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REVIEW ARTICLE

Presentation and Patterns of Celiac Disease in Indian Subcontinent: A Literature Review

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ABSTRACT

Gluten, in genetically susceptible individuals induces an immune mediated enteropathy called Celiac disease (CD). It is an established cause of malabsorption, with the worldwide prevalence being 1% in the general population. It is found across all age groups, from infants to the elderly with 20% patients being diagnosed in the seventh decade of life. It has varying clinical presentations ranging from silent asymptomatic forms which are diagnosed during screening to life threatening forms with severe malabsorption to atypical presentations, with the symptom spectrum extending beyond the gastrointestinal tract which are more common in adults. High index of suspicion, robust screening and testing, followed by strict adherence to gluten free diet is a must to curb and cure the disease. Patients tend to face difficulties not only during diagnosis, but also with compliance and availability of a gluten free diet, in addition to significant economic and psychosocial burden, which is more predominant in developing countries. Screening of high-risk groups like first-degree relatives of celiac disease, patients with severe malnutrition, other autoimmune diseases, refractory anaemia and irritable bowel syndrome should be done to enhance case detection. In low middle income countries, judicious resource utilisation takes precedence, hence, tackling a multifactorial disease such as celiac disease becomes challenging. Repeated follow ups, awareness among patients and doctors, encouragement, availability of testing and dietary counselling is necessary for management of the disease in such settings. Improving sanitation and feeding practices may also play role in decreasing incidence, considering childhood GI infections are a well-established risk factor. Increased availability of serological tests (IgA/IgG anti-tTG, anti -EMA and anti-DGP), biopsy, genetic testing and other newer modalities under research have improved the diagnostic accuracy. Poor compliance increases the risk of GI malignancy, non-Hodgkin's lymphoma, Hepatocellular carcinoma and MALToma. Hence adherence is a must to prevent complications. A wide variety of treatment modalities are being evaluated to bring into force alternative strategies for management. Only providing gluten free diet is often not sufficient for improvement of nutritional status in patients with CD. Hence, micronutrient supplementation should also be encouraged to meet the unmet needs.

OVERVIEW

Celiac disease (CD), also known as celiac sprue, nontropical sprue, gluten-sensitive enteropathy, adult CD, classical CD, idiopathic steatorrhea, and primary malabsorption typical CD, is a chronic enteropathy predominantly affecting small intestine which is precipitated by consumption of dietary gluten in genetically predisposed individuals. Mediated by T cell immune response it is characterized by villus atrophy of the small intestinal mucosa associated with malabsorption of nutrients hence the clinical manifestations. Various presentations including atypical CD, asymptomatic or silent CD, potential or latent CD, non-responsive CD and refractory CD are well documented. Atypical presentations being recognized more frequently compared to typical ones. Over the years new insights regarding global prevalence and atypical clinical presentations including obesity are now available. Owing to better knowledge, improved diagnostic modalities and enhanced understanding of its pathogenesis, the prevalence of CD in increasing. The treatment of CD primarily involves introduction of a gluten free diet, which poses compliance related issues in our setting, where gluten is a major component of the daily diet, with few cost-effective alternatives. It has been identified in a wide geographic distribution and affects individuals of various ethnic and racial backgrounds. The overall prevalence of CD in Europe has been estimated at 1%, with the highest being in Finland 2.4%. Data from Indian subcontinent suggests that occurrence of CD is more from Bengal and Punjab. Increasingly it is now been reported from southern parts of country. However, data regarding Indian patients is limited in current literature with estimated rate of diagnosis being 5%. This article aims to highlight the presentation patterns and issues related to management of CD in India. We performed an internet database search on PubMed using keywords "Celiac disease", "history of celiac disease", "prevalence of celiac disease in world", "risk factors of celiac disease", "prevalence of celiac disease in India", "guidelines for treatment", "ongoing research on new treatment modalities", "compliance in celiac disease"; selecting 57 papers published in different national and international journals in English language. The data obtained was thoroughly studied and discussed below.

HISTORY

Malabsorption syndromes have been described in Indian Literature, from as early as 15th century B.C[1].CD was first identified by Aretaeus the Cappadocian in the 1st century A.D; however, it was only in 1888, that Samuel Gee described the disease in detail, and it was first described in India as late as 1966. In the early 20th century, an attempt was made to identify the 'toxic component' in the diet. During the 1950s, Wim Dicke established that wheat, rye and oats were the main offenders and avoiding their consumption led to dramatic improvement in symptoms[2,3]. Later, gluten was identified as the inciting factor leading to autoimmunity[4]. Over the years new insights regarding global prevalence and atypical clinical presentations including obesity became available. Newer modalities of treatment are currently being identified.

EPIDEMIOLOGY

CD, an immune-mediated enteropathy is a systemic disease with a myriad of clinical presentations. It is found globally, with the worldwide prevalence an estimated ~1%. The population-based data suggests that the prevalence and incidence of the disease has increased over the last 30 years. The highest prevalence is reported to be in the Caucasian population of Western Europe, North America and Australia[5]. This increasing trend can be attributed to a significant rise in the rate of detection, and also to the changing environmental and dietary factors[6]. A recent meta-analysis revealed that the incidence of CD has been increasing at a rate of 7.5% per year for the past two decades[7]. With the increasing availability and use of serological tests, improving awareness, screening of high-risk cases and actual increase in prevalence due to changing dietary habits, a greater number of patients are now being diagnosed with the disease. However, there still exist lacunae in literature with respect to data from several countries[8].

As per available data, CD is reported to be uncommon in India and other southeast Asian countries. There is also a dearth of studies from the region. A cross sectional study conducted by Makharia et al, in Delhi reported the prevalence of CD in the north Indian community to be 1.04 % which is equal to that in the western world[9]. In fact, in a comparative study between the population of European descent and South Asian community (Punjab and Gujarat), incidence in the south Asians was reported to be 4 times higher[10]. This leads us to the conclusion that CD is grossly underdiagnosed, which may be due to several factors including low suspicion, which need to be explored further.

High prevalence of malnutrition, highly probable alternative etiologies of chronic diarrhoea including TB and parasitic infections, lack of vigilance may be

contributory to the limited research on and underdiagnosis of CD in India.

In India, regional differences have been observed in the prevalence of CD, with more cases reported from Northern India as compared to southern and north-eastern parts- mainly attributed to the dietary pattern and ethnicity. In a study conducted by Ramakrishna et al, a similar pattern was reported. The Age-adjusted prevalence in the study was 1.23% in northern, 0.87% in north-eastern, and 0.10% in southern India ($P<0.0001$). In the study, differences in the HLA-DQ 2/8 allotype prevalence were also investigated. The population prevalence of genes determining HLA-DQ2 and/or -DQ8 expression was 38.1% in northern, 31.4% in north-eastern, and 36.4% in southern India. There are many factors in play besides genetic susceptibility- the staple diet of the population being one of them[11]. The wheat intake is higher in North India in comparison to the South and North-Eastern part of the country. A typical North Indian diet contains around 25-30 gm gluten/day; whereas average gluten intake in the Western countries is about 10-20 gm/day.In recent years, the gap between prevalence in North and South India has decreased, mainly due to changes in diet due to urbanization, industrialization and adaptation of western dietary patterns[12].

Sood at al, from Ludhiana district, north India in 2006 reported a prevalence of 1 in 310 from a questionnaire-based survey conducted on 4347 school children. School going children belonging to 3-17 years age group were included. The questionnaire was based on symptoms and signs inclusive of diarrhoea, vomiting, abdominal discomfort, failure to thrive, short stature, recurrent aphthous ulcers, autoimmune disease, family history of CD and pallor on examination. The reported prevalence was less probably due to under assessment as only a selected group of children were studied and hence, asymptomatic patients with silent/ latent CD were missed[13]. In a community-based study done at rural and urban centres in Delhi, seroprevalence and prevalence was found to be 1.44% and 1.04% respectively. Hence as per this study in the north Indian community 1 in every 96 individual suffers from CD[14]. Overall, the prevalence in India varies from 0.32-1.41%.

CD, once thought to be an illness of childhood, is increasingly being recognized in adults too. In the Canadian Celiac Health Survey of 2,681 adults with biopsy-proven CD, the mean age at diagnosis was 46 years. In another study conducted in the north Indian region, mean age was reported to be 32.9 years with diarrhoea as presenting complaint in 67.7%, refractory iron deficiency in 18.7% and 9.4% had abdominal complaints[15]. Incidence of CD is highest in females and children[16].

RISK FACTORS

Gluten is the main environmental trigger of the disease. Among genetic factors associated with CD, the strongest association is with the HLA class II region. Strength of association for HLA haplotypes in the Indian population is the same as in Caucasians- up to 100% positivity has been documented for HLA DQ2[17]. The prevalence of CD in first degree relatives was found to be 9-fold higher compared to the general population in India. In a study by Singla et al., out of 202 first degree relatives of the 64 index cases with CD, 17.3 % were seropositive for IgA tTG while confirmed biopsy proven CD was diagnosed in 10.2 % of children and 8.1 % of adults. HLA DQ2/DQ8 was positive in 96.7 % of the index cases and all first-degree relatives with confirmed cases[18]. In another study, prevalence of CD in siblings was reported to be around 22%[19]. Familial clustering of CD is common with 10% of first-degree relatives having the disease. The high concordance rate for monozygotic twins (~80%) compared to HLA-identical siblings (~30%) and dizygotic twins (~10%) underscores the importance of both genetic factors (HLA and non-HLA genes)[20]. Although a varying proportion of the Indian population has the genetic background to express HLA-DQ2 and/or HLA-DQ8 ranging from 13-30%, however only 1% of the population have serological and clinical features of CD. Data regarding other risk factors is depicted below in table 1. It is however conflicting.

TABLE 1: Various studied risk factors and their association with development of CD.[21]

S.no.	RISK FACTORS	EFFECT ON CD RISK
1.	Age of gluten introduction	No association
2.	Amount of gluten introduction	Some studies suggestive of increased risk
3.	Infections (Overall)	Increased risk up to 18 months of age
4.	Infection (gastrointestinal)	Increased risk by 33%. Reduced risk in vaccinated children against rotavirus
5.	Rotavirus / Reovirus	Increased
6.	*Helicobacter pylori*	Inverse relation in some studies
7.	Season of birth	Increased risk in summer
8.	Geographic location	Increased with northern latitiude
9.	Socio economic status	Increased with higher socioeconomic status
10.	Proton pump inhibitors	Increased
11.	Antibiotic use	No increased risk
12.	Iron supplementation	Increased risk in MoBa cohort
13.	Vitamin D	No association
14.	Maternal gluten consumption	No association

Studies have demonstrated that neither the timing of gluten introduction nor breastfeeding had a significant impact on the risk of development of CD; however, delayed gluten introduction was associated with a later onset of the disease. There is No evidence suggestive of the impact of breastfeeding, its duration or persistence at the time of gluten introduction, on CD risk[22]. However, the study by Henriksson et al., concluded that breastfeeding offers protection against the development of CD in predisposed infants and it is the most significant variable in reducing the risk[23]. Certain subsets of individuals are at an increased risk of CD and should be screened for possible co existing presentation (Table 2)

TABLE 2: Group of patients to be screened for CD

First-Degree Relatives Of CD	IgA Deficiency	Autoimmune polyglandular syndrome type II
Down Syndrome	Autoimmune disorders	Cryptogenic cirrhosis
Turner Syndrome	Type 1 Diabetes Mellitus	Primary biliary cirrhosis
Williams-Beuren Syndrome	Autoimmune thyroiditis	Non cirrhotic portal hypertension
Lichen sclerosis	Psoriasis	Gastric hyperplastic polyps
Myoclonus ataxia	Autistic spectrum disorders	Pure red cell aplasia
Sjogren syndrome	Addison disease	

CLINICAL FEATURES

The clinical presentation is diverse with both intestinal and extra-intestinal manifestations and 30-50% of cases present with non-gastrointestinal symptoms[24]. Diarrhoea is the most common presenting symptom. Around 26-49 % children presenting with diarrhoea to a tertiary care hospital were diagnosed as CD[25]. Fatigue, weight loss, failure to thrive and refractory anaemia are some of the other presentations of the disease (table 3). CD is a chronic disorder, requiring lifelong compliance to therapy and if untreated, it is associated with long term complications, increased morbidity and mortality.

TABLE 3: Clinical manifestations of CD[32]

Intestinal	Extraintestinal	Long Term Complications
• Chronic or intermittent diarrhoea/ Nocturnal/ Early Morning or Postprandial diarrhoea • Constipation • Abdominal pain • Recurrent nausea / vomiting • Distention of abdomen • Irritable bowel syndrome • Functional dyspepsia • Steatorrhea • Bloating / Flatulence • Celiac crisis	• Weight loss/ Failure-to-thrive/Short stature • Iron-deficiency anaemia • Bony deformities/ Osteopenia /Osteoporosis/ pathological fractures/ Secondary Hyperparathyroidism • Delayed puberty, Amenorrhea • Chronic fatigue • Neuropathy/Ataxia/ Demyelinating disorders/Seizures • Arthritis • Autoimmune hepatitis • Recurrent aphthous stomatitis/Dental enamel defects • Ecchymoses and petechiae/Dermatitis herpetiformis/Follicular hyperkeratosis	• Gastrointestinal tract malignancy (10-fold increased risk)[26] (oropharyngeal / oesophageal/ small bowel adenocarcinoma) • Non-Hodgkin's Lymphoma (40-70 fold increased risk)[27,28] • Hepatocellular carcinoma • Microscopic colitis • Refractory sprue • Monoclonal proliferation of intraepithelial lymphocytes[29] • Enteropathy associated T cell lymphoma[30,31] • Ulcerative jejunoileitis

Extra-intestinal findings are seen in up to 60% of paediatric celiac patients [33]. Presentation of intestinal symptoms is less common in elderly patients compared to children. Anaemia is present in 60-80% of elderly patients and micronutrient deficiencies may be the first and at times the only presentation. Classical symptoms of malabsorption i.e., diarrhoea, weight loss and abdominal pain are less commonly seen in the older age groups[34].

As per an Indian study conducted by Bharadia et al, in which 176 children diagnosed as CD were recruited, chronic diarrhoea as a presenting symptom was found in 65 (37 %), short stature in 65 (37 %), abdominal distension in 33 (19 %), pain abdomen in 13 (7 %) and constipation in 9 (5 %) patients. Up to 90% (158) of the children had anemia[35]. In another study evaluating adults in India, the mean age at diagnosis was found to be 28.7 years. Chronic diarrhoea was the presenting manifestation in 44% patients, short stature in 13.3%, secondary infertility or delayed menarche in 8.8%, metabolic bone disease in 4.4% and refractory anaemia in 2.2% [36]. In a south Indian study, CD was diagnosed in 1.8% of patients labelled as having irritable bowel syndrome-Diarrhoea predominant and 1% in functional dyspepsia group. The authors opined that larger screening in different regions is required for diagnosing CD in patients labelled as functional dyspepsia or irritable bowel syndrome. The presence of anaemia can help in predicting CD in this subset of patients[37].In another study evaluating severe acute malnutrition, CD was diagnosed in 13.1% children while tuberculosis and HIV were diagnosed in 9.3% and 4%, respectively[38].

DIAGNOSIS

The diagnosis of CD requires the presence of clinical manifestations, positive serology and/or duodenal biopsy. American College of Gastroenterology (ACG), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and Indian Council of Medical Research (ICMR) have proposed guidelines for diagnosis and management of the disease. Brief outline with differences has been described in the table 4.

TABLE 4: Comparison among the guidelines provided by three societies for diagnosis of CD[32,39].

S.NO.	FEATURE	ACG	ESPGHAN	ICMR
1.	SEROLOGY	IgA anti-tTG is the preferred single test for detection of CD in individuals over the age of 2 years. When screening children less than 2 years of age, IgA anti-tTG test should be combined with anti-DGP (IgA and IgG). Diagnosis is based on history, examination, serology, biopsy and HPE.	For initial testing, both total IgA and IgA anti-tTG 2 is recommended. For diagnosis only clinical manifestations and 2 positive serology with high titres is necessary. Biopsy to be performed on case-to-case basis.	The diagnosis of CD is based on the combination of clinical manifestations, positive IgA anti-tTG, and a deep duodenal biopsy demonstrating the presence of villous abnormalities of at least Marsh grade 2. For screening IgA anti-tTG is currently the test of choice.
	In patients with IgA deficiency	In patients with IgA deficiency, IgG-based testing (IgG anti- DGP and IgG anti- tTG) should be performed	IgG-based testing (DGP, EMA or tTG) is recommended.	an IgG based test such as IgG anti-tTG Ab or IgG DGP Ab may be used.
2.	BIOPSY	Intestinal biopsy should be pursued even if serologies are negative, if suspicion of CD is high	In children with high tTG IgA values ≥10 times ULN and positive IgA EMA, biopsy is not advised.	Diagnosis of CD should not be based solely on a positive celiac serology test, even if the test was positive in very high titre, eg 10 x ULN
			Children with anti-tTG lower titres (<10 ULN) should undergo biopsies.	
		1 or 2 samples from duodenal bulb and at least 4 from distal duodenum is necessary for adequate reporting	≥4 biopsies from the distal duodenum and ≥1 from the bulb should be taken for adequate sampling.	Four to six mucosal biopsies should be obtained from the mucosal folds in the second part of the duodenum and should be oriented well for interpretation. In India, it is recommended that the number of intra epithelial lymphocytes should be 40 IELs/100 epithelial cells when considering a diagnosis of CD.
3.	GENETIC TESTING	HLA DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations	HLA testing and presence of symptoms are not obligatory criteria for a serology based diagnosis without biopsies.	HLA typing is not required routinely for the diagnosis of CD.
4.	INABILITY TO PERFORM UPPER GI ENDOSCOPY	Capsule endoscopy is indicated in patients with positive celiac serology and unable/ unwilling to undergo upper GI endoscopy. It is also recommended for assessment of small bowel in complicated CD.		Clinical manifestations and characteristic HLA profile, positive serology using two antibodies tests can be used to confirm the diagnosis. (Second test – IgA anti-EMA or IgA anti-tTG)
5.	MISCELLANEOUS	In patients with high suspicion gluten challenge to be performed to confirm or exclude diagnosis for patients already on gluten free diet		

Keywords: IgA/ IgG anti- tTG: IgA/IgG anti-tissue transglutaminase antibody, CD: Celiac Disease, anti-DGP: antibody against deamidated gliadin peptide, HPE: Histopathological examination, Ab: antibody, IgA-EMA: IgA anti-endomysial antibody, IELs: intra epithelial lymphocytes, HLA: Human Leukocyte Antigen.

The general approach towards diagnosis in India is, any patient presenting with symptoms of CD with positive serology and suggestive histopathology findings is confirmed as a case of CD. If there is discrepancy in the HPE findings with positive serology, then HLA typing or repeat biopsy is recommended. With only suggestive HPE findings with negative serology, other causes of villous atrophy are evaluated. Diagnosis is excluded if HPE and serology both are negative. Patients with positive IgA anti-tTG type 2 and IgA anti endomysial antibodies, (EMA) and no or minor small bowel histological changes are usually diagnosed as 'potential' CD; and should be kept under clinical and laboratory surveillance. Low gluten intake before biopsy, sampling error or incorrect orientation of the biopsy for reading should be excluded before labelling the patient as potential CD.

False positive serologic tests may be seen in chronic liver disease, rheumatoid arthritis, inflammatory bowel disease and other autoimmune diseases. However, these are not associated with typical histologic changes in duodenal biopsy. To avoid diagnostic uncertainty, both biopsy and laboratory testing should be performed on a diet containing gluten. Uneven distribution and variable intensity of histopathological changes in the small intestine along with multiple disorders presenting a similar specimen image may lead to invalid biopsy results. In addition to recognising the role of genetics in pathogenesis of CD, we must also recognise that differences in genetic makeup between the Caucasian and the Indian population would lead to different manifestations of the disease, and, moreover, require slight differences in the approach to diagnosing the disease. The possibility of differences in validity of diagnostic modalities in the different populations must be considered, and disease cutoffs should be explored and modified if need be. This could lead to improved detection of cases, and might give an enhanced insight into the factors affecting prognosis of the disease. Moreover, population specific tests would also lead to minimal delays, judicious resource utilization and better outcomes. [40]

MANAGEMENT

Irrespective of the presentation, the only approved treatment is a gluten free diet. The key elements in the management of CD is consultation with a skilled dietitian, educating parents and patients about the disease, lifelong adherence to gluten free diet, identification and treatment of concomitant nutritional deficiencies, access to support groups and long term follow up by a multidisciplinary team[41]. Strict dietary compliance leads to improvement of symptoms, anthropometric measures, quality of life; prevention of long-term complications and decreases mortality. Hence, the biggest challenge is to determine and rectify factors affecting dietary compliance.

In a study by Chauhan et al, 70 patients with CD were assessed in the Indian population for dietary compliance: 53(75%) were found to be compliant, 13(18%) dietary non-compliant while 4 had doubtful history regarding dietary compliance. Dietary compliance was found to be affected by education status of the mother, with better adherence reported in families where parents were aware and educated about the disease and importance of gluten restriction[42].

As the child grows older, the parental control over food selection decreases. Social interaction and pressure of peer approval in adolescent age groups affects compliance with tendency to indulge in meals without acknowledging their gluten content. In the above-mentioned study children were found to be more compliant (80%) compared to adolescent age group (44%). In adolescents, peer pressure, hectic lifestyle, consumption of ready to eat foods without labelled gluten content, and nonavailability of gluten-free food in social settings, are important contributors of noncompliance[43].

Compliance was found to be better in patients with higher socioeconomic status and in nuclear families; with a smaller number of siblings (68.3% of compliant patients had <2 siblings compared to 77% patients in non-compliant families). In a joint family, the amount of people eating on other diets may tempt the child to not comply.

CD not only affects physical health but also has a huge impact on mental wellbeing specially in the paediatric age group. Children often experience problems related to adjustment such as difficulty in maintaining diet at school, restaurants, trips, etc. Irritability, non-specific somatic complaints are also more reported in patients with CD[42].

Patients presenting with diarrhoea have better compliance (72% of the dietary compliant population in the study compared to only 15% in the non-compliant group). Diarrhoea as a presenting symptom disturbs day to day functioning of the patient hence, they have the tendency to strictly follow dietary advice. Another study

reported a compliance of 53.3% with improvement to 92.4% on repeated counselling. The most common reason of poor compliance was non availability of gluten free diet.[44]

In a low-income country like India, a common meal is prepared for all family members. It is a difficult task to cook a separate meal for a single family member. Grains are often mixed at the time of grinding it into the flour at commercial outlets. Grinders are often not thoroughly cleaned and the initial part of the flour is often contaminated. Non availability of gluten free food items, high costs and poor taste are some of the commonly reported factors affecting compliance, as noticed in Pediatric Gastro-enterology OPDs. Nutritional labelling in India is not as comprehensive as that in the western world, often gluten content isn't mentioned on food items, thus leading to increasing difficulties for patients, both in terms of accessing the right kind of diet, and disease.

Patients with CD should be followed up 6 months after diagnosis and every 6 monthly to look for symptomatic improvement, compliance with the gluten-free diet, quality of life, and progressive normalization of celiac-associated antibodies[45]. Rapid improvement in clinical symptoms is observed within 2-4 weeks in children, serological and histological changes take a longer time to respond[46]. Although histological response in children is observed within 2 years by a rate of 95%, this rate is 60% in adults[47]. As per ACG clinical guidelines; complete blood count, alanine aminotransferase, vitamins (A, D, E, B12, B6), copper, zinc, carotene, folic acid, ferritin, and iron should also be monitored at 3-6 monthly. Diet prepared for the children is often deficient in micronutrients. In a pilot study at our centre, we assessed the micronutrient status of children diagnosed to be having CD. Anaemia was found in 85% of children, thrombocytosis in 20% and vitamin B12 deficiency in 70% patients despite being on a gluten free diet. Hence, a gluten free diet, although the mainstay of treatment, is not sufficient for improvement of nutritional status in patients with CD Micronutrient supplementation is often necessary. Due to the high prevalence of micronutrient deficiencies, supplementation through diet is often encouraged at the time of diagnosis in children, an approach not adopted in the adult population, wherein we only supplement if a deficiency is diagnosed through biochemical tests. Data for prevalence of these deficiencies in adults should also be tabulated, so we're able to draw better comparisons, in addition to providing better care to our patients. Another difference in the approach is, all children diagnosed with Severe Acute Malnutrition (SAM) are screened for CD, whereas screening in adults is less stringent. These differences combined with the difference in presentations in the two cohorts, give us an insight to the pathophysiology of the disease and factors affecting it, and should be explored in order to develop better screening, diagnostic and treatment modalities.

Thus, we need a multidisciplinary and a multimodal approach towards management of CD in the country. Establishment of "Celiac Support Groups" is the way forward. Celiac support group of India is pioneering these efforts in the country. Children should also receive support through school health teams. Improving availability of palatable, cheap, and socially acceptable gluten-free food and better labelling of food will increase compliance of the patients. Providing feasible alternatives, such as grinding of flour at home, providing a list of acceptable and unacceptable food items, addressing the difficulties faced by the patients are other ways. Regular follow ups, focusing on counselling and reiterating importance of compliance should be encouraged, in order to avoid disease flares. Indulging in behavioural change communication, and making use of public health measures to increase awareness will help create a conducive environment, and improve sensitivity towards those living with the disease. Involvement of a dedicated team of dietitians to work comprehensively with the patients leads to improved patient outcomes, as was evidenced by our pilot study.

WHAT'S NEW

Before the discovery of serology, diagnosis of CD was cumbersome and biopsy was necessary in all cases. With increased diagnostic accuracy of the new emerging plasma biomarkers and those under research there has been a paradigm shift in diagnosis and management of CD.

Antigliadin antibody was the first serological marker used in the diagnosis of CD but due to poor sensitivity and specificity, utility declined over time. Currently, IgA antitissue transglutaminase (IgA anti-tTG), antideamidated gliadin peptide (anti-DGP), and antiendomysial antibody (EMA) are mostly being used for the diagnosis. Progress has been made from serology-based testing to point-of-care testing (POCT), testing of antibodies in saliva, faeces and stools; genetic testing and tests to ascertain villous atrophy; Intestinal Fatty Acid Binding Protein (I-FABP) and citrulline.

(POCT) kits are card-based which are rapid and easy to perform. These kits are based on detection of anti-DGP either IgA/IgG via

immunochromatographic principle and sensitivity and specificity is comparable to IgA anti tTG in symptomatic patients. It is also a surrogate marker for villous atrophy[48]. In a study done in India, POCT called Biocard, a lateral flow immunochromatographic strip system was used. Sensitivity and specificity of 83% and 93%, respectively, was reported from this study[49].

Detection of antibodies in saliva and stool samples can be done and being non-invasive they are easier to obtain. However, the sensitivity is poor hence cannot be used for routine practice[50].

Citrulline, a non-essential amino acid (Aa) is produced from enterocytes of the proximal part of the small intestine. Since it is a product of the urea cycle it cannot be supplemented by diet, hence it has been proposed as a marker of intestinal synthetic function. Plasma citrulline levels are a novel biomarker of reduced number of enterocytes and function in different diseases, and it correlates with the decreased enterocyte mass irrespective of nutritional and inflammatory conditions. It has been used to identify intestinal functional capacity following surgery and correlates with residual bowel length, villous atrophy, after small intestine transplantation, during necrotizing enterocolitis in newborn and in chemotherapy induced mucosal enteropathy[51]. Its utility as a marker in celiac has been evaluated in some studies.

In a study by Lomash et al, serum citrulline was studied as a surrogate biomarker in CD. Disease burden, efficacy of treatment and role in asymptomatic first-degree relatives was assessed. Mean plasma level was found to be significantly lower in first degree relatives and study suggested higher sensitivity to identify mucosal atrophy in children. In majority of patients, serum tTG-IgA levels correlate with the histopathological changes but it becomes a challenge in patients with concomitant IgA deficiency which is reported more commonly in patients of CD. In such cases citrulline levels can complement or replace tTG-IgA. Healing of mucosa increases production of citrulline and is dependent on the number of enterocytes. Study also suggested that plasma citrulline can differentiate between serology negative and serology positive first-degree relatives irrespective of their HLA genotypes considering the prevalence of up to 47.7% in healthy population[52].

Intestinal-Fatty Acid Binding Protein (I-FABP) is a small cytosolic protein found in mature enterocytes and is a marker of injury to the small intestine. Since it is found in more concentration in the distal part of the small intestine, it can be used to assess the extent of intestinal epithelial cell injury[53]. It has been used in the evaluation of a number of diseases such as mesenteric infarction, intestinal ischemia, and necrotising enterocolitis to name a few. Its utility in CD has also been explored with 100% positive predictive value in patients with positive serology or genetic susceptibility[54]. Moreover, plasma levels declined rapidly on gluten free diet implying a possible role in monitoring disease activity. Diagnostic accuracy of I-FABP >1100 pg/ml was 78% in a cohort study of celiac patients done in India. In the same study a comparison was made between plasma citrulline and I-FABP levels. Plasma citrulline level was found to be most consistent and reproducible non-invasive biomarker that can predict the presence of villous abnormality and hence duodenal biopsies could be possibly avoided in 78% patients suspected to have CD.[55]

Various other modalities are under research like assessment of autoantibody deposits in biopsies, count of CD3+ T-lymphocytes per 100 epithelial cells, REG Iα (Regenerating Gene Iα) levels, detection of HLA-DQ-gluten tetramers. All these modalities either provide evidence of inflammation of the small intestine or response to a gluten free diet. However, none is specific or diagnostic of CD. Neurotensin is found to be higher in the serum of CD patients at diagnosis compared to controls[56].

There are new emerging treatment options for treatment of CD under study (table 5)

TABLE 5: Therapeutic options under study for CD[57]

MECHANISM	THERAPEUTIC AGENTS	
Hydrolysis of toxic gliadin	ALV003	Glutenenases and endoprotease
	AN-PEP	Prolyl endopeptidase
	VSL#3	Lyophilised bacteria, including Bifidobacteria, Lactobacilli and Streptococcus salivarius
Prevention of gliadin absorption by reducing paracellular transport of gluten across mucosa	Larazotide	Hexapeptide derived from zonula occludens toxin of Vibrio cholera Synthetic polymer polyhydroxyethylmethacrylate-co-styrene sulfonate Anti-gliadin IgY
tTG2 inhibitor: inhibits conversion of gluten to a more immunogenic form		Dihydroisoxazoles Cinnamoyltriazole Aryl β-aminoethyl ketones
Peptide vaccination	Nexvax2	Three deamidated peptides derived from wheat α-gliadin, ω-gliadin and β-hordein Human hookworm (Necator americanus) inoculation
Modulate immune response: prevents activation of gluten specific T-cells		HLA-DQ2 blocker Interleukin blocker NKG2D antagonist
Nanoparticle encapsulating gliadin delivered intravenously	Nanoparticle therapy	TIMP-GLIA
Restore intestinal architecture		R-spondin-1
Sequester gluten in intestinal lumen	Gluten binding agent	BL-7010
Modified or selectively bred cereals devoid of toxicity		Non toxic gluten

With better understanding of the disease pathogenesis, alternative treatment options targeting these pathways are now under study including agents that hydrolyse toxic gliadin peptide, prevent toxic gliadin peptide absorption, blockage of selective deamidation of specific glutamine residues by tissue, restoring immune tolerance towards gluten, modulation of immune response to dietary gliadin, and restoration of intestinal architecture.

CONCLUSION:

1. Immune tolerance to gluten is responsible for CD. It has a strong association with HLA DQ.
2. Infections in early childhood, especially gastrointestinal infections and those with rotavirus are important risk factors for CD.
3. All children with severe acute malnutrition, adults with irritable bowel syndrome and any patient with any autoimmune disease should be screened for CD.
4. Diarrhoea is commoner in children and atypical presentations are seen more often in adults. Hence knowledge about the symptom spectrum is necessary to correctly diagnose CD.

5. Efforts should be made to augment diagnostic modalities and make them robust enough to cater to the patient load in a timely and efficient manner.
6. Patient Education and involvement plays a key role in the management of the disease.
7. Improving access to Celiac Friendly diet is the need of the hour in resource limited settings.
8. The majority of patients either remain undiagnosed, misdiagnosed or experience a significant delay in the diagnosis[8]. Hence, a high degree of suspicion, and increased vigilance is required to timely identify cases of CD.

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