REVIEW ARTICLE

CELIAC DISEASE IN ADULTS

Shahid Jamal, Rida Iftikhar

Army Medical College / National University of Medical Sciences (NUMS) Rawalpindi, Pakistan

INTRODUCTION

Celiac disease is the most important cause of malabsorption. Other conditions include tropical sprue, Whipple's disease and giardiasis[1]. Celiac disease is caused by intolerance to storage protein gluten which is found in wheat, barley and rice. Initially it was considered to be pediatric disease but according to some studies, it is now being diagnosed more commonly in adults and elderly population[2]. It is defined as an exaggerated immune response to ingested gluten seen in genetically susceptible individuals[1]. It roughly affects nearly 1% of world's population but according to new studies its incidence is increasing in different geographical areas partly owing to better diagnostic tools and public awareness[3]. It is associated with large variety of autoimmune diseases. This correlation is seen more in adult population.

Presenting complaints are anemia, chronic diarrhea, bloating, flatulence, abdominal pain and altered bowel habits. Non gastrointestinal symptoms include short stature, abnormal liver function, metabolic bone disease, arthritis and infertility[3]. According to a study, latent form of celiac disease may affect both central and peripheral nervous system as well[4]. This latent form is more prevalent than previously thought and has shown some association with atopy[5].

Pathogenetic mechanism involves injury to the small intestinal mucosa with decreased absorptive surface area, reduction of digestive enzymes resulting in impaired absorption of micronutrients such as fat-soluble vitamins, B 12, iron and folic acid[6]. Mucosal injury results in inflammation which leads to net secretion of fluids causing diarrhea. The usual age of presentation in adults is third or fourth decade of life being more prevalent above 34 years of age[7]. The average risk group in Western countries has a prevalence ranging from 0.033% to 1.17% on biopsies. This rising trend has been observed more in Asian countries[8]. Celiac disease has immunogenetic basis. It has strong association with HLA phenotype B8, DR 3 and DQw2. Siblings who share HLA phenotype have a high chance of concordance of celiac disease[9]. Celiac disease is more common in females of all age groups. Female to male ratio in celiac is 2:1[10]. It involves all portions of small intestine but proximal portion seems to be more affected than the distal portion. Healing process begins from distal to proximal portion of small intestine[11].

Clinical detail and serological testing have a significant role in forming the diagnosis. HLA typing can also be done in seronegative patients. However, biopsy of the small intestine remains the gold standard[12]. It is performed when clinical suspicion is high, irrespective of the results of serological tests[6]. Currently, the diagnosis is made on the basis of modified European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria that is, suggestive history, histology and unequivocal response to gluten free diet. Histopathological parameters are analyzed according to Marsh criterion which includes altered appearance of duodenal folds (scalloping and attenuation), crypt hyperplasia and increased number of intraepithelial lymphocytes[13]. The density of inflammation and type of inflammatory cell infiltrate in lamina propria which differs in various forms of

Correspondence: Professor Shahid Jamal, Department of Histopathology, Army Medical College, Rawalpindi Pakistan
Email: sjarjawj@gmail.com

malabsorption, along with mucosal edema and epithelial cell damage are also noted in severe forms[14]. Increased number of intraepithelial lymphocytes is a typical feature of active disease. It is usually pronounced in early phases even when disease has not manifested clinically and there is little or no villus shortening on histopathological evaluation. Majority of these lymphocytes are of CD3/CD8 +T cell type[15]. A substantial subpopulation of these cells bears natural killer cell receptors and may respond to stress signals. Serological tests such as positive tissue transglutaminase and anti-endomysial antibodies are also helpful in establishing a diagnosis[16].

Not much of data about morphological and immunohisto chemical markers studies regarding types of intestinal lesions presenting as malabsorption in Pakistani population is available. It may be due to under diagnosis and treatment on empirical grounds as the facilities of serological testing, gastric endoscope and histopathology of intestinal biopsy are still lacking even in tertiary care centers. Exact frequency of this group of diseases in adult population of Pakistan is not known and not much of clinical data has been documented about presentation of this disease[7].

Initially, prevalence of celiac disease was around 1:8000 and patients would present with obvious gastrointestinal symptoms such as diarrhea, weight loss, steatorrhea and anemia[17]. According to research in 2012 the prevalence of celiac disease in the United States was 0.71% (1 in 141) which is similar to several European countries. Celiac disease was rare among minority groups but it affected 1% of non-Hispanic white population[18]. A recent study showed that prevalence of celiac disease in the United States has increased five folds in 25 years which was only 0.2% in year 1975[18].

According to a study the prevalence of celiac disease is 2-3% in Finland and Sweden, whereas it is 0.2% in Germany. An increase of 6 fold in incidence has been observed in Scotland from 1990 to 2009[19]. Particularly classical cases of celiac disease are increasing indicating an increase in the incidence of pediatric celiac disease. Reason for this discrepancy in prevalence is unknown although these area share same causal factors. Environmental factor also seem to play a role. An increased risk of celiac disease has been seen in infants with weaning of gluten-containing food before the age of 4 months or after 6 months which supports the theory of ''window'' period of facilitated tolerance[19]. In the Arab population of Western Sahara, the prevalence of celiac disease in the general population is remarkably high i.e. 5.6%. The reasons are currently unclear. The data concerning the epidemiology of celiac disease in the Asia Pacific region is still very limited and is mostly restricted to India, where celiac disease is now being more often recognized in children as well as adults. Existing data suggest that incidence of celiac disease is increasing and disease is currently more common in some areas than previously appreciated20. Epidemiological studies conducted in areas which are considered free of celiac disease such as Africa, the Middle East and Asia show that the disease is under diagnosed. Even though the celiac disease is now being more diagnosed clinically yet significant part of the ''celiac iceberg'' remains undetected, with a ratio of 1:3 to 1:5 between diagnosed and undiagnosed cases[18].

Celiac disease can be diagnosed for the first time at any age. Adult celiac disease is now more common than pediatric celiac disease. In Finland, distribution of celiac disease is around 2.7% in adult population as compared to children which is around 2%[21]. According to study conducted in UK, prevalence of celiac disease in adult population is around 1.2%[22]. In British Columbia, age group between 20 and 50 is more commonly involved. Some studies have shown increased frequency of celiac disease in infancy and adolescence than in adulthood. In adults, the bulk of patients with celiac disease do not have classic symptoms[23]. Celiac disease shows a clear female predominance in all age groups like other autoimmune diseases[24]. Female to male ratio of

celiac disease is 2:1. In both women and men, the incidence of celiac disease keeps increasing until 65 years of age. At this point the incidence rate starts decreasing in women, while gradually increasing in men. However the incidence rate is still high in elderly female over 65 years of age as compared to the males of the same age group.

Many studies have shown that proximal small intestine show more severe histological changes. These changes can extend into the distal portion of small intestine in most severe forms of celiac disease. With dietary restriction of gluten, there is improvement from distal to proximal side of small intestine since process of healing begins from distal portion of small intestine. So changes may be less apparent and hard to see in distal portion of small intestine if it is biopsied after gluten free diet. Histological improvement in the proximal small intestine requires several weeks or months of gluten free diet[25].

Celiac Disease With Associated Disorders

Although celiac disease primarily is a disorder of the mucosa of small intestine which leads to malabsorption but now more cases are found on screening blood tests in anemic patients or patients with conditions such as type 1 diabetes, thyroid disease, connective tissue disorder and Addison's disease. Endoscopic biopsies of small intestine carried out for suspicion of conditions such as dyspepsia or gastroesophageal reflux disease may show celiac disease instead[26]. An association of diabetes with celiac disease has been observed since 1960s and the incidence is substantial. Prevalence of celiac disease is 4–6% in type 1 diabetes. A study shows no difference in metabolic control of diabetes with treatment of celiac disease[27]. Thyroid dysfunction has been increasingly reported in patients with celiac disease. A study from Sweden shows that the prevalence of celiac disease was 95.5 per 10,000. It has also been observed that thyrotoxicosis occurs in 5% and spontaneous hypothyroidism in 5.8% of the patients with celiac disease. These thyroid disorders can be found before or after diagnosis of celiac disease. This coexistence is thought to be due to a common genetic predisposition. It is not known whether treatment of celiac disease decreases the probability of developing autoimmune disorders[28]. Addison's disease is a relatively rare endocrine condition which has shown a strong correlation with celiac disease. The reason may be similar immunogenetic basis of both diseases. Coexistence of celiac disease with Addison's disease may have serious implications. Due to extensive steroid use, diagnosis of celiac can be relatively delayed since there is a crossover of gastrointestinal symptoms due to adrenocortical insufficiency[29]. Recent studies have shown a strong correlation in biopsy proven myocarditis and celiac disease. Prevalence on intestinal inflammatory disease in patients with myocarditis is around 4%. Treatment with gluten free diet has shown a significant improvement in clinical manifestation of myocarditis such as heart failure[30].

Genetics

The risks of developing celiac disease are drastically increased if two genes are present: HLA – DQA1 and HLA – DQB1 which helps in delivering instruction for proteins that play vital role in immune system. These two genes are part of family of genes called human leukocyte antigen (HLA) complex. These HLA complexes helps body's immune system to recognize its own proteins from proteins made by foreign invaders such as viruses and bacteria's[31].

The protein products of HLA – DQA1 and HLA – DQB 1 genes bind with each other to form a functional protein complex known as DQαβ heterodimer which is present on surface of immune cells and attaches to peptides outside the cell. If these peptides are recognized as foreign by immune system, a response is triggered against invading viruses and bacteria. Celiac disease causes immune system activation against gluten protein, gliadin which leads to inflammation. This inflammation damages body's organs and leads to manifestation of clinical symptoms of celiac disease. Although these variants of genes

are present in 30% of population and only 3% develop celiac disease which leads to a belief that environmental factors also play a huge role[31].

Pathogenesis

Manifestation of celiac disease is associated with multiple environmental and genetic factors along with immune mechanisms. Dietary proteins play an important role in development of celiac disease[32]. There are disease activating proteins which are present in wheat, rye and barley. Strictly speaking gluten is present only in wheat. The other disease activating proteins, hordeins and secalins are present in rye and barley. Gluten includes two major proteins gliaden and glutenin which contain disease activating peptides. The analogous proteins in rice, maize and tef are distantly related but do not cause celiac disease. These disease activating proteins have a high proline and glutamine content. The high proline renders these proteins indigestible by pancreatic, gastric and brush border enzymes. Since these enzyme lack poly endopeptidase activity, relatively large peptide fragment accumulate in small intestine[32]. Gliadin present in these peptide is directly cytotoxic to enterocytes. It leads to over expression of IL15 along with upregulation of MICA and NKG2D over expression in intra epithelial lymphocytes. These intraepithelial lymphocytes then drive a lymphocyte-mediated cytotoxic response against enterocytes which is IL15 dependent. Tissue transglutaminase plays an important role as it crosslinks gliadin and cause its deamidation into glutamic acid and gliadin peptide. These peptides are then more efficiently presented to CD4 T cells which increase their immunogenicity[33]. Tissue transglutaminase autoantibodies are produced by antigen presenting cells which initially target the toxic gliadin peptides and take up tissue transglutaminase-gliadin complexes and resulting in an immune reaction against both gliadin and transglutaminase. These autoantibodies play a role in disease pathogenesis. Therefore, there is a combination of innate and adaptive immune system in the formation of gliadin-reactive T cells, a cytotoxic response, and autoantibdy formation[33].

Presentation

Celiac disease show large variety of symptoms which are determined by severity and proximal to distal intestinal lesion. Symptoms usually appear in childhood and then disappear only to appear late in adulthood. In some individuals symptoms present for the first time in age of 60 years[34]. If proximal part of small intestine is involved, there is some functional reserve and individual show little to no symptoms. However if distal portion of small intestine is involved, individual develop diarrhea and nutritive malabsorption. Clinical symptoms are also closely related to age, sensitivity to gluten, amount of gluten ingested along with environmental factors[35]. Patients usually present with classical symptoms of diarrhea, steatorrhea, extreme lethargy and abdominal distention. Osteopenia is often the first clinical symptoms. Overall onset of symptom is much slower. Patients usually complain of bloating, altered bowel habits and fatigue in the absence of nutritive malabsorption. More severe cases show anemia, seizure, weight loss and malabsorptive diarrhea[35]. Latent celiac disease present with short stature, osteoporosis, infertility, recurrent abdominal distention, dental enamel defects and peripheral neuropathies[36]. Due to increased awareness and extensive serological testing, a shift in clinical manifestation has been observed. Patients with earlier manifestation and suspicion for celiac disease are diagnosed before further complications could develop.

Morphology

In small intestinal biopsy done for malabsorption following parameters are assessed: Villous architecture, crypt, lamina propria, muscularis mucosae, inflammatory cell infiltrate and brush border[37]. Depending on the severity of disease, villi show focal, partial and complete villous atrophy. Initial stages of disease show increased intraepithelial lymphocytes which can be decreased in advanced form of disease. Pattern

of increased intraepithelial lymphocytes can be crescendo and decrescendo. Crescendo pattern is defined as increase in number of intraepithelial lymphocytes from base to villous tip and decrescendo patter is defined as decrease in number of intraepithelial lymphocytes from base to villous tip[38]. Normal crypt to villous ratio (3:1–5:1) is disturbed. Shape of normal enterocytes in also changed. Goblet cell depletion is seen as well in some cases[39].

Histopathological parameters are defined by modified marsh criteria. Marsh 0 is normal intestinal mucosa. Marsh 1 shows increased number of intraepithelial lymphocytes (>25/100 enterocytes) with normal intestinal mucosa. Marsh 2 is crypt hyperplasia with normal mucosa. Marsh 3 is villous atrophy which is further subdivided in A, B and C categories according to focal, partial and complete villous atrophy respectively. Then there is Marsh 4, in which there is total villous atrophy without crypt hyperplasia, rather there is crypt destruction[40].

Diagnosis

Diagnosis of celiac disease is a stepwise procedure. The guidelines are defined by European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). According these guidelines patients suspected of celiac disease should undergo serological testing before formulation of a provisional diagnosis[41].

Serological testing is done in patients presenting with characteristic symptoms or at high risk individuals. All the tests are done before starting gluten free diet or before use of any immunosuppressive. The most sensitive and specific serological marker is either IgA anti-transglutaminase antibodies or anti-endomysial antibodies. The IgA isotope is considered the most sensitive for celiac disease than IgG isotype and is recommended for initial screening. However is some patients IgA deficiency is more prevalent, hence total IgA is also recommended as a part of initial testing. In case of IgA deficiency, IgG anti-transglutaminase/ anti-endomysial antibodies or IgG anti-gliadin antibodies are recommended. The combination of these markers increase the sensitivity and specificity for celiac disease[42]. According to a study, a new generation of anti-gliadin antibody test include specific deamidated peptide instead of whole gliadin protein mixture for increased sensitivity for celiac disease.

However biopsy of small intestine remains the gold standard in diagnosis of celiac disease. It is said that ideally six biopsies should be submitted. It is recommended in patient suspected of celiac with constitutional symptoms or patients with positive serological test. At least 4 biopsy specimen are recommended for diagnosis as involvement of gut is considered to be patchy according to few clinicians. Mucosal biopsy is seen by pathologist to look for evidence of celiac disease through structure and shape of villi, crypt to villous ratio and count of intraepithelial lymphocytes[38]. Intraepithelial lymphocytes increase as the disease progresses. This is the earliest change observed in small intestinal biopsy. These are T lymphocytes which are positive with CD3/ CD8 immunostain. B lymphocytes are positive for CD20 immunostian and are usually seen when there is lymphoid follicle formation with germinal center in lamina propria of mucosal biopsy. CD 3 and CD 20 immunostains show membrane positivity[43].

In Pakistan majority of the patients with malabsorption belong to age group of twenty one to thirty years with males more frequently affected than females. Clinically present with iron deficiency anaemia along with chronic diarrhoea. The detailed histopathological examination of small intestinal biopsy specimen in adult Celiac disease is very important to gain maximum benefit from current treatment modalities. Small intestinal biopsies comprising of minimum of four mucosal fragments should be recommended in patient with negative serology having high suspicion of Celiac disease before incorporating gluten free diet in treatment plan.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Hopper AD, Hadjivassiliou M, Butt S, Sanders DS. Adult coeliac disease. B.M.J 2007; 335: 558-62.
2. Rampertab SD, Pooran N. Brar P, Singh P, Green PH. Trends in presentation of celiac disease. Am J Med 2006; 119: 355.e9-355.e14.
3. Snell RS. Abdomen, In: Clinical anatomy by regions. Ed: R.snell. (Eds.) Lippincot Williams and Wilkins, a Wolters Kluwer Business: Philadelphia. 2012. p:172-178.
4. Kaukinen K, Collin P, Ma¨ki M. Latent coeliac disease or coeliac disease beyond villous atrophy. Gut 2007; 56: 1339-1340.
5. Zipser DR, Patel S, Yahya ZK, Baisch WD, Monarch E. Presentation of adult celiac disease in a nationwide patient support group. Dig Dis Sci 2003; 48(4): 761-764.
6. Green P, Celliar C. Celiac disease. New. Eng. J. Med 2005; 357:1731-43.
7. Abbas Z, Raza S, Yakoob J, Abid, S, Hamid S, Shah H, et al. Varied Presentation of Celiac Disease in Pakistani Adults. J Coll Physicians Surg Pak. 2013; 23(7): 522-524.
8. Mahadov S, Green PHR. Celiac disease: A challenge for all physicians. Gastroenterol Hepatol 2011; 7(8): 554-556.
9. Murray JA. Widening spectrum of celiac disease. Am J Clin Nutr. 1999; 69:354–56.
10. Rashtak S, Murray JA. Celiac disease in elderly. Gastroenterol Clin North Am. 2009; 38(3): 433–46.
11. Freeman HJ. Celiac disease: a review. B C Med J 2001; 43: 390-395.
12. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. GUT 2014; 0:1-20.
13. Freeman HJ. Adult celiac disease in elderly. World J Gastroenterol 2008; 14(45): 6911-14.
14. Yadav P, Das P, Mirdha B, Gupta S, Bhatnagar S, Panday R et al. Current spectrum of malabsorption syndrome in adults in India. Indian. J. Gastroenterol 2011; 30(1): 22-28.
15. Sollid LM. Intraepithelial Lymphocytes in Celiac Disease: License to Kill Revealed. Immunity. 2004; 21: 303–304
16. Collin P, Wahab P, Murray J. Intraepithelial lymphocytes and coeliac disease. In: Best Practice and Research Clinical Gastroenterology; Ed: Collin P. Elsevier, 2005;19(3): 341-350.
17. Leeds JS, Hopper AD, Sanders DS. Coeliac disease.British Medical Bulletin. 2008; 88: 157–170.
18. Rubio-Tapia A, Ludvigsson JF, Branter TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012; 107(10): 1538-44.
19. Catassi C, Gatti S, Fasano A. New epidemiology of celiac disease. JPGN 2014; 59: S7-S9.
20. Gujral N, Freeman HJ, Thompson AB. Celiac disease: Prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012; 18(42): 6036-59.
21. Vilppula A, Kaukinen K, Luostarinen L, Krekela I, Patrikainen H, Valve R, et al. Increasing prevalence and high incidence of celiac disease in elderly people: a population based study. BMC Gastroenterol 2009; 9: 49.
22. Vivas S, Vaquero L, Rodriguez-Martin L, Caminero A. Age-related differences in celiac disease: Specific characteristics of adult presentation. World J Gastrointest Pharmacol. 2015; 6(4): 207-212.
23. Laass WM, Schmitz R, Uhlig HH, Zimmer K, Thamm M, Koletzgo S. Prevalence of celiac disease in children and adolescents in Germany. Dtsch Arztebl Int. 2015; 112: 553–60.
24. Marine M, Farre C, Alsina M, Vilar P, Cortijo M, Salas A. The prevalence of coeliac disease is significantly higher in children compared with adults. Aliment Pharmacol Ther. 2011; 33: 477–86.
25. Lebwohl B, Granath F, Ekbom A, Smedby EK, Murray AJ, Neugut I.A et al. Mucosal Healing and Risk for Lymphoproliferative Malignancy in Celiac Disease: A Population-Based Cohort Study. Ann intern Med. 2013; 159(3): 169-175.
26. Nachman, F, Vazquez H, Gonzalez A, Andrenacci P, Compagni L, Reyes H. Gastroesophageal reflux symptoms in patients with celiac disease and the effects of a gluten-free diet. Clin Gastroenterol Hepatol. 2011;9(3):214-9.
27. Scaramuzza EA, Mantegazza C, Bosetti A, Zuccotti VG. Type 1 diabetes and celiac disease: The effects of gluten free diet on metabolic control. World J Diabetes. 2013; 4(4): 130-34.
28. Collins D, Wilcox R, Nathan M, Zubarik R. Celiac disease and hypothyroidism. Am J Med 2012; 125(3): 278-82.
29. Lauret E, Rodrigo L. Celiac disease and autoimmune associated conditions. Biomed Res Int; 2013: 1-19.
30. Boskovic A, Kitic I, Prokic D, Stankovic I. Cardiomyoptahy associated with celiac disease in childhood. Gastroinetstinal medicine; 2012:1-4.
31. Abraham G, Tye-Din JA, Bhalala OG, Kowalczyk A, Zobel J, Inouye M. Accurate and Robust Genomic Prediction of Celiac Disease Using Statistical Learning. P Gen 2014; 10(2): e1004137.
32. Lebwohl B, Ludvigsson FJ, Green RHP. Celiac disease and Non celiac gluten sensitivity. Brit J Med 2015; 351: 4347.
33. Barker JM, Lie E. Celiac Disease: Pathophysiology, Clinical Manifestations and Associated Autoimmune Conditions. Adv Pediatr 2008; 55: 349–65.
34. Aronsson AC, Lee H, Liu E, Uusitalo U, Hummel S, Yang J, et al. Age at Gluten Introduction and Risk of Celiac Disease. J Pediatr. 2015; 135(2): 239-45.
35. Gokce S, Arslantas E. Changing face and clinical features of celiac disease in children. Pediatr. Int 2015; 57: 107-112.
36. Nurminen S, Kivela L, Taavela J, Huhtala H, Maki M, Kaukinen K, et al. Factors associated with growth disturbance at celiac disease diagnosis in children: A retrospective cohort study. BMC Gastroenterol 2015; 15: 125.
37. Villanacci V, Ceppa P, Tavani E, Vindigni C, Volta U. Coeliac disease: The histology report. Digest Liver dis. 2011; 43S:S385-S395.
38. Svajdler M, Daum O, Rychly B. Diagnosing Celiac Disease: Role of the Pathologists. International Journal of Celiac Disease. 2014; 2:70-75.
39. Zulfiqar S, Fahim A, Qureshi A, Adnan S, Siddiqui SS, Kashif S. Celiac disease; Histopathological evaluation of endoscopic duodenal biopsies in patients. Professional Med J. 2015; 22(1): 072-075.
40. Evans KE, Aziz I, Cross SS, Sahota GRK, Hopper AD, Hadjivassiliou M. A Prospective Study of Duodenal Bulb Biopsy in Newly Diagnosed and Established Adult Celiac Disease. Am J Gastroenterol 2011; 106: 1837-42.
41. Murray JA, Herlein J, Mitros F, Goeken JA. Serologic Testing for Celiac Disease in the United States: Results of a Multilaboratory Comparison Study. Clin Diagn Lab Immun. 2000; 7(4):584-587.
42. Schyum AC, Rumessen JJ. Serological testing for celiac disease in adults. United European Gastroenterol J 2013; 1(5): 315-319.
43. Pena SA. Counting Intraepithelial Lymphocytes. Immunohistochemistry and Flow Cytometery are Necessary New Steps in the Diagnosis of Celiac Disease. International journal of Celiac Disease. 2015; 4(1): 1-2.