

COELIAC DISEASE – AN OVERVIEW

Atul Sachdev

Department of General Medicine, Government Medical College & Hospital, Chandigarh

ABSTRACT

Celiac disease (CD) is a chronic inflammatory enteropathy resulting from unique autoimmune cause in genetically susceptible individuals by irritant gluten and other environmental cofactors. This disorder is characterised by diverse clinical presentations ranging from asymptomatic to severely symptomatic which could be in the form of malabsorption and association with other autoimmune diseases. The diagnosis is based on serological tests- IgA Endomysial Antibody (EMA) and anti tissue Transglutaminase (anti t-TG), and ESPHAGN criteria. The treatment of celiac disease is gluten free diet and response to therapy is poor in up to 30% of patients. Dietary non-adherence results in recurrence or persistence of symptoms. It is complicated rarely by refractory CD and enteropathy associated T cell lymphoma.

INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disease characterised by flattened villi on small bowel histology and is induced in genetically susceptible individuals by ingestion of gluten containing proteins of wheat, rye and barley. It causes impaired digestion and absorption of macronutrients and micronutrients and results in increased net secretion of water and solutes. The entity was described previously as celiac sprue, based on the Dutch word *sprue*, which was used to describe a disease similar to tropical sprue that is characterised by diarrhoea, emaciation, aphthous stomatitis, and malabsorption.

It has a diverse clinical profile. It can present with intestinal or /and with extraintestinal symptoms, or may be detected in asymptomatic individuals as part of the screening of populations at increased risk for celiac disease. Untreated CD increases both morbidity and mortality.

EPIDEMIOLOGY

There is limited data on prevalence of celiac disease in India. The majority of CD cases remain undiagnosed based on epidemiological studies from Europe and United states.

The overall prevalence of CD in India seems to be between 1:500 and 1:5000. The prevalence of CD is more in Northern and North West India.¹ In India, CD is more

frequently diagnosed in children than in adults. However one of the first reported series of adult onset CD is from our hospital where most of the patients presented with malabsorption.

In order to determine the incidence of CD, a study was conducted, based on history and physical examination conducted in Ludhiana and a structural questionnaire was completed by 4347 children in the region. Those with gastrointestinal symptoms, failure to thrive, short stature or pallor (a total of 198 children) were screened for celiac disease by the detection of transglutaminase antibody. Of 21 positive children, 14 had typical histological changes on small bowel histology and showed improvement after a gluten-free diet.² CD is also common in the siblings of patients with CD and the overall prevalence was 22% in India.³ The prevalence in west of monozygotic and dizygotic twins is 75% and 11%¹ respectively. The prevalence of CD in first degree relatives is 13%.

PATHOGENESIS

The interaction of the water-insoluble protein moiety (gluten) of certain cereal grains, immune system and environmental factors in genetically susceptible persons is central to the pathogenesis of CD (Fig. 1).

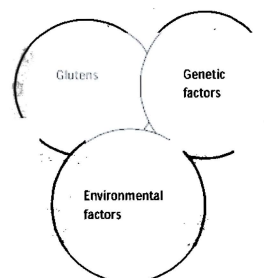


Fig. 1 : Pathogenesis of Coeliac disease - interaction of factors.

Corresponding Author :

Dr. Atul Sachdev, Professor & Head,
Department of General Medicine,
Govt. Medical College & Hospital,
Sector 32, Chandigarh

Role of gluten

Coeliac disease is induced by gluten, which is derived from wheat, barley, and rye. This protein is rich in glutamine and proline and is poorly digested in the human gastrointestinal tract by enzymes. Gluten is the rubbery mass left over when wheat dough is washed to remove starch granules and other soluble granules. This protein has different solubility in alcohol water solutions and can be separated into gliadins and glutenins.¹ The gliadin is the alcohol-soluble fraction of gluten that contains the bulk of the toxic components. Gliadin can be separated electrophoretically into α , β , γ and ϕ gliadins and all four fractions are toxic to the patient with CD.⁴

Cereals have two different protein fractions – prolamins and glutenins. The prolamins of wheat are referred to as gliadins. Prolamins from other cereals also are considered to be gluten and are named according to their source (secalins from rye, hordeins from barley, avenins from oats, and zeins from corn). Although most toxicity studies have been performed with prolamins, there are data to suggest that glutenins also can damage the celiac intestinal mucosa.

The taxonomic relationships of the major cereal grain families provide a framework on which their toxicities in celiac disease can be predicted. Wheat, rye, and barley belong to the tribe known as Triticeae, and oats belong to a neighbouring tribe known as Aveneae. Avenin is genetically less similar to gliadin than gliadin is to secalin and hordein. Despite their genetic differences, however, prolamins from oats, barley, wheat, and rye still have immunologic cross-reactivity because of their common ancestry.⁵

Rice, corn, sorghum and millet grains do not activate disease and are separated from wheat, rye, and barley in terms of their derivation from the primitive grasses.

Undigested molecules of gliadin (α -gliadin fraction) are resistant to degradation by gastric, pancreatic, and intestinal brush-border membrane proteases and thus remain in the intestinal lumen after gluten ingestion. These peptides cross through the epithelial barrier of the intestine during increased permeability of intestine or during infections and interact with antigen-presenting cells in the lamina propria.

Mucosal Immune response

There is role of humoral and cell mediated immune

responses to gliadin and related prolamins. In untreated patients of CD there is six fold increase in number of immunoglobulin producing B cells in lamina propria of small intestine. There is also increase in IgA and IgG serum antibodies to gliadin in untreated patients of celiac disease. These antibodies do not play central role in pathogenesis of CD and simply reflect non-specific response. Other antibody levels are also increased against antigen food proteins, such as β -lactoglobulin, casein, and ovalbumin and this reflects a general aberrant immune responsiveness to food antigens in patients with CD or enhanced systemic exposure to these proteins because of increased small intestinal permeability.⁶

IgA antibodies to endomysium connective tissue surrounding smooth muscle are virtually pathognomic for CD and are rarely found in absence of celiac disease.⁷ The target autoantigen present in the endomysium is enzyme tTG2.

In lamina propria, gliadin interacts with HLA DQ2 or DQ8 cell surface antigen through antigen presenting cells, probably dendritic cells to sensitized T lymphocytes that express α/β T cell receptor (Fig 2). Tissue transglutaminase (tTG) deamidates gliadin peptides and deamidated gliadins have increased immunogenicity and result in activation of CD4+Tcells, which generate Th1 response that leads to epithelial damage, intraepithelial lymphocytosis, chronic inflammatory response in small intestine, villous atrophy and crypt hyperplasia (Fig 4). There is increased expression of IL15, which leads to intraepithelial lymphocytosis. There is also increased expression of pro-inflammatory cytokines particularly IFN- γ that result in activation and release of matrix metalloproteinase and other tissue damaging mediators and result in crypt hyperplasia and villous atrophy.

Role of genetics

The role of genetics can be explained on the basis of its familial occurrence. The evidence for genetic basis can be explained on the basis of ethnic differences in its incidence and prevalence. The concordance for CD in first degree relatives ranges from 8 -18%. The concordance for monozygotic twins is 83 to 86% and 11% for dizygotic twins.⁸

The association between HLA genes (COELIAC 1 locus on chromosome 6p21) and CD is very strong compared with other HLA linked diseases. The HLA class II molecule DQ2 is present in more than 90% of persons with CD compared with approximately 35% of the general white population. The majority of celiac disease patients have variant of DQ2 (alleles DQA1*05/

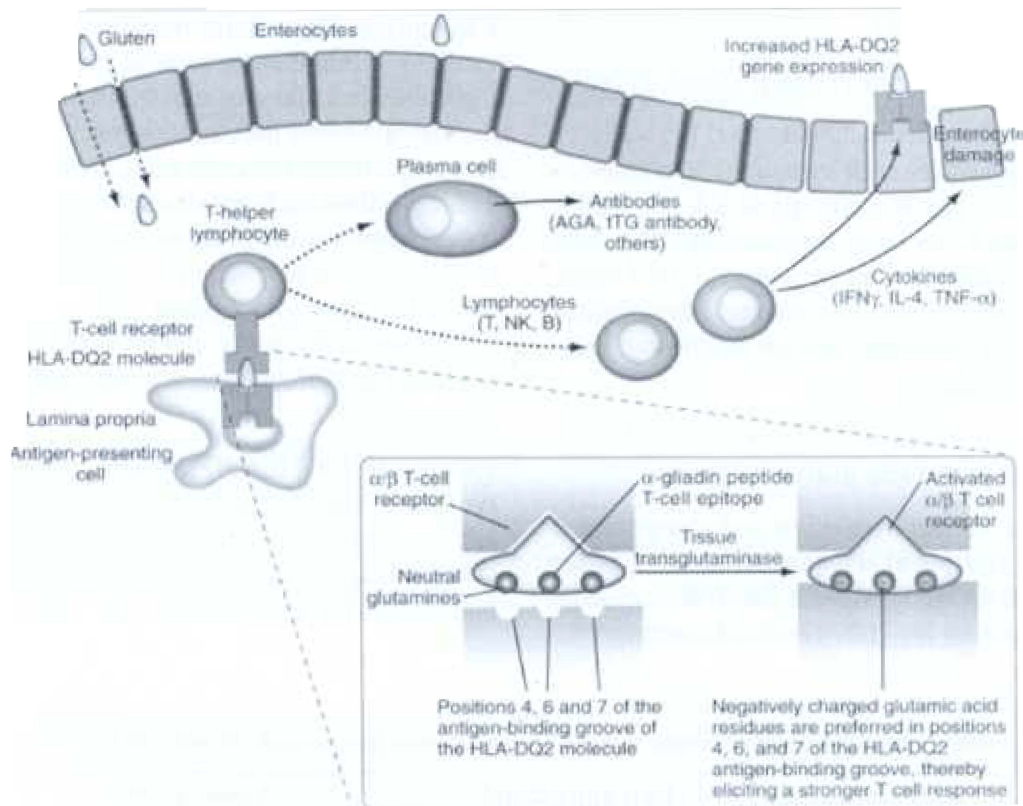


Fig. 2: Pathogenesis of coeliac disease (9th edition Sleisenger and Fordtran's text book of Gastrointestinal and Liver diseases)

DQB1*02) and others carry a variant of DQ8 (alleles DQA1*03/DQB1*0302).

Recent research has found that other susceptibility loci for celiac disease are COLEIAC 2 (5q31-33), which encodes for cytokine gene clusters, COLEIAC 3 (2q33) that encodes the negative co-stimulatory molecule CTLA4 and COLEIAC 4(19p13.1) which contains myosin IXB gene variant encoding a conventional myosin that alters epithelial actin remodelling⁹.

Genome wide association studies have shown single nucleotide polymorphisms of loci COELIAC 6 (4q27) encoding IL2 and IL21 for intestinal inflammation and few other loci as risk for CD.⁹

Role of environmental cofactors

There is protective role of breast feeding in prevention of CD. Study from Sweden has shown that changes in infant feeding practices might affect the rise and fall of the disease.¹⁰ Some drugs like interferon alfa can have a role in enhancing a person's susceptibility to gluten.

Intestinal infections might cause a transient rise in small bowel permeability and could lead to up-regulation and release of tissue transglutaminase that in turn

enhances gluten immunogenicity. Repeated rotavirus infections could lead to celiac disease in high risk children.¹¹

CLINICAL PRESENTATION

Definition

Coeliac disease is characterised by small intestinal malabsorption of nutrients after the ingestion of wheat gluten or related proteins from rye and barley, villous atrophy of the small intestinal mucosa, prompt clinical and histologic improvement following strict adherence to a gluten-free diet, and clinical and histologic relapse when gluten is reintroduced.¹²

Coeliac disease exhibits a spectrum of clinical presentations. Atypical CD is fully expressed gluten-sensitive enteropathy manifesting only by extraintestinal symptoms and signs including short stature, anaemia, osteoporosis, and infertility. Silent CD is fully expressed gluten-sensitive enteropathy usually found after serologic screening in asymptomatic patients. The atypical and silent variants are more common than classic or typical CD, which is fully expressed gluten-sensitive enteropathy found in association with the classic gastrointestinal

symptoms of malabsorption.

The clinical profile varies in great extent according to age group.

The mean age of onset of symptoms in children is 2.5 to 3 years and age at diagnosis is 2.5 -14years in Indian population. In the west, children with CD present at 9 -18 months of age and majority by two years. Prolonged breastfeeding and delay in introduction of gluten in the diet could be the reason for late manifestations of celiac disease in India.

Coeliac disease can be diagnosed in silent or asymptomatic stage and also in atypical forms.

Common manifestations in infants and young children are diarrhoea (80-90%) as compared to western population (25-50%), failure to thrive (90- 100%), anaemia (80-90%), short stature (60-100%) and undernutrition (62-87%)¹.

Clinical manifestations in adults – Limited studies are available in adults with classical manifestations. Most of the studies have been conducted in patients with chronic diarrhoea. One of the studies showed chronic diarrhoea in 44%, refractory anaemia in 22% and short stature in 13%. The time lag from onset of symptoms to diagnosis was 6 months to 40 years.¹³ Other study based on histology consistent with CD showed that most of the adults had diarrhoea, weight loss and anemia.¹⁴ There was history of anti-tubercular treatment in 15% of cases.¹⁵ Atypical manifestations were more common in adults than children.

Gastrointestinal manifestations – The gastrointestinal symptoms depend upon severity of intestinal involvement and the presence of focal or diffuse involvement. The symptoms are not specific to CD, but may occur in other malabsorptive conditions. The classic features of

Table 1 Manifestations of coeliac disease- Coeliac disease may virtually involve all organs¹⁶

General	Gastrointestinal	Extraintestinal	Association
Short stature	Diarrhoea, steatorrhoea, flatulence	Laboratory abnormalities Iron and folate deficiency anaemia	Definite association IDDM
Weight loss	Abdominal distension, discomfort	Hypocalcemia, 1ALP	Hypothyroidism, hyperthyroidism
Failure to thrive	Anorexia, nausea, vomiting	Prolonged PT	IgA deficiency
Lassitude,	Recurrent aphthous stomatitis	Hypertransaminasemia	Sjogren's syndrome
lethargy	Angular cheilosis, glossitis	Skin	Microscopic colitis
Clubbing	Hepatic steatosis	Dermatitis herpetiformis	Primary biliary cirrhosis
Koilonychia		Follicular keratosis	IgA mesangial nephropathy
Delayed puberty		Pigmentation, bruising	Rheumatoid arthritis
Oedema		Hematological Splenic atrophy, thrombocytosis	Down syndrome
		Musculoskeletal Osteopenia, osteoporosis, fractures	Epilepsy (cerebral calcification)
		Bone pain, joint pain	Fibrosing alveolitis
		Dental enamel defects	Recurrent pericarditis
		Arthritis, myopathy, cramps, tetany	Idiopathic pulmonary hemosiderosis
		Neurological Peripheral neuropathy, paraesthesia	Possible association Congenital heart defects
		Ataxia	Inflammatory bowel disease
		Epilepsy (cerebral calcification)	Systemic lupus erythematosus
		Night blindness	Polymyositis, vasculitis
		Reproduction Female and male infertility	Myasthenia gravis
		Recurrent abortion	Iridocyclitis, choroiditis
		Psychiatric/psychological Anxiety, depression	Sarcoidosis
		Irritability, poor school performance	Cystic fibrosis
			Addison's disease
			Autoimmune haemolytic anaemia
			Autoimmune thrombocytopenia
			Schizophrenia

Table 1: Manifestations of Celiac Sprue

malabsorption are diarrhoea with pale, greasy, voluminous, foul-smelling stools and weight loss. However, this presentation is relatively uncommon and majority of patients have relatively mild gastrointestinal symptoms, which may mimic conditions like irritable bowel syndrome. Few cases may present with anorexia, flatulence, abdominal distension and borborygmi and other patients may be asymptomatic.

APPROACH TO DIAGNOSIS (Fig.3)

When the index of suspicion is low to moderate (asymptomatic patients with a family history, unexplained iron deficiency anaemia, or possible extraintestinal manifestations), a negative result for either IgA antiendomysial antibody (AEA) or IgA tissue transglutaminase (tTG) antibody has a high negative predictive value and may obviate the need for small bowel

biopsy, as the specificity of IgA AEA is nearly 100% and its positive predictive value is high even in low risk populations.¹⁷ However, the specificity of IgA tTG antibody is closer to 95%, and consequently patients in low risk populations with a positive IgA tTG antibody should have their IgA AEA tested before being referred for small intestinal biopsy. When the index of suspicion is high (e.g., GI symptoms and a family history of celiac sprue, steatorrhoea, or failure to thrive in children), we recommend that both IgA and AEA (or IgA tTG antibody) assay and a small bowel biopsy be performed. This approach provides the best means of making a definitive diagnosis.¹⁶

DIAGNOSIS

Serum IgA, EMA and tTG antibodies and intestinal biopsies are the reliable diagnostic tests for celiac disease. Biochemical, haematological, stool and radiological

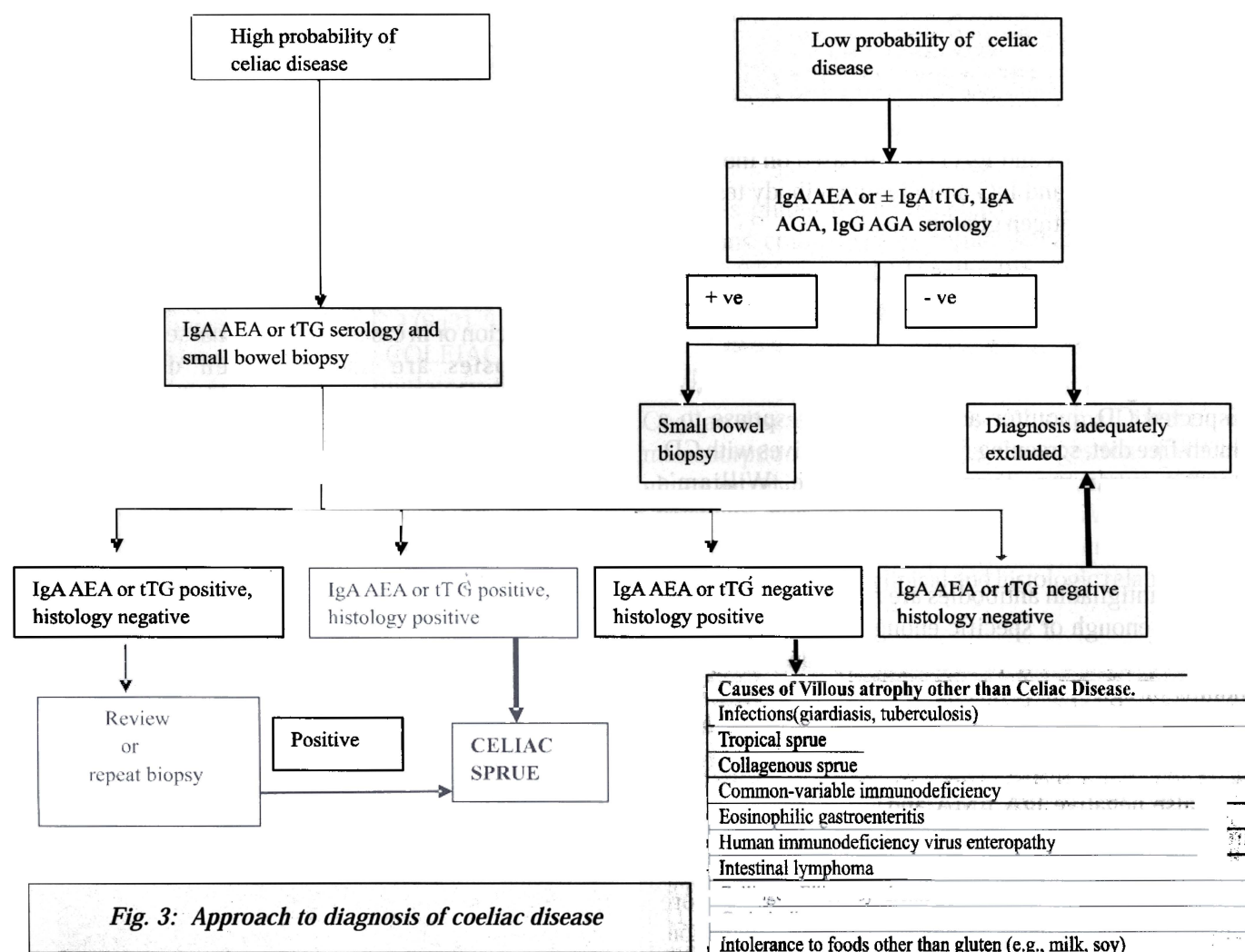


Fig. 3: Approach to diagnosis of coeliac disease

Table 2

Sensitivity, Specificity, and Positive and Negative predictive values of serologic tests for untreated Coeliac disease¹⁷

SEROLOGIC TEST	SENSITIVITY* (%)	SPECIFICITY* (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE VALUE (%)
Immunoglobulin A Endomysial Antibody				
Indirect immunofluorescence assay	85-98	97-100	98-100	80-95
Guinea pig tTG ELISA	95-98	94-95	91-95	96-98
Human tTG ELISA	95-100	97-100	80-95	100
Antigliadin Antibodies (AGAs)				
IgA	75-90	82-95	28-100	65-100
IgG	69-85	73-90	20-95	41-88

(9th edition Sleisenger and Fordtran's text book of Gastrointestinal and Liver diseases)

studies may be abnormal, but may not help in diagnosis because they may be abnormal in other malabsorptive conditions.

SEROLOGY

The most useful serological assays are IgA EMA and IgA tTG. IgA EMA and IgA tTG are based on the target antigen tTG. IgA and IgG anti gliadin antibody tests are based on target antigen gliadin.

AGA, anti gliadin antibodies; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; tTG, tissue transglutaminase.

Serological tests are used to evaluate patients with suspected CD, monitor adherence and response to a gluten-free diet, screening first degree relatives with CD, Down's syndrome, Turner's syndrome, William's syndrome, Ig A deficiency, thyroiditis and diabetes mellitus.

The anti gliadin antibodies are no longer considered sensitive enough or specific enough to be used for the detection of CD, except in children younger than 18 months of age. The levels of antibody titres vary with mucosal damage and levels decrease with clinical remission.

False negative IgA EMA and IgA tTG test results are more likely to occur in very young children (<2 years of age), those with mild celiac enteropathy, and, of course, in IgA deficiency. Selective IgA deficiency is more common in patients with CD than in the general population. Patients with CD and selective IgA deficiency lack IgA

endomysial antibodies and IgA antitissue antibodies against tissue transglutaminase. It is recommended that the test for anti-tissue trans-glutaminase antibodies be used as a single screening test for CD. If the levels of this marker are within the normal range (or if it is absent) and there is a high suspicion of celiac disease, selective IgA deficiency needs to be ruled out by measuring total IgA levels. In such cases, a test for IgG antibodies against tissue trans-glutaminase should be performed.

Histology – It remains the standard for diagnosing celiac disease and should always be done in cases of high suspicion or in cases with abnormal serological tests. The biopsies are usually taken during upper gastrointestinal endoscopy from second part of duodenum. There is no recommendation on the number of biopsies but at least 6-8 biopsies should be taken.

The endoscopic features like scalloping or absence of duodenal folds has been noted in some patients with

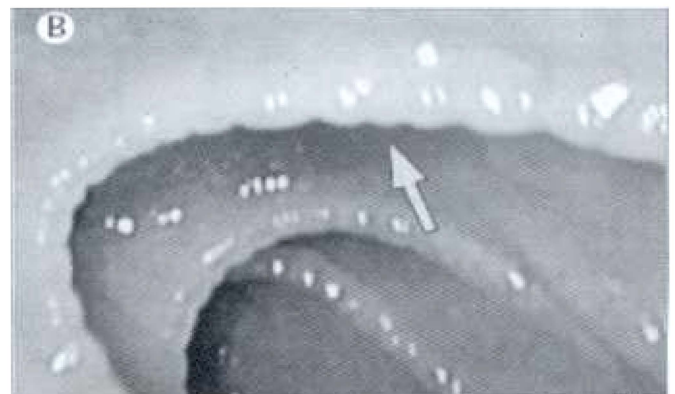


Fig. 4: Endoscopic finding showing scalloping of duodenal mucosa

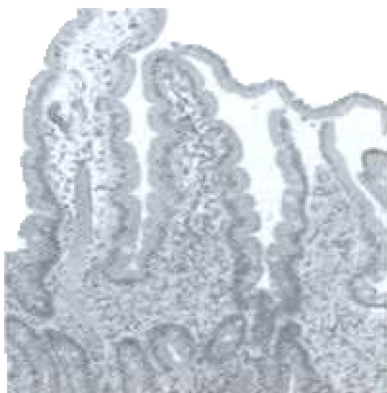


Fig.5: Normal histology (duodenum)

celiac disease (Figure 4). Scalloping is not specific for celiac disease and may be seen in eosinophilic enteritis, giardiasis, amyloidosis, tropical disease, and human immunodeficiency virus enteropathy. Other endoscopic features include multiple fissures or a mosaic-like appearance. Normal small intestinal mucosa contains long villi, varying in length depending on orientation and depth of biopsy (Figure 5). The histological features in celiac disease comprise small intestinal mucosal injury, increased intraepithelial lymphocytes, crypt hyperplasia and villous blunting or flattening (Figure 6).

The classification according to Marsh and its modification as described by Rostami should be applied, which includes Marsh I lesion (lymphocytic enteritis); Marsh II (lymphocytic enteritis with crypt hyperplasia; Marsh IIIA in addition shows partial villous atrophy; Marsh IIIB, subtotal villous atrophy; and Marsh IIIC, total villous atrophy.¹⁸

The accepted criteria for diagnosing celiac disease are the modified European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria. According to the criteria, only intestinal biopsy changes and clinical response to gluten free diet are sufficient to make a diagnosis of CD.¹

GLUTEN CHALLENGE

Gluten challenge means discontinuation of the gluten-free diet, followed by repeat biopsy of the small intestine—was considered an important confirmatory step in the diagnosis of CD. Now these days this is reserved for the few patients in whom the diagnosis remains in doubt after a period of treatment with a gluten-free diet.

A gluten challenge should be considered in patients who began a gluten-free diet empirically without



Fig. 6: Coeliac disease

documentation of a characteristic intestinal lesion or the presence of IgA EMA antibody. In such patients, symptomatic response to a gluten-free diet might indicate the presence of gluten-sensitive enteropathy or simply reflect a change in gastrointestinal function in response to a major dietary change.

Gluten challenge also should be considered if a diagnosis of CD was made during childhood based on small intestinal biopsy abnormalities in the absence of a positive IgA EMA or IgA tTG.

Patients who experience substantial symptoms following gluten ingestion are unlikely to tolerate formal gluten challenge and might prefer to remain on a gluten-free diet despite diagnostic uncertainty. Serologic studies and HLA typing for DQ2 and DQ8 may be helpful as negative result excludes celiac disease. A small bowel biopsy should be obtained as a baseline because an abnormal biopsy likely obviates the need for challenge.

Genetic studies – HLA typing - The negative predictive value of HLA-DQ2/DQ8 is almost absolute and is useful for ruling out CD in high-risk individuals such as first-degree relatives and patients with type 1 diabetes. Negative results avoid future concerns about the condition and reduce the cost of further serological tests.

COMPLICATIONS

The serious complications associated with CD are refractory celiac sprue, ulcerative jejunoileitis and enteropathy associated T cell lymphoma. The majority of symptoms recurrent or new are due to gluten ingestion intentionally or unintentionally.

Refractory coeliac sprue is characterised by absence of histological and clinical response to gluten free diet. Refractoriness is very often only apparent and mostly attributable to, dietary non-compliance or unintentional gluten intake. Approximately 5% of patients with celiac disease develop refractory CD. There are two types of refractory celiac disease (RCD), type 1, in which there is a normal intraepithelial lymphocyte phenotype, or type 2, in which there is a clonal expansion of an aberrant intraepithelial lymphocyte population.

Patients with RCD may never have responded to a gluten free diet or may have relapsed despite adherence and initial response to the gluten free diet. RCD type 1 usually improves after treatment with a combination of aggressive nutritional support, adherence to a gluten free diet, and alternative pharmacological therapies. In contrast, clinical response to alternative therapies in RCD type 2 is less certain and the prognosis is poor. Severe complications such as ulcerative jejunitis and enteropathy-associated T cell lymphoma may occur in a subgroup of patients with RCD.¹⁹

Ulcerative jejunoileitis is characterised by multiple ulcerations that evolve in strictures of the intestinal wall. It shares many immunopathological features with type 2 refractory CD. The important clinical features are colicky central abdominal pain, distension, low-grade fever, diarrhoea, and weight loss. The rate of death is very high—resulting from obstruction, bleeding, and perforation.

Enteropathy-associated T-cell lymphoma is usually prevalent in adults over 60 years and is mainly localised in the proximal small intestine. It usually develops in the jejunum but may also be found in the ileum or extraintestinal sites (e.g., liver, brain, chest, and bone) and is often multifocal and characterised by multifocal ulcerating nodules with strictures and perforation. The alarming symptoms are unexplained weight loss, abdominal pain, diarrhoea, loss of albumin and blood, increased lactate dehydrogenase, fever, and night sweating. 18F-FDG-PET and histological identification of lesions are regarded as the best options for diagnosis. The patients have a very poor outcome with a 2-year survival rate of 15–20%.²⁰ The treatment of this tumour is chemotherapy based, although there is a role for surgery in the treatment of localized or complicated tumours. Successful autologous stem-cell transplantation has been reported.

Coeliac disease may associate with increased risk

of carcinoma of oropharynx, oesophagus and small intestine. The mechanisms responsible for the increased prevalence of malignancy in CD are unknown. Increased crypt mitotic activity, increased turnover of lymphoid cells within the mucosa, penetration of the damaged intestinal mucosa by carcinogens, infection with oncogenic viruses, and underlying abnormalities in the mucosal immune system and surface epithelium are all potential factors.

Untreated CD may develop splenic hypofunction, and may result in spleen atrophy and depletion of IgM memory-B cells that protect against encapsulated bacteria. It is associated with autoimmunity and pneumococcal septicaemia.²¹

TREATMENT

Dietary treatment – The only accepted treatment is the complete dietary withdrawal of gluten throughout life. This includes complete elimination of wheat, rye and barley along with all derivatives because even small contamination can be harmful. Hidden gluten is present in a wide variety of processed foods, because wheat flour is used widely in food industry in many products like precooked meal, ice cream, pasta, sausages, cheese, soups and sauces. The cereals like corn, maize, rice and gram flour can be given. Homemade bakery products made from rice, corn or arrowroot should be used. Another important issue in management of celiac disease is the compliance of gluten free diet.

The patient education is very important and detailed food list with instructions should be provided by the physician and the dietician.

Untreated CD patients may have accompanied lactase deficiency secondary to epithelial damage. Therefore milk and dairy products should be avoided during initiation of gluten free therapy, later can be reintroduced during remission.

On gluten free diet, most of the patients improve within a few weeks. A study showed, 70% of patients returned quickly to normal health within two weeks.²² The histological response lags behind the clinical response.

The patient should be assessed for deficiencies of vitamins and minerals, including folic acid, B12, fat-soluble vitamins, iron, and calcium and any such deficiency should be treated. All patients with CD should undergo screening for osteoporosis, which has a high prevalence in this population.

There should be a dietician who monitors the patient's nutritional status and dietary adherence on a regular basis.

Meat, dairy products, and fruits and vegetables are naturally gluten-free and help to make up for a more nutritious and varied diet.

Future treatment

Novel therapies for CD are based on improved knowledge of molecular pathogenesis. It includes wheat variants and genetic modification which result in decreased or no immunotoxicity. Intraluminal therapies include degradation of gluten peptides in intestine by glutenase such as propyl endopeptidases, which remove proline rich and glutamine rich gliadin peptides in safer sequence. Other intraluminal therapies are gluten binders and gluten neutralizing antibodies. Zonulin receptor antagonist (octapeptide AT-1001) may be used to decrease the intestinal permeability as another option.²³

The attractive therapies like tissue transglutaminase inhibitors and HLA DQ2 /DQ8 inhibitors can prevent deamidation and subsequent immunological potentiation of gluten peptide²³.

Another promising alternative, especially for patients with RCD, is directly targeting the immune cells either by lymphocyte blocking (anti-IL-15, anti-CCR9, anti- $\alpha 4\beta 7$) or tolerance induction.²³

REFERENCES

1. Yachha SK, Poddar U. Celiac disease in India. *Indian J Gastroenterol* 2007;26:230-7.
2. Sood A, Midha V, Sood N, Avasthi G, Sehgal A. Prevalence of celiac disease among school children in Punjab, North India. *J Gastroenterol Hepatol* 2006;21:1622-5.
3. Gautam A, Jain BK, Midha V, Sood A, Sood N. Prevalence of celiac disease among siblings of celiac disease patients. *Indian J Gastroenterol* 2006;25:233-5.
4. Ciclitira PJ, Ellis HJ. Investigation of cereal toxicity in coeliac disease. *Postgrad Med J* 1987;63:767-75.
5. Troncone R, Auricchio S, De Vincenzi M, Donatiello A, Farris E, Silano V. An analysis of cereals that react with serum antibodies in patients with coeliac disease. *J Pediatr Gastroenterol Nutr* 1987;6:346-50.
6. Hvatum M, Scott H, Brandtzaeg P. Serum IgG subclass antibodies to a variety of food antigens in patients with coeliac disease. *Gut* 1992;33:632-8.
7. Chorzelski TP, Beutner EH, Sulej J, Tchorzewska H, Jablonska S, Kumar V, Kapuscinska A. IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. *Br J Dermatol* 1984;111:395-402.
8. Nistico L, Fagnani C, Coto I, Percopo S, Cotichini R, Limongelli MG, et al. Concordance, disease progression, and heritability of coeliac disease in Italian twins. *Gut* 2006;55:803-8.
9. Di Sabatino A, Corazza GR. Coeliac disease. *Lancet* 2009;373:1480-93.
10. Weile B, Cavell B, Nivenius K, Krasilnikoff PA. Striking differences in the incidence of childhood celiac disease between Denmark and Sweden: a plausible explanation. *J Pediatr Gastroenterol Nutr* 1995;21:64-8.
11. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am J Gastroenterol* 2006;101:2333-40.
12. Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180-8.
13. Makharia GK, Baba CS, Khadgawat R, Lal S, Tevatia MS, Madan K, Dattagupta S. Celiac disease: variations of presentations in adults. *Indian J Gastroenterol* 2007;26:162-6.
14. Sachdev A, Srinivasan V, Maheswary S, Mohan H, Ashish B, Singh LS. Adult onset celiac disease in north India. *Trop Gastroenterol* 2002;23:117-9.
15. Sood A, Midha V, Sood N, Malhotra V. Adult celiac disease in northern India. *Indian J Gastroenterol* 2003;22:124-6.
16. Farrell RJ, Kelly CP. Diagnosis of celiac sprue. *Am J Gastroenterol* 2001;96:3237-46.
17. Stern M. Comparative evaluation of serologic tests for celiac disease: a European initiative toward standardization. *J Pediatr Gastroenterol Nutr* 2000;31:513-9.
18. 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;5:838-43.
19. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. *Gut*;59:547-57.
20. Gale J, Simmonds PD, Mead GM, Sweetenham JW, Wright DH. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. *J Clin Oncol* 2000;18:795-803.
21. Ludvigsson JF, Olen O, Bell M, Ekblom A, Montgomery SM. Coeliac disease and risk of sepsis. *Gut* 2008;57:1074-80.
22. Pink IJ, Creamer B. Response to a gluten-free diet of patients with the coeliac syndrome. *Lancet* 1967;1:300-4.
23. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. *Gastroenterology* 2009;137:1912-33.