Review Article

Celiac Disease in India

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Abstract

Celiac disease (CeD) is an autoimmune enteropathy and is driven by dietary gluten in genetically susceptible individuals with prevalence of around 1% in general population globally. The prevalence of celiac disease in India is comparable to the rest of the world and even within India also, the gap between prevalence in North and South India is getting narrower because of changing dietary patterns. The clinical presentation is diverse with both intestinal and extra-intestinal manifestations and importantly, 30-50% of cases present with non-diarrhoeal celiac disease and lack of awareness regarding them lead to delay in diagnosis and subsequent complications of CeD. The diagnosis of CeD requires clinical features, serology and intestinal biopsy. The only available treatment currently is life long gluten free diet (GFD) which not only ameliorates clinical symptoms but also prevent the complications such as refractory CeD and malignancy. Presently, most of CeD patients are being seen by primary care physicians, therefore more awareness about this disease is required for an early diagnosis and effective management. In this review article, we attempted to provide a thorough review on CeD epidemiology, diagnosis, clinical features and management to help physicians in clinical practice.

Introduction

Celiac disease (CeD) is a chronic, systemic autoimmune disorder characterized by immune mediated enteropathy in genetically susceptible individuals (HLA DQ2 and DQ8 positive) induced by gluten proteins present in wheat, barley, and rye. Contrary to common belief, gluten enteropathy is a systemic disease rather than merely a disease of intestine. Genetically susceptible persons develop autoimmune injury to the intestine, liver, spleen, bones, and other organs. CeD is thought to be a disease of childhood, however it is a disease of lifetime "once a celiac, always a celiac".[1–7]

Changing epidemiology of CeD world over

CeD is a multisystem autoimmune disorder that is currently believed to affect about 1% of the general population world over.[8] The highest reported prevalence is in Caucasian population in Western European countries and in those countries where Caucasians emigrated, notably North America and Australia.[9–13] However, greater awareness of its presentations and the availability of new, accurate serologic tests have led to the realization that CeD is relatively common, affecting 1 of every 120 to 300 persons in North America.[10–12,14]

Similarly, until a few years ago, there were only limited case studies and occasional observations of CeD in Latin America,[15] in North Africa[16,17] and in the Middle East,[18] where gluten intolerance was believed to be rare. CeD now is also a common disorder in Latin America,[19] both in the more developed (e.g. Brazil and Argentina) and in the less developed (e.g. Cuba, Chile, Uruguay) countries.[8,9,20–22] This phenomenon is noteworthy because a large proportion of Latin American people share common European ancestry and because wheat is commonly present in their staple diet. One point is very clear that CeD has shown a rising trend even in those areas where it was considered to be uncommon. The rising trend of CeD in recent times is due to both, apparent and true reasons. With advent of serological tests and with increase in awareness about this disease, there has been an increase in the detection of CeD in many continents of the world (apparent). Furthermore, because of improvement in hygiene, while there has been a decrease in the incidence infectious diseases, a true increase in the incidence of inflammatory bowel disease, multiple sclerosis,

Location	Pooled sero-prevalence (95% CI)	Pooled prevalence of CeD
Europe	1.3 (1.1, 1.5)	0.8 (0.6, 1.1)
N America	1.4 (0.7, 2.2)	0.5
S America	1.3 (0.5, 2.5)	0.3 (0.1, 0.6)
Asia	1.8 (1, 2.9)	0.6 (0.4, 0.8)
Africa	1.1 (0.4, 2.2)	0.8 (0.2, 1.7)
Oceania	1.4 (1.1, 1.8)	0.5 (0.2, 0.9)

Table 1: Prevalence of CeD across various continents[24]

CeD, CeD; CI, Confidence Interval

and celiac disease. A recent meta-analysis on the incidence of CeD has shown that the incidence of CeD has been increasing at a rate of 7.5% per year for past two decades.[23] We did a meta-analysis which showed pooled global seroprevalence and prevalence of CeD to be 1.4% and 0.7% respectively. The prevalence of CeD is 0.4% in Latin America, 0.5% in North America and Africa, 0.6% in Asia and 0.8% in Europe and Oceania.[24] The same has been depicted in table 1 and figure 1.

Epidemiology of CeD in India

The true prevalence of CeD is difficult to ascertain, because many patients have atypical symptoms or none at all. Therefore, both greater attention and awareness among physicians as well as serological screenings in the general populations are needed to establish the real prevalence of CeD in these countries.[11,12,24,25]

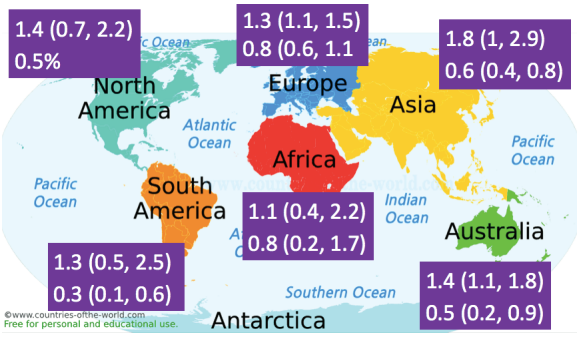

Figure 1: Figure showing seroprevalence and prevalence of celiac across continents. (Violet boxes over continents show seroprevalence [Confidence interval] and prevalence)

Evidences of CeD in India

Despite the belief that CeD is rare in India, Walia et al[25] in children and Misra et al[26] in adults described the first reports of celiac in India. Thereafter, there was a long silence about occurrence of CeD in India. Landmark work at tertiary care centers at Delhi, Chandigarh and Lucknow led to more frequent reporting of CeD from India. Most of the subsequent reports on CeD are from northern India (Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh) where wheat is the staple cereal in the diet.[27,28] There is thus an apparent regional variation of occurrence of the disease in India which could be due to differences in genetic predisposition to CeD, differences in consumption of wheat or both.[29]

Sood at al reported a prevalence of CeD to be 1 in 310 after a questionnaire based survey of 4347 school children (3-17 years).[27] In a community based study conducted at a rural and urban centres in Delhi, seroprevalence and prevalence of CeD was found to be 1.44% and 1.04%.[30] Prevalence was more

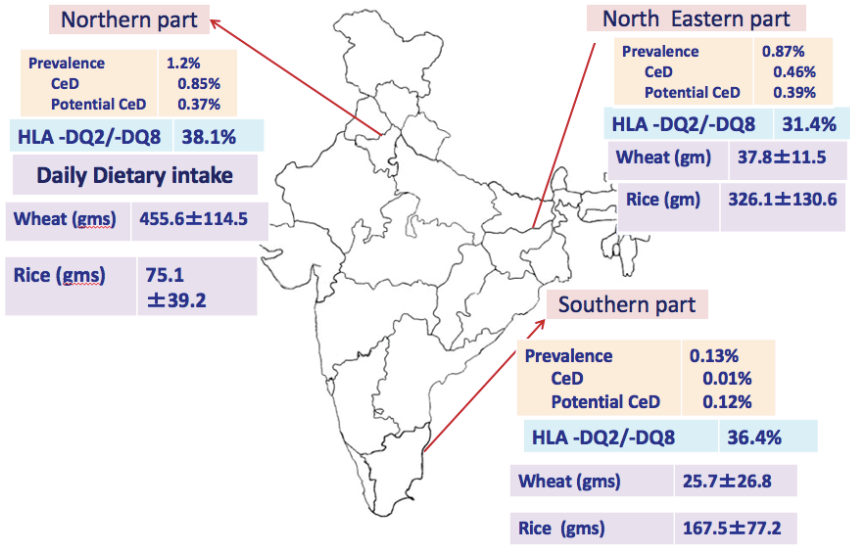

Figure 2: Diagrammatic depiction of prevalence, HLA genotype and wheat intake across three geographical regions in India.

CeD; CeD, gm; gram

in children than adults and also more in women than men. The regional differences and genetic as well as dietary factors associated with CeD has been highlighted in figure 2.[29] Similar strength of association as in Caucasians has been found in Indian children for HLA haplotypes with one study showing 100% showing positivity for HLA DQ2.[31]

Children Vs Adults

CeD generally has been recognized by pediatricians only and there had been a notion and belief that CeD is a disease of children and does not occur in adults ignoring the very fact that all these children will grow in adults. Also, those children with CeD in whom diagnosis was either missed or remain undiagnosed will present in adulthood with either a typical manifestation or atypical manifestations to endocrinologists for short stature, hematologists with anemia, orthopedic surgeons with metabolic bone disease or dentists with dental enamel defects.[32,33]

South India Vs North India

CeD in India has mostly been reported from North India and there are occasional case reports from South India. In a multicentre pan-India study including 23,331 healthy adults from the northern, the north-eastern part, and the southern part, the age adjusted seroprevalence of CeD was 1.23% in Northern India, 0.87% in north-eastern India, and 0.10% in Southern India. This study demonstrated regional differences in the prevalence of CeD and this difference was most likely not due to population prevalence of predisposing gene for CeD such as HLA-DQ2 and/or -DQ8, but it was likely because of difference in the wheat (gluten) eating pattern, which was highest in Northern part of India and lowest in Southern part of India. In fact, most of the cities and even villages in Southern India, people are now exposed to gluten. The belief, that CeD does not occur in South India; the same was thought about CeD in India about three decades back which was proven wrong with time. The prevalence of CeD and daily wheat intake in 3 geographical regions of India has been shown in Figure 2.

Changing causes of chronic diarrhea and malabsorption in India

In India, tropical sprue has been a the most common cause of malabsorption syndrome (MAS) and most clinical researchers have concentrated on investigating various aspects of tropical sprue[34,35] but data from our centre has shown CeD (65% of all causes) to be the most common cause.[36] For more than 30 years, the definition and diagnostic criteria of CeD is based on the histopathology of proximal small intestinal mucosa.[6,37,38] In developing countries, diagnosis of CeD remains in dilemma because the histological changes consistent with CeD are seen in a number of conditions such as tropical sprue, parasitic infestations and small intestinal bacterial overgrowth, and may not be pathognomonic of CeD.[39]

Clinical presentation

CeD traditionally has been defined as a gastrointestinal malabsorptive disorder that can present early in childhood after the introduction of gluten. It is now recognized, however, that the clinical manifestations are highly variable, may present at any age, and involve multiple organ systems. A delay in diagnosis varying from months, years to decades is common. Since CeD is a multisystem disorder, the clinical presentation is highly variable. Gastrointestinal manifestations may include chronic or intermittent diarrhea, weight loss, failure to grow, vomiting, abdominal pain, bloating and distension, anorexia, and constipation. What is important to highlight is that 30-50% of all patients present with non diarrhoeal CeD (NDCD), which is usually quite antagonistic to perception of many general physicians and gastroenterologists.[40–42] It is very common for CeD to present with extra-intestinal manifestations, sometimes with little or no gastrointestinal symptoms.[1–4,6] Anemia is a common presenting feature of CeD patients.[43,44] In a study from our centre, 15% of 338 CeD patients studied didn't have anemia and those who had anemia, had more severe disease manifesting with lower albumin, longer duration of symptoms and higher titre of tissue transglutaminase (tTG) antibody.[43]

CeD with atypical symptoms is characterized by few or no gastrointestinal symptoms, and extra-intestinal manifestations predominate (Table 2). Patients may present with unexplained short stature, delayed puberty, infertility, recurrent fetal loss, osteoporosis, vitamin deficiencies, fatigue, protein calorie malnutrition, recurrent aphthous stomatitis, elevated transaminases, and dental enamel hypoplasia. Bhadada et al in a prospective study involving 176 children with short stature from a tertiary care hospital in North India reported CeD as the single most common (15.3%) cause of short stature, followed by various endocrine disorders.[45] In a meta-analysis involving 17 studies with 3759 patients, seroprevalence of CeD in patients with all cause and idiopathic short stature was 11.2% and 9.7% respectively and prevalence of biopsy confirmed CeD in patients with all cause and idiopathic short stature was 7.4% and 9.6% respectively.[46] CeD may also be associated with myriad set of endocrinopathies such as thyroiditis, type 1 diabetes, hypogonadism and hypopituitarism. In a study from our centre involving 74 patients with CeD, single and multiple endocrinopathies were seen in 40% and 12% patients respectively.[47] A variety of neuropsychiatric conditions such as depression, anxiety, peripheral neuropathy, ataxia,

Common Features	Less Common Features	Associated conditions
Chronic or intermittent diarrhea (50-70%)	General features	Definite associations
Iron-deficiency anemia (85-90%)	Short stature (~10%)	Dermatitis herpetiformis
Failure to thrive	Recurrent aphthous ulcer	Autoimmune thyroiditis
	Recurrent abdominal pain	Microscopic colitis
	Steatorrhea	IDDM
	Extraintestinal features	Rheumatoid arthritis
	Osteopenia or osteoporosis (30-70%)	Sjogren's syndrome
	Hypertransaminasemia (40%)	IgA nephropathy
	Epilepsy	*Possible associations*
	Ataxia (0-6%)	Autoimmune hepatitis
	Infertility	Primary biliary cirrhosis
	Dental-enamel hypoplasia	Schizophrenia
	Recurrent abortions	

Table 2: Spectrum of clinical presentation of CeD[3,4,6]

epilepsy with or without cerebral calcifications, and migraine headaches have been reported in individuals with CeD.[48,49] In a systematic review by Hadjivassiliou, it was concluded that neuropathy (0-39%) is commoner in CeD than ataxia(0-6%).[50] Bone mineral density changes are seen in 32-70% due to altered vitamin D and calcium absorption.[51,52] Hypertransaminasemia is seen in 40-50% of cases and gets resolved in majority (95%) of patients after gluten free diet (GFD) for 1 year.[49] Recurrent aphthous ulcers and dental enamel hypoplasia can occur, more commonly in children.[53] Late menarche, early menopause, recurrent abortions and unexplained infertility are also associated with CeD.[54]

In a study from our centre, we reported variations of presentation of CeD in adults. Chronic diarrhea was the presenting manifestation in 20 (44%) patients only. Twenty-two (49%) patients were referred to us by hematologists, endocrinologists or gynecologists for evaluation of refractory anemia in 10 (2.2%), short stature in 6 (13.3%), metabolic bone disease in 2 (4.4%) and secondary infertility or delayed menarche in 4 (8.8%). Therefore, we concluded that more than half of adult patients with CeD present with atypical manifestations. A high index of suspi¬cion is required for diagnosing variant forms of CeD in adults.[36]

Reasons for an increase in prevalence of CeD in India

The rarity of CeD in India may not be real. A low index of suspicion and reliance on classic symptoms may be resulting in the significant under diagnosis of CeD in India. Sood at al[31] from Ludhiana reported a rising incidence of CeD in their hospitalized patients with CeD over last 10 years. We at our center also have observed a year wise rise in number of patients with CeD. In recent years, CeD is recognized much more frequently in India not only in children[29,30,35-37,42] but in adults also.[32,38,39]

There are many misconceptions about CeD which has contributed to/or contributing to under diagnosis of CeD in India:

1) That CeD is a disease of children.

2) That it is a disease of European nations and is uncommon in our part of the world,

3) That involvement of the intestine is a must for the diagnosis of CeD.

The gluten sensitivity which has been regarded principally as a disease of the small intestine is a historical misconception.[7] CeD may solely be manifested in the skin (dermatitis herpetiformis),[60] liver (asymptomatic increase in transaminases)[61] and nervous system (seizure, peripheral neuropathy)[62]

without involvement of intestine. Furthermore, all patients with CeD may not have small intestinal manifestations such as chronic diarrhea. In fact 30% to 50% of patients with CeD present predominantly with extra intestinal manifestations.[40,41,55]

4) Recognition of tropical sprue and gastrointestinal tuberculosis as major causes of chronic diarrhea and malabsorption syndrome,

5) Moderate to severe villous abnormalities are required for diagnosis of CeD in India:

It is well known that the CeD evolves over a period of time. At one point of time, the patients with CeD in a community are in varying states of evolution from Marsh 1 to Marsh 3 grades.[63] In other words, if we look at their mucosal histology, some will have mild, some will have moderate and some will have severe villous abnormalities. Bhatnagar, et al from our institution have shown that 25% of children with chronic diarrhea and with mild villous abnormality have CeD.[64]

Diagnosis of CeD

The most commonly used criteria for diagnosis of CeD is provided by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[38] The diagnosis of CeD requires positive celiac specific serology with demonstration of villous atrophy on duodenal histopathology in a patient with classical manifestations.[54] Latest guidelines from ESPGHAN also states that IgAtTG > 10 -fold and positive IgA anti endomysium (EMA) must be present to make a diagnosis of CeD without biopsy.[38] Now, we also have our own Indian Council of Medical Research (ICMR) criteria for diagnosis of CeD.[56] All criteria rely mainly on clinical presentation, serology, histology and/or genetic testing and response to GFD.

Serological tests

Although an intestinal biopsy is required to confirm the diagnosis of CeD, serological tests are frequently used to identify individuals for whom the procedure is indicated.[1-5,65] Commercially available tests include anti-gliadin antibody IgA and IgG (AGA IgA and AGA IgG), anti-reticulin IgA (ARA), anti-endomysium IgA (EMA) and anti-tissue transglutaminase IgA (TTG) antibodies.

IgA anti gliadin antibodies (AGA) developed in 1980s became obsolete from clinical practice because of low sensitivity and specificity are now used to recognize other gluten related disorders such as Non celiac gluten sensitivity (NCGS) and gluten ataxia.[37] The anti-endomysial antibody test is based on an immunofluorescent technique using either monkey esophagus or human umbilical cord as substrate; the accuracy of the test is similar for either substrate. The nature of this test renders it more time consuming to perform, generally more expensive and, because the interpretation is operator dependent, potentially more prone to errors. The sensitivity and specificity of EMA is 93.7% and 99% respectively.[57] Later on, TG2 was identified as target autoantigen for EMA and Enzyme linked immunosorbent assay (ELISA) was developed for the detection of IgA TG2, which demonstrated high sensitivity and specificity at lower cost. Sensitivity and specificity for IgA TG2 test ranges from 93- 96% and 91-94% respectively.[58–60] IgA anti DGP has lower sensitivity (83- 88%), equivalent specificity and are costly, when compared to IgA anti TG2 tests, thus limiting their use as initial screening test. IgG anti DGP has low sensitivity but has higher specificity (~98%) and are useful in in the setting of selective IgA deficiency where IgA based test will give false negative results.[57,58] IgA deficiency is seen in 2-3% of CeD patients and therefore IgA levels shall be measured along with other serological tests.[61]

Endoscopy and Histology

Endoscopic findings include mucosal fissuring, bulb atrophy, reduction and scalloping of mucosal folds in duodenum. CeD affects the mucosa of the proximal small intestine with damage gradually decreasing in severity towards the distal small intestine, although in severe cases, the lesion extends to the ileum. Involvement of mucosa may be patchy and thus requires multiple biopsies including duodenal bulb region (5 biopsies) to increase diagnostic yield.[62,63] The characteristic histologic appearance of small intestinal mucosa from a patient with untreated CeD classically exhibits a flat mucosa with reduction in the normal villous height to crypt depth ratio from between 5:1 and 3:1. Histopathological evaluation in CeD shows intra epithelial lymphocytes (IELs) >30/ 100 epithelial cells, crypt hypertrophy and varying degrees of villous atrophy and grading is done as per modified Marsh criteria (Table 3).[64,65]

Genetic testing

More than 90% of CeD patients show HLA DQ2 positivity and rest are HLA DQ8 positive. Testing negative for these HLA heterodimers virtually rules out CeD.[66] It is not a good test for initial screening as only 3% of those tested positive for these HLA heterodimers will develop CeD.[67] It can be helpful in clinical scenarios where diagnosis of CeD is uncertain, GFD has been started before confirming diagnosis, to reassure siblings of CeD patients who are tested negative and ensuring follow up of those tested positive.

Who should be tested for CeD?

At this phase of time, the evidence is not enough to justify mass screening . Hence, we should screen all those who are at risk for CeD(Table 4).[1–4]

Marsh-Oberhuber grade	Histologic criterion		
Type	Increased IELs	Crypts	Villi
0	No	Normal	Normal
1	Yes	Increased	Normal
2	Yes	Increased	Normal
3a	Yes	Increased	Partial villous atrophy, villi blunt and shortened
3b	Yes	Increased	Subtotal villous atrophy, villi atrophic but still separate and recognisable
3c	Yes	Increased	Total villous atrophy, villi rudimentary or absent, resembling colonic mucosa

Table 3: Marsh Oberhuber classification showing spectrum of changes in duodenal histology in CeD

IELs, Intraepithelial lymphocytes

Chronic diarrhea with malabsorption
Short stature
Refractory anemia
Osteomalacia, osteoporosis
Infertility
Dermatitis herpetiformis
Type I diabetes mellitus
Family members of CeD
Idiopathic seizures
Ataxia and polyneuropathy
Other autoimmune diseases

Table 4: Conditions with increased risk of Celiac disease

CeD, Celiac Disease

Never start GFD before confirmation of a diagnosis

The hypersensitivity to gluten is permanent and lifelong. The only treatment known at present is GFD which is to be continued lifelong. It is always advisable to confirm the diagnosis and then start GFD. After gluten withdrawal for weeks, changes the mucosal histology normalize and even serological titre regress. If the mucosal biopsy now shows no definite villous abnormality, it is difficult to ascertain that the normal histology is a response to treatment or the histology was normal even prior to initiation of GFD. This is a trap like situation and we have faced a real difficulty in solving the diagnosis in some of such patients. Therefore, one must have a strong ground for starting a patient on GFD and should not justify the diagnosis based only on serological evidences.

Approach towards making a diagnosis of CeD

The single most important step in diagnosing CeD is to first consider the disorder by recognizing its myriad clinical features. There is no single test that can definitively diagnose or exclude CeD in every individual. Just as there is a clinical spectrum of CeD, there is also a continuum of laboratory and histopathological results. The combination of clinical and laboratory features may result in a diagnosis of CeD.

All diagnostic tests need to be performed while the patient is on a gluten-containing diet. The first step in pursuing a diagnosis of CeD is a serologic test. Based on very high sensitivities and specificities, the best available tests are the IgA-TTG and IgA-endomysial antibody tests that appear to have equivalent diagnostic accuracy.

Biopsies of the proximal small intestine are indicated in individuals with a positive CeD antibody test. Multiple biopsies should be obtained because the histologic changes may be focal. The pathology report should specify the degree of crypt hyperplasia and villous atrophy as well as assess the number of intraepithelial lymphocytes. Some degree of villous atrophy is considered necessary to confirm a diagnosis of CeD. The finding of intraepithelial

lymphocytes with crypt hyperplasia without villous blunting is less definitive. Communication between the pathologist and the individual's physician is encouraged to help correlate the biopsy findings with laboratory results and clinical features.

In an individual with suggestive symptoms and a negative serology test, three scenarios are possible. First, the individual may have selective IgA deficiency. If an IgA deficiency is identified, an IgG-DGP test should be performed. Second, the serologic test may be a "false negative," and if this is suspected the test could be repeated, an alternative serologic test could be conducted, and/or a small intestinal biopsy could be performed. Third, the patient may not have CeD.[3,4] When the diagnosis of CeD is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) can stratify individuals to high or low risk for CeD.

Treatment of CeD

The only treatment currently available for CeD is strict adherence to a GFD for life. There are evidences which suggest that diagnosed but untreated patients with CeD have significantly higher morbidity and mortality. Prolonged adherence to a GFD may reduce both morbidity and mortality to the levels found in the general population.[1–4,6]

GFD is defined as one that excludes wheat, rye, and barley.[68] Even small quantities of gluten may be harmful. The strict definition of a gluten-free diet remains controversial due to the lack of an accurate method to detect gluten in food products and the lack of scientific evidence for what constitutes a safe amount of gluten ingestion. Though, the safe limit of gluten intake without development of histological changes is <10mg/ day.[69] The patient and their relatives should be counseled by a trained dietician. Vitamin and mineral deficiencies, including iron, calcium, phosphorus, folate, B12, and fat-soluble vitamins should be looked for and treated. Patients should be screened for osteoporosis. It is important to have a team-based approach to management. In addition to treatment by a physician and participation in a local advocacy group, consultation with a skilled nutritionist is essential. Regular follow up is essential. The following are six key elements in the management of individuals affected by CeD:

1. Consultation with a skilled dietitian
2. Education about the disease
3. Lifelong adherence to a gluten-free diet
4. Identification and treatment of nutritional deficiencies
5. Access to an advocacy group
6. Continuous long-term follow up by a multidisciplinary team

Learning about CeD and how to identify gluten-containing products is associated with improved self-management. Participation in an advocacy group is also an effective means of promoting adherence to a gluten-free diet and may provide emotional and social support.

Following initial diagnosis and treatment, individuals should return for periodic visits with the physician and nutritionist to assess symptoms and dietary adherence and monitor for complications. During these visits, health care providers can reinforce the benefits of adhering to a strict GFD for life. Patients should be examined at least twice in first year post diagnosis and should be assessed for symptoms, CeD serology trend, dietary adherence and specific biochemical parameters depending upon abnormalities detected at time of diagnosis.[70] Symptoms can be objectively evaluated by Celiac symptom index (CSI) and dietary adherence can be evaluated by Celiac dietary adherence test (CDAT).[71,72] Celiac specific serology declines with increasing duration of GFD with 80% becoming negative after 1 year and more than 90% after 5 years.[73] Lack of decline of serology warrants diet review for possible willful or inadvertent gluten intake. Gluten immunogenic peptides (GIPs) are immunodominant peptides in gluten which resist digestion and are excreted in stool and urine. Their detection in urine and stool serve as useful biomarker for recent dietary non-compliance.[74,75] The association between clinical improvement and CeD serology with mucosal recovery is poor.[76,77] A study with follow up biopsy after mean duration of 1.3 years showed persistence of villous atrophy (VA) in ~40% of patients.[78] Hence, it may seem reasonable to do a follow up biopsy after 1-2 years of GFD because persistence of VA requires review of dietary compliance and work up for refractory CeD (RCD).

Complications

Refractory CeD (RCD)

RCD may be defined as persistence or recurrence of sign/symptoms of malabsorption and villous atrophy in CeD patients despite being on GFD for one year or more, in the absence of other disorders including overt lymphoma.[79,80] Cumulative incidence rates for RCD ranges from 0.04-1.5%.[81,82] Its prevalence among NRCD ranges from 0-20% in various studies.[81,83–85] It may be classified as Primary RCD (non-response to GFD after diagnosis of CeD) or secondary RCD (loss of response after initial response). The mean age of diagnosis is around 50

years and is rare in younger age group. RCD is 2-3 times more common in females.[86,87] Most common clinical manifestations involves persistent diarrhoea, weight loss and pain abdomen.[88] Based on absence or presence of aberrant IELs, it is classified into Type 1 and Type 2 RCD respectively. Aberrant IELs can be detected by[87–89]

- Loss of normal surface markers (CD3, CD4, CD8) with preserved intracytoplasmic CD3 (iCD3) in more than 50% of IELs on immunohistochemistry or >25% IELs by flow cytometry.
- Detection of λδ-TCR clonal rearrangement by PCR analysis

This distinction is important for prognosis and therapeutic management. RCD 1 has 5-year survival rates of 80-96% and RCD 2 has poor prognosis with survival of 44-56%.[87,90] Ulcerative jejunitis is considered as RCD 2. Management involves strict GFD in both subtypes. Type 1 RCD responds well to systemic steroids and azathioprine with complete normalization of villi in ~50% of cases.[91,92] Oral budesonide (non-slow release) resulted in clinical improvement but no histological response in majority. Infliximab has also shown to induce responses in few case reports.[93,94] Type 2 RCD requires treatment with additional medications including Cladribine and autologous stem cell transplantation (ASCT).[95,96] Anti-IL-15 monoclonal antibodies (AMG 714) have shown promising results initially but a phase 2a clinical trial have shown disappointing results and warrants further research. An approach to a patient not responding to GFD has been elucidated in Figure 3.

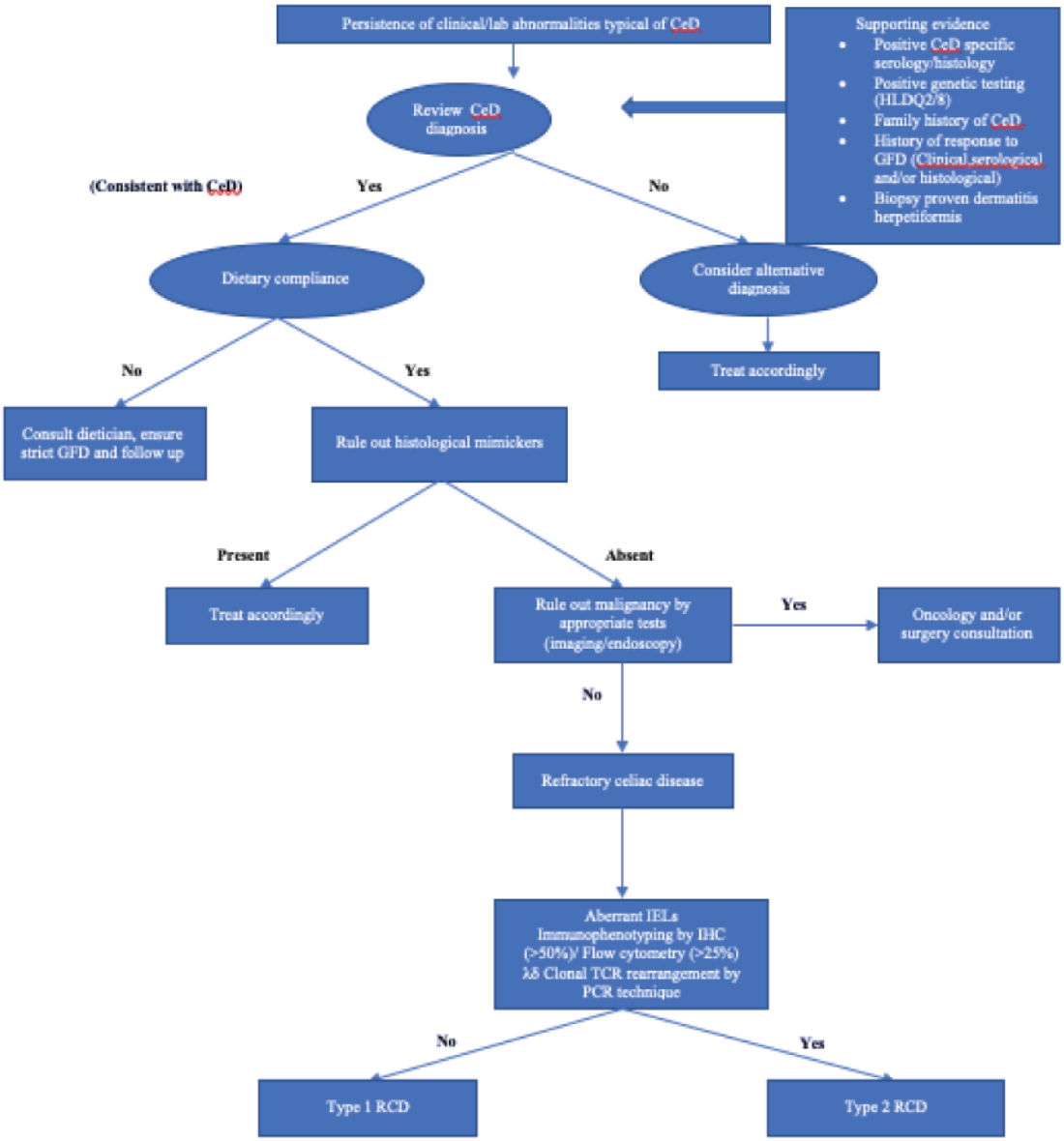

Figure 3: Diagnostic approach to Non-responsive CeD

CeD, Celiac Disease; GFD, Gluten free diet; IELs, intraepithelial lymphocytes; IHC, Immunohistochemistry; TCR, T cell rearrangement; PCR, Polymerase chain reaction; RCD, Refractory celiac disease

Malignancy

GI lymphomas are rare but RCD 2 has a poor prognosis because of high risk of developing enteropathy associated T cell lymphoma (EATL) (~50% after 5 years of RCD 2 diagnosis).[90] Abnormal IELs may be present in lymph nodes, blood, bone marrow, lungs and skin. Likewise, EATL may develop from any of these sites and is not limited to small intestine only.[97] Patients should be evaluated with cross-sectional imaging, capsule endoscopy, enteroscopy and/or PET CT. On immunohistochemistry, more than 80% of cases have lymphocytes expressing CD 30 positivity.[98] Management involves anthracycline based chemotherapy followed by ASCT with low overall response rates.[99] Brentuximab, an anti CD30 monoclonal antibody can be combined with chemotherapy in patients expressing CD30 positivity.[98]

Conclusions

CeD is an immune-mediated intestinal disorder with protean manifestations. There are now specific and sensitive serologic tests available for diagnosis that need to be used more widely. The treatment of CeD remains a lifelong GFD, which results in remission in most individuals. The classic presentation of diarrhea and malabsorption is less common and atypical and silent presentations are increasing. Most individuals are being seen by primary care physicians and specialists other than gastroenterologists. Therefore, heightened awareness of this disease is required. Education of physicians, dieticians, and other health care providers is needed.

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