also known as gluten sensitive enteropathy, is a chronic, systemic, autoimmune disorder that leads to mucosal inflammation, villous atrophy and crypt hyperplasia in genetically predisposed individuals on exposure to dietary gluten present in certain grains such as wheat, barely and rye. Patients with celiac disease usually present with gastrointestinal manifestations in addition to complications as a result of nutrient malabsorption such as Calcium, iron fat soluble vitamins and minerals leading to osteoporosis, anemia, dental enema defects and aphthous ulcers. The gold standard for diagnosing celiac disease is small bowel biopsy. Serologic tests are used to screen for celiac disease. Celiac disease is associated with significant morbidity and mortality if left untreated. The condition is potentially reversible once gluten has been excluded from the diet.

In this article, we describe the nature of the disease, its pathogenesis, diagnosis, and clinical manifestations with emphasis on the dental manifestations and update on treatment including novel treatments.

Keywords: Celiac disease; Autoimmune; Gluten; Enamel; Aphtous ulcers

Abbreviations

CD: Celiac Disease; HLA: Human Leukocyte Antigen; EMA: Endomysial Antibodies; IgA: Immunoglobulin A; a-TTG: Anti-Tissue Transglutaminase; IgG: Immunoglobulin G; PEP: Prolyl Endopeptidases; ZOT: Zonula Occludens Toxin; EATL: Enteropathy-Associated T Cell Lymphoma

Introduction

Celiac disease is one of the rare chronic immune mediated disorders that results from the ingestion of gluten proteins found in certain grains such as wheat, barley, and rye and triggers an autoimmune response resulting in villous atrophy as well as injury to the skin, liver, joints, uterus, and other organs leading to complications such as malabsorption. It is estimated to occur in 1% of the population, however, this figure is likely to be an under estimate of the true incidence [1]. Previously, the condition was identified in individuals with malabsorption or failure to thrive. Nowadays, with the availability of serological testing, many people are diagnosed with non-classical or evenno symptoms. It is likely that the many of CD cases remain undiagnosed in the community [2,3].

Pathogenesis

CD is strongly associated with human leukocyte antigen (HLA) class II gene (DR3, DR5/ DR7 or DR4) known as HLA-DQ2 and HLA DQ8 located on chromosome 6p21. Homozygosity for HLA DQ2 has been associated with an increased risk for celiac disease and enteropathy-associated T-cell lymphoma [4].

Clinical Manifestations

Clinical symptoms can be diverse and vague (similar to irritable bowel syndrome), they may present with depression, osteoporosis, short stature, neuropathy, ataxia) but common presentations include iron deficiency anaemia and fatigue. Oral and dental manifestations in CD include enamel defects, recurrent aphtous ulcers, delayed eruption, cheilosis, oral lichen planus and atrophic glossitis [5,6] (Table 1).

In a study by Aine et al it was found that 69% of the permanent teeth in adults with CD were defected, while in clinical controls only 19% were defected. In addition, adults with CD the enamel defects were symmetrically and chronologically distributed in all four sections of dentition in contrast to those in controls [6]. Dental enamel defects in CD are further classified according to Aine et al into 4 grades:

Grade 1: Defects in color of enamel (Single or multiple cream, yellow or brown opacities.

Grade 2: Slight structural defects: rough enamel surface with horizontal grooves or shallow pits.

Grade 3: Evident structural defects: deep horizontal grooves which vary in width or have large vertical pits. Large opacities of different colors or strong discoloration may be in combination.

Grade 4: Severe structural defects: The shape of the tooth is changed.

Although immune-mediated damage is suspected to be the primary cause, Nutritional deficiencies such as hypocalcemia, may play a role [7-9].

Stimulation of naïve lymphocytes by gluten in the oral cavity has been hypothesized as a cause [8].

Diagnosis

Laboratory investigations may reveal iron deficiency, hypocalcaemia, low folate and less commonly vitamin B12 deficiency. Serology should be used first line in suspected cases using specific endomysial antibodies (EMA), IgA (immunoglobulin A) anti-tissue

Citation: Nasr IH, Nasr IH, Al Wahshi HA and Nasr IH. Celiac Disease in Dentistry. J Dent App. 2018; 5(1): 396-398.

Table 1: Clinical manifestations of celiac disease.

Gastrointestinal	Diarrhoea, flatulence, abdominal cramps, nutrient deficiency, weight loss, abnormal liver enzymes. Rare: ulcerative jejunitis, enteropathy-associated T-cell lymphoma (EATL).
Haematological	Anaemia (iron or folate less common B12), hyposplenism, bleeding disorders.
Musculoskeletal	Osteopenia and osteoporosis, stunted growth in children, vitamin D deficiency and hypocalcaemia.
Skin	Dermatitis herpetiformis (blistering intensely itchy rash on extensor surfaces.
Neurological	Muscle weakness, paraesthesia and ataxia Seizures (may occur secondary to cerebral calcification).
Hormonal	Amenorrhoea, infertility
Oral and Dental	Enamel defects, recurrent aphtous ulcers, delayed eruption, cheilosis, oral lichen planus and atrophic glossitis.

Table 2: Marsh criteria.

Marsh classification	Intraepithelial lymphocytes (IEL) > 30	Crypts	Villi
Marsh 0	Normal	Normal	Normal
Marsh 1	Increased	Normal	Normal
Marsh 2	Increased	Hyperplasia	Normal
Marsh 3	Increased	Hyperplasia	Villous atrophy: • Mild • Subtota • Total
Marsh 4	Total mucosal hypoplasia (rare)		

transglutaminase (a-TTG). False negatives can occur in IgA tests because 2% of the coeliac population is IgA deficient. In this case IgG (Immunoglobulin G) anti-tissue transglutaminase is performed. More frequently false negatives occur if the patient has already started a gluten free diet. In vague cases where serology is normal but CD is highly suspected such as the presence of villous atrophy, HLA DQ2 and DQ8 haplotypingmay be of benefit.

Histology remains the gold standard for diagnosing and assessing tissue damage in CD where at least 4 duodenal biopsies should be taken to increase the diagnostic yield. The findings can be classified histologically based on the modified Marsh criteria [10] (Table 2).

Treatment

The current accepted treatment for the management of celiac disease is lifelong adherence to a diet devoid of gluten. However, there is a tendency towards poor dietary compliance in individuals suffering from CD. As a result, and with the insight into the pathogenesis this has led to the development of new diagnostics and encouraged research into novel treatments. Therapies can be divided according to target location as intraluminal, epithelial, or subepithelial action.

Novel Therapy

Intraluminal therapies

This involves reducing gluten immunogenicity or sequestering gluten to prevent its uptake across the intestinal epithelium. The former can be achieved by using wheat strains with a decreased number of T-cell epitopes such as hexaploid Triticumvariant [11]. Pretreatment of sourdough with certain lactobacilli has been shown to decrease the toxicity of wheat through praline/glutamine-rich gluten peptides proteolysis [12]. Incubating gliadin with TTG and lysine methyl ester leads to formation of lysine-modified gliadins with a loss of affinity to bind to HLA-DQ2. Oral enzyme therapy has been examined. Gluten detoxifications with oral enzyme therapy using prolyl endopeptidases (PEP) from Aspergillus niger, an active at acidic pH, can inactivate immunodominant gluten epitopes. Other PEPs have also been tested. However, it has been reported that PEP requires 3 hours incubation with the protein which indicates that the ingestion of PEP may not avoid the immune response to gluten [13].

Probiotics orally ingested IgG is highly resistant to gastric acidity, and roughly 50% of neutralizing activity survives when reaching the terminal ileum [14].

Epithelial

Inhibition of intestinal permeability is another novel approach for treating CD. Zonula occludens toxin (ZOT) receptor antagonist larazotide (AT1001) in clinical trials was able to block the ZOT/zonulin receptor and maintains the integrity of tight junctions [15].

Subepithelial

This is by dampening of the adaptive immune system using TTG inhibitors. By inhibiting gliadin peptide de-amidation, the binding to HLA is disrupted preventing T-cell activation [16]. An alternative method is by blocking DQ2 directly. Immune modulators are promising especially in RCD and enteropathy- associated T cell lymphoma (EATL).Biologics such anti-IL-15-antibodies have been tested in patients with rheumatoid arthritis. This provides a promising outlook on improving treatment for CD and especially for refractory celiac disease type 2 which has a 5-year mortality rate of 50%, and EATL but it has not been clinically tested [17].

Autologous bone marrow transplantation can induce remission in patients with EATL. Residual cells in the transplant may induce relapses [18]. Another novel treatment is the infusion of mesenchymal stem cells [19]. These cells differentiate into osteoblasts, adipocytes, and chondrocytes. They have low immunogenicity as they lack HLA class I or II. Clinical studies on this treatment method are required.

Conclusion

In summary, Celiac disease is a chronic, systemic, autoimmune disorder that leads to mucosal inflammation, villous atrophy and crypt hyperplasia in genetically predisposed individuals on exposure

to dietary gluten present in certain grains. It can lead to nutrient malabsorption leading to complications such as osteoporosis, anemia, dental enema defects and aphtous ulcers.

Dental enamel defects in CD are further classified according to Aine et al into 4 grades depending on the degree of enamel defect.

Celiac disease is associated with significant morbidity and mortality if left untreated. The condition is reversible once gluten has been excluded from the diet and therefore, prompt recognition of this disease by the dentist can potentially lead to earlier treatment preventing complications and mortality if left untreated.

References

1. Lionetti E, Gatti S, Pulvirenti A, Catassi C. Celiac disease from a global perspective. Best Pract Res Clin Gastroenterol. 2015; 29: 365-379.
2. Ferguson A. The Coeliac Iceberg. CME J Gastroenterol Hepatol Nutr. 1999; 2: 52-56.
3. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the Presentation of Celiac Disease. Am J Med. 2006; 119: 355.e9-14.
4. Al-Toma A, Goerres MS, Meijer JW, Peña AS, Crusius JB, Mulder CJ. Human leukocyte antigen-DQ2 homozygosity and the development of refractory celiac disease and enteropathy-associated T-cell lymphoma. Clin Gastroenterol Hepatol. 2006; 4: 315-319.
5. Aine L, Mäki M, Collin P, Keyriläinen O. Dental enamel defects in celiac disease. J Oral Pathol Med. 1990; 19: 241-245.
6. Rashid M, Zarkadas M, Anca A, Limeback H. Oral manifestations of celiac disease: a clinical guide for dentists. J Can Dent Assoc. 2011; 77: b39.
7. Pastore L, Carroccio A, Compilato D, Panzarella V, Serpico R, Lo Muzio L. Oral manifestations of celiac disease. J Clin Gastroenterol. 2008; 42: 224-232.
8. Pastore L, Campisi G, Compilato D, Lo Muzio L. Orally based diagnosis of celiac disease: current perspectives. J Dent Res. 2008; 87: 1100-1107.
9. Fraser D, Nikiforuk G. The etiology of enamel hypoplasia in children-a unifying concept. J Int Assoc Dent Child. 1982; 13: 1-11.
10. Corazza GR, Villanacci V, Zambelli C, Milione M, Luinetti O, Vindigni C, et al. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol. 2007; 5: 838-843.
11. Molberg O, Uhlen AK, Jensen T, Flaete NS, Fleckenstein B, Arentz-Hansen H, et al. Mapping of gluten T-cell epitopes in the bread wheat ancestors: implications for celiac disease. Gastroenterology. 2005; 128: 393-401.
12. Di Cagno R, De Angelis M, Lavermicocca P, De Vincenzi M, Giovannini C, Faccia M, et al. Proteolysis by sourdough lactic acid bacteria: effects on wheat flour protein fractions and gliadin peptides involved in human cereal intolerance. Appl Environ Microbiol. 2002; 68: 623-633.
13. Matysiak-Budnik T, Candalh C, Cellier C, Dugave C, Namane A, Vidal-Martinez T, et al. Limited efficiency of prolyl-endopeptidase in the detoxification of gliadin peptides in celiac disease. Gastroenterology. 2005; 129: 786-796.
14. Warny M, Fatimi A, Bostwick EF, Laine DC, Lebel F, LaMont JT, et al. Bovine immunoglobulin concentrate-clostridium difficile retains C difficile toxin neutralising activity after passage through the human stomach and small intestine. Gut. 1999; 44: 212-217.
15. Leffler DA, Kelly CP, Green PH, Fedorak RN, DiMarino A, Perrow W, et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology. 2015; 148: 1311-1319.
16. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. Gastroenterology. 2009; 137: 1912- 1933.
17. Abadie V, Jabri B. IL-15: a central regulator of celiac disease immunopathology. Immunol Rev. 2014; 260: 221-234.
18. Al-toma A, Nijeboer P, Bouma G, Visser O, Mulder CJ. Hematopoietic stem cell transplantation for non-malignant gastrointestinal diseases. World J Gastroenterol. 2014; 20: 17368-17375.
19. Ciccocioppo R, Cangemi GC, Roselli EA, Kruzliak P. Are stem cells a potential therapeutic tool in coeliac disease? Cell Mol Life Sci. 2015; 72: 1317-1329.

Citation: Nasr IH, Nasr IH, Al Wahshi HA and Nasr IH. Celiac Disease in Dentistry. J Dent App. 2018; 5(1):