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Review Article

Exploring typical and atypical variants of celiac disease: a narrative review

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ABSTRACT

There are many different clinical manifestations of celiac disease (CD), including the classical form, in which intestinal symptomatology predominates on the contrary there is atypical forms, in which extra-intestinal clinical features predominate, and the silent form, in which there are no clinical symptoms. Few or no gastrointestinal symptoms and a predominance of extra-intestinal features, including liver, kidney, skeletal, psychiatric, neurologic, dermatologic, hematologic, endocrinological, and reproductive involvements, define the atypical forms of the disease. Through screening high-risk groups, silent presentations of CD may be found. It is crucial for healthcare professionals to have a high level of suspicion for the atypical presentations of CD because it is now well known that CD may account for a number of chronic health issues.

Keywords: Atypical celiac disease, Extra intestinal celiac disease, Celiac disease, Gluten free diet, Typical celiac disease

INTRODUCTION

Celiac disease (CD) is a chronic disorder of small bowel and its main mechanism is thought to be immune related. Celiac disease can be divided into typical and atypical celiac disease. Typical celiac disease includes steatorrhea, weight loss and malabsorption of important nutrients while on the other hand atypical celiac disease have extra gastrointestinal symptoms. CD is often ignored because people are not aware of its unusual presentations. Low bone mineral density (LBMD) is one of the most important atypical and extra intestinal CD manifestations.[1] Osteopenia and osteoporosis have prevalence rates of 14.4% and 39.6%, respectively and can lead to bone fractures, primarily in the hip, vertebral column, and wrist.[2] Similarly celiac disease can be associated with many other extra intestinal manifestation.

GENETICS

Majority of CD patient have genetic marker name human leukocyte antigen 2 (HLA 2) on 6 chromosome.[3] Two genes of HLA mostly responsible for the pathogenesis of CD are DQ 2 and DQ 8.[4] Out of which major portion is covered by DQ2 which is around 90-95% and rest 5-10% is caused by DQ8.[5] Some research have found that there are 39 non HLA genes which play role in pathogenesis of CD.[6]

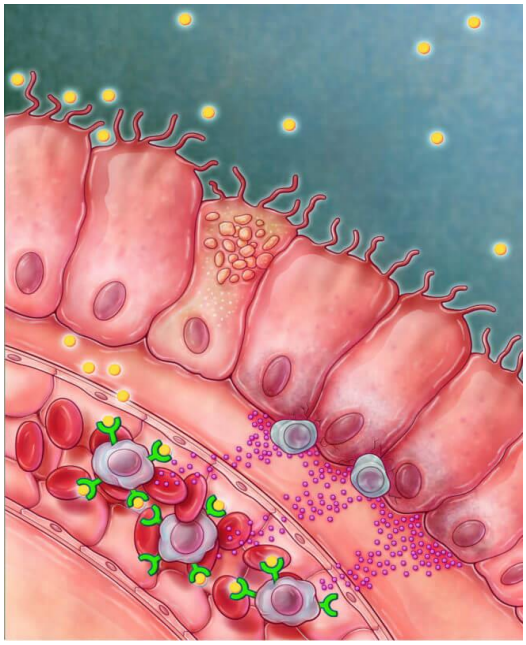

Figure 1: Since 1990, celiac diagnoses have increased 5-fold ©Evan Oto/Science source.

EPIDEMIOLOGY

Table 1: Prevalence of celiac disease worldwide.

Places	Prevalence
Worldwide[7]	0.6-1
European countries[8]	0.3 -1
North America[9]	0.5- 1
Egypt[10]	0.53
Libya[11]	0.79
Tunisia[12]	0.6
Iran[13]	0.88
India[14]	0.7

ETIOLOGY

The determining cause behind CD is thought to be methods of gluten production, dietary levels of gluten, persistent enteric infection or any physiological stressor can cause immune mediated reaction against gluten.[4]

However, the gluten intolerance cannot be explained till date and also role of some environmental factors have been playing a role in etiology of CD.[4,15]

There is a shocking relation between socioeconomic status and celiac disease. It is found out that people living in a low socioeconomic state have low prevalence of CD compared too high socioeconomic state. There was study conducted in UK in 2015 which surprisingly showed that 80% more CD in high socioeconomic state. They were classified under Townsend socioeconomic status which uses four criterias.[16] Although CD incidence is increased in all socioeconomic background nowadays

TYPES OF CELIAC DISEASE

Typical CD

Initially in 1887 CD was been characterized as Gastrointestinal (GI) symptoms like diarrhoea, fatigue and failure to thrive.[3] This was been labelled as typical CD.

Atypical CD

Eventually as the time went different symptoms emerged and that too in different forms. They were named as atypical.[17-19]

Atypical form: In this patient has symptoms like iron deficiency anaemia, infertility, osteoporosis but absent GI symptoms.

Silent form: Patient is usually asymptomatic and it is occasionally diagnosed.

Latent form: They are divided into 20 variants. Patient is having normal histology despite having CD and also having a good response to gluten free diet (GFD); or patient might develop CD in future but normal histology even under GFD.

Refractory form

Patient shows no improvement under GFD diet.

SYMPTOMS

Atypical CD can be present with several symptoms that are not related to gastrointestinal system.[3] The symptoms were anemia, chronic fatigue, dermatitis herpetiformis, peripheral neuropathy, epilepsy, constipation, osteopenia, recurrent apthous stomatitis, white matter lesion, intracranial calcification, recurrent abdominal pain, osteoporosis, headache, cerebellar ataxia, autism, recurrent abortions.

AUTOIMMUNE DISEASE ASSOCIATION

CD has an association with many autoimmune disorders.[3,20] Few of them are mentioned in Table 2.

Association of celiac disease with various autoimmune disorders can be explained with various mechanisms.

Association with type 1 DM

There is a significant relation between celiac disease and type 1 DM.[21-25] Prevalence of 4.4% (adult) and 11% (pediatric) of CD is found in type 1DM patient.[26] Several studies were performed showing their relations, however its pathophysiology still remains undetected.[27]

The genetic loci for HLA and non-HLA gene are similar for CD and type 1DM according to genetic studies.[21] Gluten-free diet (GFD) work as an excellent treatment for type 1 DM patient with CD symptoms although the shaky evidence has been found about the glycaemic control with the help of GFD in CD patient with type 1 DM.[28-30]

Association with addison disease

Studies shows that the Addison disease has a correlation with genes HLA DQ 2 AND HLA DQ 8, which are also responsible for CD.[28,29]

Table 2: Association of celiac disease with autoimmune disorders.

Organ system	Disease
Liver pathology	Primary biliary cirrhosis Autoimmune hepatitis Primary sclerosing cholangitis
Endocrine	Type 1 Diabetes Mellitus Autoimmune thyroid disease Addison's disease
Rheumatological/connective tissue diseases	Rheumatoid arthritis Juvenile rheumatoid arthritis/Juvenile idiopathic arthritis Sjogren's syndrome Systematic lupus erythematosus
Cardiological diseases	Dilated cardiomyopathy Autoimmune pericarditis
Dermatological diseases	Dermatitis herpetiformis Alopecia areata Vitiligo Dermatomyositis
Neurological diseases	Gluten ataxia Peripheral neuropathies
Others	Psoriasis Sarcoidosis Immune thrombocytopenic purpura Microscopic colitis Enteropathy-associated T-cell lymphoma

Association with autoimmune thyroid disease

Both adult and pediatric patients have been showing close correlation between autoimmune thyroid disorders (Hashimoto and graves) and CD via HLA DQ 2 and HLA DQ 8.[35-40,41]

Association with autoimmune liver disease

Most common outcome among the liver disease is cryptogenic hepatitis and autoimmune hepatitis being second most common.[31-33] Cryptogenic hepatitis has mild inflammation of lobules and portal tracts with isolated increase of transaminase.[34] Cryptogenic hepatitis have been reversed in both adult and pediatric patients with use of GFD for one year.[32,35]

DIAGNOSIS OF CD

Serological screening

Serological tests are vital for screening celiac disease. For initial testing, serum IgA anti-tissue transglutaminase antibodies are recommended in those without IgA deficiency due to their high sensitivity (94%) and high specificity (97%). IgG anti-tissue transglutaminase antibodies can be measured in persons with IgA deficiency.[5] Anti-gliadin antibodies were previously used but were replaced due to low specificity. Serological diagnosis now relies on highly predictive tests including EmA, anti tTG, and DGP. IgA class antibodies are more specific, while IgG markers have limitations, particularly in patients with IgA deficiency.[15]

First-degree relatives of individuals with a positive celiac disease diagnosis should also undergo serologic screening

Specific diagnosis

IgA anti-endomysial antibodies are nearly 100% specific for active celiac disease, but they should be used for confirmation. A biopsy of the small intestine is necessary to confirm diagnosis in most suspected celiac disease cases.

Histological changes include increased intraepithelial lymphocytes (>25 per 100 enterocytes), elongated crypts, and partial to total villous atrophy. However, false positives and false negatives are possible.[5]

Seronegative CD

Not all patients have positive CD serologic markers initially. The presence of related CD antibodies correlates with villous atrophy and disease presentation. Lesser degrees of villous atrophy led to less likelihood of positive celiac serology.

In children younger than 2 years, EMA and tTG antibodies are absent. HLA typing may be necessary in certain cases.[3]

HLA typing

All CD patients carry HLA-DQ2 or HLA-DQ8, necessary for CD development.

HLA typing helps investigate relatives of CD patients, especially 1st-degree relatives, guiding further evaluation with biopsy.[3]

Gold standard diagnosis

The gold standard for CD diagnosis combines mucosal changes from duodenal biopsy with positive serological test results (anti-tTG, EmsA, DGP antibodies).

No currently available antibody test provides 100% sensitivity and specificity, necessitating intestinal biopsy for accurate diagnosis.

Hematology and blood biochemistry tests

Routine blood tests can suggest CD. Hemoglobin, albumin, calcium, and other levels may be abnormal. Iron deficiency microcytic anemia with low ferritin is common.

Bone-specific alkaline phosphatase elevation and vitamin D deficiency occur with osteopenia/osteoporosis.

Changes in red blood cell structure may indicate hyposplenism.[15]

Histological criteria and biopsy

Histological criteria for CD have evolved, now including mild villous atrophy and minimal lesions. This is characterized by an increase in Intraepithelial Lymphocytes and may possibly express gluten have related intestinal damage.

Current recommendations suggest multiple biopsies for accurate evaluation. 4 biopsies to be done on the second duodenal portion and 2 biopsies at the bulb.

Different types of CD-related lesions are categorized based on the Marsh-Oberhuber classification.[15]

Seronegative CD

Around 2-3% of CD patients test negative for serological markers.

Genetic testing is important to rule out CD and explore other causes of villous atrophy.

Seronegative CD can be confirmed after a year of a gluten-free diet, revealing improvement in symptoms and histology. Differential diagnosis includes other conditions causing villous atrophy.[15]

MANAGEMENT

The management of CD primarily involves strict adherence to a GFD and lifelong medical follow-up. This approach is effective for most patients, resulting in an excellent clinical response. However, nonresponsive CD can occur, characterized by persistent or recurrent symptoms despite being on a GFD. In such cases, it's crucial to conduct a systematic workup to rule out specific conditions, particularly unintentional gluten contamination. Refractory CD is a rare form of nonresponsive CD often associated with a poor prognosis.[36]

The GFD is the cornerstone of CD treatment, eliminating wheat, rye, and barley proteins from the diet. Various gluten-free substitutes are available for celiac patients. Adherence to a GFD typically leads to the gradual disappearance of symptoms and serum celiac antibodies, as well as healing of intestinal damage, which usually occurs within 6 to 24 months after initiating the diet. It's worth noting that even when compliance with a GFD is reported as good, some patients may still have minimal intestinal damage. The lifelong elimination of gluten has psychological and social implications, especially for adolescents and adults, who may require support and education for adaptation to the new diet.[5]

Follow-up is a critical aspect of CD management. Patients should undergo regular monitoring, usually on an annual basis, to assess adherence to the diet. Serologic monitoring for celiac disease is essential, as abnormal levels of IgA anti-tissue transglutaminase antibodies often indicate poor dietary compliance. Additionally, monitoring for associated conditions like osteoporosis and autoimmune thyroid disease is recommended.[5]

Furthermore, follow-up of CD patients should include: (1) dietary guidance by a clinical dietitian; (2) measurement and substitution of vitamin and mineral levels in the plasma until normalization; (3) monitoring adherence to a GFD through antibody measurements and dietary intake interviews; (4) biochemical control of vitamin and mineral deficiencies; (5) bone mineral density testing (DXA scan) for newly diagnosed CD patients.[5]

In summary, the management of celiac disease revolves around a lifelong gluten-free diet, regular follow-up and monitoring for associated conditions. Ensuring patient adherence to the diet is crucial for successful management. Support and education are essential for helping patients adapt to this dietary regimen.

DISCUSSION

CD manifests with different symptoms and there are several ways of diagnosing celiac disease. Attention should be given to all the extra intestinal symptoms that does not make sense and can show relation to celiac disease to improve the prognosis of the patents. Serology, blood test, genetic testing and many more can be done to diagnose celiac disease. Main stay treatment of celiac disease is GFD. Although there are several patients in whom GFD is not so effective, they still might show some damage. Patient should be educated and encouraged to follow GFD diet to ensure body has minimum damage.

CONCLUSION

Celiac disease is an emerging disease around the world. To be the best diagnostician, a clinician should be aware of the silent feature of celiac disease and should be able to differentiate from other diseases. Atypical celiac disease is been growing worldwide and the screening test should be made available for the high risk individual to diagnose it as early as possible. Gluten free diet should be encouraged to the susceptible patient to prevent the symptoms from happening.

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