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College of Medicine

Celiac Disease

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ABSTRACT

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten and related prolamines in genetically susceptible individuals, characterized by presence of various combinations of small intestinal damages, celiac specific antibodies, human leukocyte antigen (HLA)-DQ2 or HLA-DQ8, and gluten-dependent clinical manifestations. .Gluten is found in wheat, barley, rye, and oat

INTRODUCTION

Celiac disease (gluten-sensitive enteropathy) is a relatively common cause of severe diarrhea and malabsorption in infants and children. Children with celiac disease commonly present symptoms between 9 to 24 months of age with failure to thrive, diarrhea, abdominal distention, muscle wasting, anemia and hypotonia.This review will involve the pathogenesis , epidemiology, clinical manifestation of celiac disease and aims to provide a simple approach for diagnosis and management

PATHOGENESIS

The key elements of the celiac disease, an autoimmune disease, are genetics HLA-DQ2 and HLA-DQ8 genotypes, environmental factors (gluten intake), and autoantigen to tissue transglutaminase (tTG),that play an important role in the pathogenesis. In addition to genetic susceptibility and gluten exposure, loss of intestinal barrier function, gluten-induced proinflammatory innate immune response, inappropriate adaptive immune response, and unbalanced gut microbiome all seem to be components of the celiac disease autoimmunity (1).It has been suggested that breast milk, mode of delivery, and the age of gluten intake in infants are a risk for developing celiac disease and may affect the incidence of celiac disease. there is a limited information in retrospective studies that those factors affect the risk of developing celiac disease (2)(3).It has been suggested that gastrointestinal system (GIS) infections such as rotavirus may increase the risk of developing

celiac disease, and therefore rotavirus vaccine may significantly reduce the risk of celiac disease (4)

EPIDEMIOLOGY

The prevalence of celiac disease in the general population is estimated to be 1% in the world(5). The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the world is 1.4% and 0.7%, respectively(6).Its prevalence varies depending on geographical and ethnic variations. The highest prevalence is in Europe (0.8%) and Ocenia .(0.8%), and the lowest prevalence is in South America (0.4%)

The biopsy-proven prevalence of celiac disease was found to be two times higher in children than adults.The reason for this difference may be genetic factors [human leukocyte antigen (HLA) and non-HLA genes], environmental factors such as wheat consumption, age at gluten intake, gastrointestinal infections, antibiotic use, and the rate of cesarean section(6)(1)

The prevalence of celiac disease has increased significantly in the last 30 years, the reason for this is not only the increased knowledge and awareness of physicians about celiac disease but also due to the widespread use of highly sensitive and specific diagnostic tests for celiac disease(7)(8)

Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed(9)(10)

There are many undiagnosed cases even in developed countries. Very few patients have clinically significant signs of celiac disease. The majority of cases have atypical signs or vague symptoms, so the diagnosis could not be made or diagnosis is delayed (11)(12). The reason for delayed or overlooked diagnosis may be the limited accessibility to serological diagnostic tests in developing countries(13)

The risk of developing celiac disease is higher in first- and second-degree relatives of celiac patients, Down syndrome, type 1 diabetes mellitus (DM), selective immunoglobulin (Ig)A deficiency, autoimmune thyroiditis, Turner syndrome, and Williams syndrome(11)

Table 1

Groups with higher risk of developing celiac disease

Groups with higher risk of developing celiacdisease
First-degree relatives of celiac patients
Second-degree relatives of celiac patients
Type 1 diabetes mellitus
Autoimmune thyroid disease
Autoimmune liver disease
Down syndrome
Turner syndrome
Williams syndrome
Selective IgA deficiency
Systemic lupus eryhtematosus
Juvenile chronic arthritis

Table1 (14)

screening tests for celiac disease at risk groups such as type 1 DM, autoimmune thyroid diseases, and first degree relatives of celiac patients also contributed to the increase in prevalence of celiac disease (15)(16) (17)The prevalence of celiac disease in first degree relatives of celiac patients is as high as 10%-20% (1)In a recent study the prevalence of celiac disease (CD) in siblings of pediatric celiac patients is reported to be 3.9%. The prevalence of CD in monozygotic twins has been found as high .as 75%-80% (18)

CLINICAL MANIFESTATIONS

Symptoms usually occur in children after ingestion of gluten containing grains between 4 and 24 mo. There may be a delay or latent period between gluten intake and the onset of symptoms (19)

GIS and extra-intestinal manifestations are common in celiac disease(20) .The main GIS manifestations of celiac disease are chronic diarrhea, recurrent abdominal pain, nausea, vomiting, and abdominal distension. Common extra-intestinal manifestations are failure to thrive,

short stature, chronic anemia, osteopenia, osteoporosis, delayed puberty, dental enamel defect, irritability, chronic fatigue, neuropathy, arthritis, arthralgia, amenorrhea, and increased liver enzymes (1) (20)Symptoms are usually different in infants than older children. Diarrhea, anorexia, abdominal distension, and abdominal pain are usually seen in younger children. GIS symptoms such as diarrhea, nausea, vomiting, abdominal pain, abdominal distension, weight loss, and constipation may occur in older children depending on the amount of gluten intake (2). Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. GIS symptoms are mild or nonspecific (21)(22) It has been shown that pediatric patients diagnosed with celiac disease who are younger age at the diagnosis have less severe symptoms in the last 20 years.Recently, the clinical symptoms of children with celiac disease are observed to change from GIS symptoms to extra-intestinal symptoms.The exact reason for this is unclear, but it has been suggested that there may be increased awareness and widespread use of highly .sensitive and specific serologic tests

EXTRA-INTESTINAL MANIFESTATIONS

Extra-intestinal findings are seen in up to 60% of pediatric celiac patients (Table2) (23) Short stature is the most common finding in children(23) (24). It has been reported that 10%-47.5% of pediatric celiac patients have short stature at the time of diagnosis(24)(25)(26)
Starting a gluten-free diet in the early period causes rapid growth and weight catch up, especially in the first 6 mo. The target height is usually reached within 3 years after diagnosis. If the target height is not reached despite a strict gluten-free diet, endocrinological evaluation should

done to rule out growth hormone deficiency (27)(28)(29)

Extra-intestinal manifestations of celiac disease

Extra-intestinal manifestations of celiac disease
Short stature
Anemia
Osteopenia/osteoporosis
Delayed puberty
Dental enamel defects
Dermatitis herpetiformis
Recurrent aphtous stomatitis
Neurological manifestations; peripheral neuropathy, epilepsy, ataxia, headache
Arthritis, arthralgia
Infertility

Hypogonadism in girls and delayed puberty in boys due to androgen resistance is a common finding in undiagnosed or untreated pediatric celiac patients(27)(30). Delayed puberty is seen in 10%-20% of celiac patients(23)(31) . Iron deficiency anemia is seen in up to 40% of pediatric celiac patients(23)(32)(33). Since iron is absorbed from the first part of the duodenum, which is mainly affected by celiac disease, iron deficiency anemia is common in celiac patients. It has been reported that 84% of pediatric celiac patients have the complete recovery of iron deficiency anemia with a strict gluten-free diet and iron supplementation therapy within 12-24 mo(23)

Osteopenia and osteoporosis are usually seen in patients with celiac disease. Approximately 75% of celiac patients have osteopenia and 10%-30% have osteoporosis(34). Secondary hyperparathyroidism occurs due to the insufficient absorption of vitamin D and calcium from the damaged duodenal mucosa. It is commonly seen in 12%-54% of celiac patients[35]. Normal blood levels of vitamin D and calcium is observed within the first year after a strict gluten-free diet(36)(37)

The most common joint and muscle disorders seen in celiac disease are myopathy, arthralgia, and non-erosive arthritis(27)(38). Since arthralgia is mostly seen after the age of 12, the most common finding in pediatric celiac patients is subclinical synovitis. It is most commonly seen in the

knee joint. Its incidence is 5%-10%[24]. Since symptoms are mild, ultrasonography is important in the diagnosis of joint disorders
The most common finding of neurological manifestations is headache, which is seen in up to 20% of celiac patients. More rarely, ataxia and neuropathy (0.1%-7.4%) are seen[38]. Dermatitis herpetiformis is thought to be an extra-intestinal manifestation of celiac disease, but it is relatively rare in pediatric celiac patients in Finland(39)

ASSOCIATED DISEASES WITH CELIAC DISEASE

The most common accompanying disease is type 1 DM since it has common genetic factors and pathogenic mechanisms with celiac disease (40).The prevalence of celiac disease in patients with autoimmune [thyroid disease is found to be 3.0%-4.8%] (1)

The increased prevalence of celiac disease is also seen in autoimmune liver disease, Turner syndrome, and Williams syndrome (1)

Silent celiac disease

Silent celiac disease is defined by the presence of celiac antibodies and HLA-DQ2 or HLA-DQ8 and small intestinal biopsy findings compatible with celiac disease especially in patients with autoimmune disease or a genetic disorder or relatives of celiac disease but without any symptoms suggestive of CD (1) Table(3) (1)

Other diseases causing villous atrophy

Other diseases causing villous atrophy
Parasitic infections (*Giardia lamblia*)
Autoimmune enteropathy
Small intestinal bacterial overgrowth
Common variable immunodeficiency
Cow's milk or soya protein hypersensitivity
Intractable diarrhea of infancy
Eosinophilic gastroenteritis
Drug induced enteropathy (*e.g.*, olmesartan, mycophenolate)
Intestinal lymphoma
Crohn's disease
Human immunodeficiency virus enteropathy
Tropical disease

DIAGNOSIS

Celiac patients may present with symptoms of GIS or extra-intestinal symptoms or no symptoms at all. Therefore, serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous, stomatitis, and abnormal liver enzyme elevation(1) . celiac disease should be investigated in patients with high risk of developing celiac disease, such as type 1 DM, Down syndrome, autoimmune thyroid disease, Turner syndrome, selective IgA deficiency, autoimmune liver disease, and first-degree relatives of celiac patients, even if they are asymptomatic (1)

Celiac disease is diagnosed by a variable combination of symptoms, positive celiac antibodies(deamidated gliadin peptide (DGP) IgA test is recommended for children under 2 years of age, the tTG-IgG test or the EMA-IgG test), presence of HLA-DQ2/DQ8 and duodenal histology
If serological tests are negative for tTG-IgA and total IgA level is normal, celiac disease is unlikely. In this condition, the reasons leading to the false negative tTG result should be considered. Those are low gluten intake, protein-losing enteropathy, use of immunosuppressive drugs, and patients under 2 years of age. If the tTG is found as positive [lower than 10 times] , gastroduodenoscopy and multiple biopsies of the small intestine should be performed to confirm the diagnosis (1)

If the tTG is higher than 10 times upper limit of normal in a symptomatic patient, it should be discussed with the parents in order to make a diagnosis of celiac disease without biopsy.
If the parents agree, EMA test and HLA-DQ2/DQ8 analysis are performed. To rule out false positivity of the tTG test, an EMA test is performed from a second blood sample.

If EMA and HLA-DQ2 or HLA-DQ8 are positive celiac disease is diagnosed without biopsy (1)

The modified Marsh classification

	IEL	Crypts	Villi
Type 0	< 40	Normal	Normal
Type 1	> 40	Normal	Normal
Type 2	> 40	Hypertrophic	Normal
Type 3a	> 40	Hypertrophic	Mild atrophy
Type 3b	> 40	Hypertrophic	Marked atrophy
Type 3c	> 40	Hypertrophic	Absent

IEL: Intraepithelial lymphocyte count/100 epithelial cells.

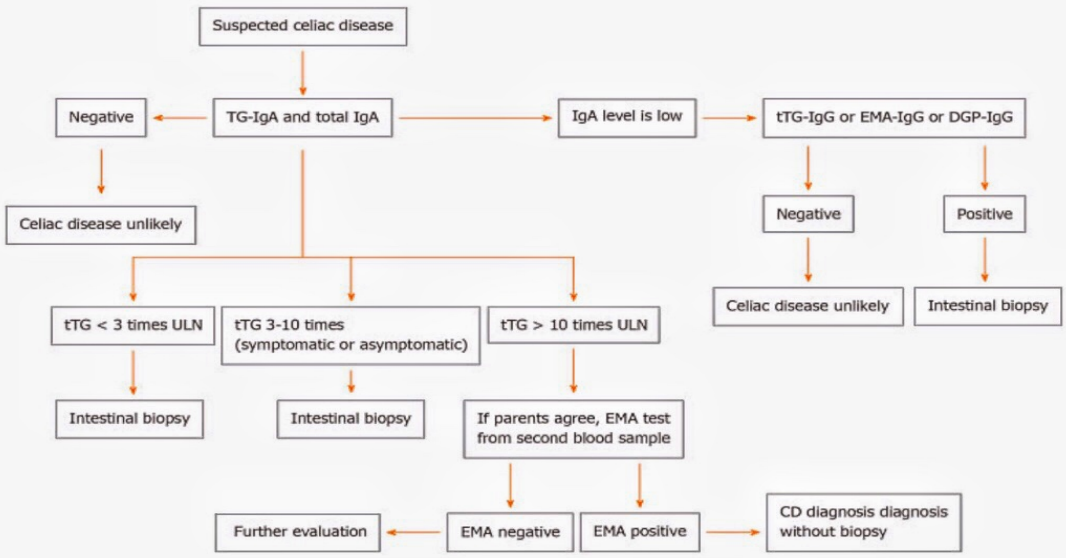
Table (4) (1)

If the patient has the gluten-free diet for a long time or gluten-free diet for short time before testing, false negative results may occur [23] .If the patient is strongly suspected of celiac disease, multiple intestinal biopsy and HLA-DQ2/DQ8 analysis are recommended, even if the serological tests for celiac disease are negative. If the histology is compatible with celiac disease but HLA-DQ2/8 negative celiac disease is unlikely and other causes of enteropathy should be investigated (1)

Celiac disease is diagnosed if the celiac serological tests are positive . and the biopsy is compatible with celiac disease. (1)

Table (5) (1)

Figure 1



Algorithm for diagnosis of celiac disease. CD: Celiac disease; DGP: Deamidated gliadin peptide; EMA: Endomysial antibody; tTG: Tissue transglutaminase antibody; ULN: Upper limit of normal.

MANAGEMENT

the only effective treatment is a lifelong gluten-free diet. Significant improvements in symptoms, normalization of biochemical tests, and improvement in quality of life with a strict gluten-free diet are seen . Rapid improvement in clinical symptoms is observed within 2-4 wk in children. Serological and histological responses are slower compared to clinical symptoms. Although histological response in children is observed within 2 years by a rate of 95%, this rate is 60% in adults

The amount of tolerable gluten varies from patient to patient. As little as 50 mg of gluten, present in a few amounts of bread crumbs or a small piece of cake or traces of contamination, may cause symptoms and/or enteropathy in asymptomatic patients .Adherence to the gluten-free diet is better in children diagnosed with CD at an early age and those who

continue to follow up regularly. It is less in adolescents compared to adults.Since celiac disease is a multisytemic disease that affects multiple organs, a lifelong gluten-free diet may reduce malignant and non-malignant complications (41) Vaccination (Nexvax2) is therapeutic option intended to be used for desensitization in celiac patients against gliadin peptides. Although its major side effects are abdominal pain and vomiting, it passed phase 1. Given the effectiveness of vaccines, it can be a definitive cure for celiac disease (42)

FOLLOW-UP

Patients with celiac disease should be followed up 6 mo after diagnosis and every 6 mo in terms of improvement in symptoms, compliance with the gluten-free diet, quality of life, and progressive normalization of celiac-associated antibodies. Screening tests should be done in terms of autoimmune thyroid disease. A control duodenal biopsy is not required after a gluten-free diet, if there is a partial or no response to the gluten-free diet, careful examination should be done for involuntary gluten contamination or poor compliance with the gluten-free diet. If the response to a strict gluten-free diet is poor, duodenal biopsy can be performed (43)

Earlier diagnosis of celiac disease in asymptomatic patients is associated with better quality of life as well as better compliance with the gluten-free diet Routine testing for vitamin and mineral deficiency is reported to be unnecessary in the vast majority of children who follow up to regular controls and have normal growth and development and have no symptoms.The essential marker of the success of the gluten-free diet is still satisfactory height and weight gain in children and adolescents.The best marker of proper follow-up and management is the decline in the antibody levels and the return of antibody levels to normal in follow-up. The presence of persistent positive antibodies usually indicates ongoing intestinal damage and gluten exposure. Serological follow-up should be done within 6 mo and 12 mo after diagnosis and then once a year to

return to normal The average time to return to the normal levels of the tTG test in patients with strictly adherent to the gluten-free diet is 1 year it has been reported that gluten consumption can be shown in symptomatic and asymptomatic patients who are unaware of celiac disease (41)

CONCLUSION

Celiac disease is a lifelong multi-systemic disease triggered by intake of gluten in genetically susceptible individuals

Serologic tests for CD should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme .elevation

Since tTG-IgA test and total IgA test combination give more accurate results than other test combinations, It is recommended to considered them the initial test for suspected celiac disease regardless of age. While interpreting the serological test results of celiac disease, serum total IgA levels, the amount of gluten consumption, use of immunosuppressive .drugs, and age of the patient should be considered

Early diagnosis of CD is very important to prevent long-term complications such as failure to thrive, osteopenia, infertility, and malignancy

Currently, the only effective treatment is a lifelong gluten-free diet

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