JGH Open An open access journal of gastroenterology and hepatology
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JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.13003

ORIGINAL ARTICLE

Clinical and demographic comparison of celiac disease diagnosed during adulthood *versus* childhood and adolescence: A single-center experience

Ajay K Jain,* Debi Chatterji,* Priyanka Bhagat,† Deepika Jain,‡ Shohini Sircar* and Satish Phatak†

Departments of *Gastroenterology, †Pathology and ‡Biostatistics, Choithram Hospital & Research Centre, Indore, India

Key words
adult celiac disease, anti-transglutaminase antibodies, celiac disease, celiac sprue, gluten-free food product, gluten-sensitive enteropathy, non-tropical sprue, pediatric celiac disease, villous atrophy.

Accepted for publication 30 October 2023.

Correspondence
Ajay K Jain, Department of Gastroenterology, Choithram Hospital & Research Centre, Indore 452014, MP, India. Email: ajayvjain@yahoo.com

Declaration of conflict of interest: The authors declare no conflict of interest.

Abstract

Background and Aim: Celiac disease (CeD) is mainly reported from the northern and western parts of India. In central India, it is believed to be a disease of children, with limited data among adults diagnosed for the first time after the age of 18 years. Hence, we aimed to describe CeD's clinical and demographic features among adults and children/adolescents in central India.

Methods: This is a retrospective analysis of a prospectively maintained database of all patients diagnosed for CeD from 2010 to 2019. The disease in adults was confirmed when symptoms developed for the first time after 18 years and had positive anti-transglutaminase antibodies with villous atrophy on duodenal biopsy. It was compared with pediatric patients with CeD diagnosed during the same time period.

Results: Of the 170 patients diagnosed with CeD, 118 were adults and 52 were children or adolescents. The mean age of presentation of adult CeD was 37.3 ± 11.93 years, while in the pediatric and adolescent group it was 9.19 ± 5.4 years. Classical presentation with chronic, painless, small-bowel-type diarrhea was seen in 44.1% of adults compared to 57.7% in the pediatric age group. Among the adult patients, 55.9% presented with nonclassical symptoms, which included abdominal pain (40.7%) and weight loss (36.4%). The common presenting symptom in children other than diarrhea was weight loss (50%) and abdominal pain (34.6%).

Conclusion: CeD is common in central India, with an increasing number of patients being diagnosed for the first time after 18 years of age and presenting more often with nonclassical symptoms.

Introduction

Celiac disease (CeD), an immune-mediated disease seen in children and young adults, is triggered by exposure of small intestinal mucosa to dietary gluten in genetically susceptible individuals.[1] The worldwide prevalence of CeD is 0.6–1%,[2] but the exact prevalence of CeD in India is still unknown. It is believed that in India, the prevalence is high in the northern and western parts of the country, where wheat is the staple food, compared to the southern and eastern regions, where rice is the staple food.[3] The North–South divide is clearly visible in India, with the prevalence of CeD in the state of Haryana reported to be 8.53/1000, while it is 0.11/1000 in the state of Tamil Nadu, even though predisposing genetic factors, that is, HLA DQ-2 and HLA DQ-8, are common in the whole of the Indian population.[4] This difference is possibly due to different staple foods consumed in the North and the South. Secondly, in the last few decades, it was thought that CeD patients are mostly young or older adults. The age of clinical onset (based on diagnosis) is bimodal: the first peak is at 8–12 months, and the second is during the third to fourth decades of life.[5] However, recent studies suggest that CeD should be considered a disorder that has the risk of developing throughout life, even in the elderly.[6] Despite increased awareness about CeD being diagnosed for the first time in young adults and the elderly, there is still delay in the diagnosis of CeD. This delay is due to the lack of typical symptoms such as diarrhea or refractory anemia in this population and the lack of awareness among general practitioners about developing symptoms for the first time after the age of 18 years. The clinical presentation in these older individuals ranges from "silent" disease to vague abdominal complaints.

Further, in the last decade, studies have demonstrated that the clinical profile of CeD has changed over time with an increasing rate of nonclassical and subclinical phenotypes. Some

adult patients are treated for functional bowel disorder or irritable bowel syndrome for months and years before being diagnosed with CeD.[7] Therefore, we aimed to characterize the clinical and demographic profile of CeD diagnosed after 18 years in Central India and compare it with the disease diagnosed during childhood and adolescence in the same population.

Material and methods

The present study is a retrospective analysis of a prospectively maintained database where case records of all patients who had a proven diagnosis of CeD between 2010 to 2019 were reviewed. All patients with newly diagnosed CeD based on positive serology (anti-transglutaminase antibodies) and classical features of blunting of villi on endoscopic duodenal biopsies were recruited in this study. All potential CeD patients were excluded.

Ethical clearance was taken from the institutional ethical committee to conduct the study.

This was a retrospective, descriptive observational study conducted from July 2010 to December 2019.

Data collection method. Outpatient (OP) and inpatient (IP) records of all patients diagnosed with CeD for the first time were reviewed and entered in a proforma. The proforma consisted of information on the demography, socioeconomic status, presenting symptoms, age at the time of presenting symptoms, presence of any comorbidities (especially any autoimmune disease), family history of CeD and autoimmune disease, addictions, menstrual and obstetric history (if applicable), dietary history, hemogram, iron profile, serum vitamin B12, serum calcium levels, IgA anti-tTG (tissue transglutaminase) titer, serum IgA levels, upper gastrointestinal (UGI) endoscopic findings, and duodenal biopsy report. The information was compiled in an Excel sheet and analyzed accordingly. The anti-tTG antibody tests were done in all these patients using the AESKULISA tTg-A new-generation solid-phase enzyme immunoassay kit (Aesku Diagnostics, GmbH, Wendelsheim, Germany) for the quantitative and qualitative detection of IgA antibodies against neo-epitopes of tTG in human serum. Patients with a value >18 U/mL were considered positive, while those with a value <12 U/mL were considered negative. Values between 12 and 18 U/mL were labeled as equivocal. Patients with equivocal values were tested further for IgA levels to confirm or rule out IgA deficiency. All biopsies were seen by the same two histopathologists from 2010 to 2019 and were reported as per Marsh Classification.[8]

Counselling. After the diagnosis of CeD, all patients were explained about the gluten-free diet and were counseled by the treating unit physicians and specially trained dieticians working exclusively for the gastroenterology unit. The list of common everyday local food items containing wheat, oats, and barley (which were to be avoided) was given in writing and was explained to the other family members. Another important advice given to all the patients was to buy a domestic flour mill to grind other cereals at home and never to use this domestic flour mill for wheat, oats, or barley. Almost everybody bought domestic flour mills as a part of treatment. In the case of unmarried young patients, especially girls, parents were advised to explain the wheat allergy to their prospective spouse and gift a domestic flour mill. Similarly, all patients were advised not to use grains ground in mills where wheat is also ground. Lastly, guidance was given to prepare some of the everyday items, such as bread, pastries, crackers, and biscuits, using other cereals, for example, rice, ragi, millet, and so on.

Results

A total of 170 patients were diagnosed for the first time with CeD during the study duration and were included in this study. There were 52 patients who were below 18 years and constituted the pediatric CeD group, while 118 patients had their first symptoms after the age of 18 years and were combined as the adult CeD group. The mean age at presentation of adult CeD was 37.3 ± 11.93 years (range 19.0–68.0 years) with a male/female ratio of 0.81:1. The mean age of presentation of pediatric CeD was 9.19 ± 5.4 years with a male/female ratio of 1.3:1. The majority of patients had a rural background and were from the economically disadvantageous section of the society. Agriculture and related activities were the main occupations of these patients. Chronic, painless, small-bowel-type diarrhea was seen

Table 1 Comparison of various symptoms among different age groups in adult population.

	Age group					
	19–30 years	31–40 years	41–50 years	51–60 years	61 years or more	Total
Clinical symptom	$n = 36$	$n = 41$	$n = 27$	$n = 9$	$n = 5$	$n = 118$
Dysphagia	1 (2.8%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	3 (2.5%)
Malena	0 (0.0%)	2 (4.9%)	1 (3.7%)	2 (22.2%)	1 (20.0%)	6 (5.1%)
Abdominal pain	15 (41.7%)	19 (46.3%)	12 (44.4%)	1 (11.1%)	1 (20.0%)	48 (40.7%)
Vomiting	10 (27.8%)	7 (17.1%)	8 (29.6%)	2 (22.2%)	0 (0.0%)	27 (229%)
Abdominal bloating	6 (16.7%)	7 (17.1%)	3 (11.1%)	0 (0.0%)	1 (20.0%)	17 (14.4%)
Diarrhea	17 (47.2%)	21 (51.2%)	8 (29.6%)	5 (55.6%)	1 (20.0%)	52 (44.1%)
Weight loss	17 (47.2%)	17 (41.5%)	5 (18.5%)	3 (33.3%)	1 (20.0%)	43 (36.4%)
Abdominal distension	1 (2.8%)	3 (7.3%)	1 (3.7%)	1 (11.1%)	1 (20.0%)	7 (5.9%)
Pedal edema	0 (0.0%)	3 (7.3%)	1 (3.7%)	1 (11.1%)	1 (20.0%)	6 (5.1%)

Malena was significantly more in the age group 51–60 years.

in 44.1% of adult patients, while 55.9% had no diarrhea. Significant non-diarrheal symptoms were chronic nonspecific abdominal pain (40.7%), weight loss (36.4%), vomiting (22.9%), abdominal bloating (14.4%), abdominal distension (5.9%), melena, pedal edema (5.1% each), and dysphagia (2.5%).

When symptoms were analyzed among adults according to age (Table 1), it was found that abdominal pain and weight loss were more common in young adults compared to older patients who were aged >60 years, while melena was more common in the age group 51–60 years. These patients primarily presented with melena and had either erosive mucosal disease or ulcers on UGI endoscopy. It was during the investigations that CeD was diagnosed. None of these patients in the present study was diagnosed with complications of CeD at presentation. The common presenting symptoms of pediatric CeD were chronic diarrhea (57.7%), followed by weight loss (50%) (Table 2). Only a minority of adult patients had other comorbidities at presentation. Diabetes Type I was seen in 2.2% of patients, Type II diabetes in 3.4%, and hypothyroidism in 8.6%. One patient each had coexisting Sjogren's syndrome and rheumatoid arthritis. One patient had Down syndrome. None of the patients reported a family history of CeD at presentation. However, a family history of Type II diabetes was seen in 16.8% of patients. All the female patients had unremarkable menstrual and obstetric history. No primary infertility was seen in this study. There was no history of mental retardation in any offspring of the patients. When symptoms were compared according to gender, both groups had no significant difference.

Clinical examination revealed Grade I clubbing in 4.6% of patients. The mean hemoglobin was 8.9 g/dL (Fig. 1), and the mean corpuscular volume (MCV) was 64.74 fl. The mean serum iron was 29.32 mg/dL. Hypoalbuminemia was seen in 31% of patients. Most patients had normal serum calcium, while 64% and 32% of patients had vitamin D and vitamin B12 deficiency, respectively. IgA deficiency was seen in 4.3% of patients. Serum transaminases were normal in all patients (the upper limit for normal transaminases is 40 IU/L in our hospital). There was no biochemical or sonographic evidence of chronic liver disease or cirrhosis of the liver in any of the patients. Apart from macroscopic findings of CeD on UGI endoscopy, the majority of patients in both adult (88.2%) and pediatric CeD (90.4%) groups had Marsh grade II or more on duodenal biopsy (Fig. 2). *H. pylori*-related gastritis was seen in 31% of patients. One patient each had associated upper esophageal web, distal esophageal cancer, and fundal polyp.

Table 2 Comparison of frequency of different symptoms between adult and pediatric patients.

	Adult	Pediatric			
Clinical symptom	$n = 118$	$n = 52$	Chi-square value	df	*P*-value*
Dysphagia	3 (2.5%)	1 (1.9%)	0.060	1	>0.05
Malena	6 (5.1%)	2 (3.8%)	0.123	1	>0.05
Abdominal pain	48 (40.7%)	18 (34.6%)	0.559	1	>0.05
Vomiting	27 (22.9%)	10 (19.2%)	0.282	1	>0.05
Abdominal bloating	17 (14.4%)	3 (5.8%)	2.594	1	>0.05
Diarrhea	52 (44.1%)	30 (57.7%)	2.683	1	>0.05
Weight loss	43 (36.4%)	26 (50.0%)	2.752	1	>0.05
Abdominal distension	7 (5.9%)	6 (11.5%)	1.606	1	>0.05
Pedal edema	6 (5.1%)	2 (3.8%)	0.123	1	>0.05

*Chi-square test.

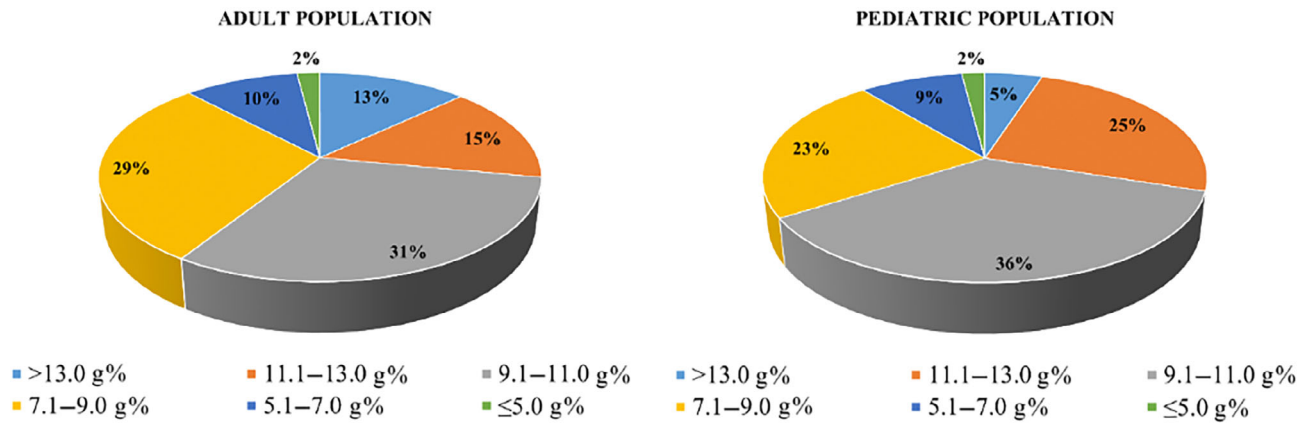

Figure 1 Frequency distribution of adult and pediatric patients based on hemoglobin concentration.

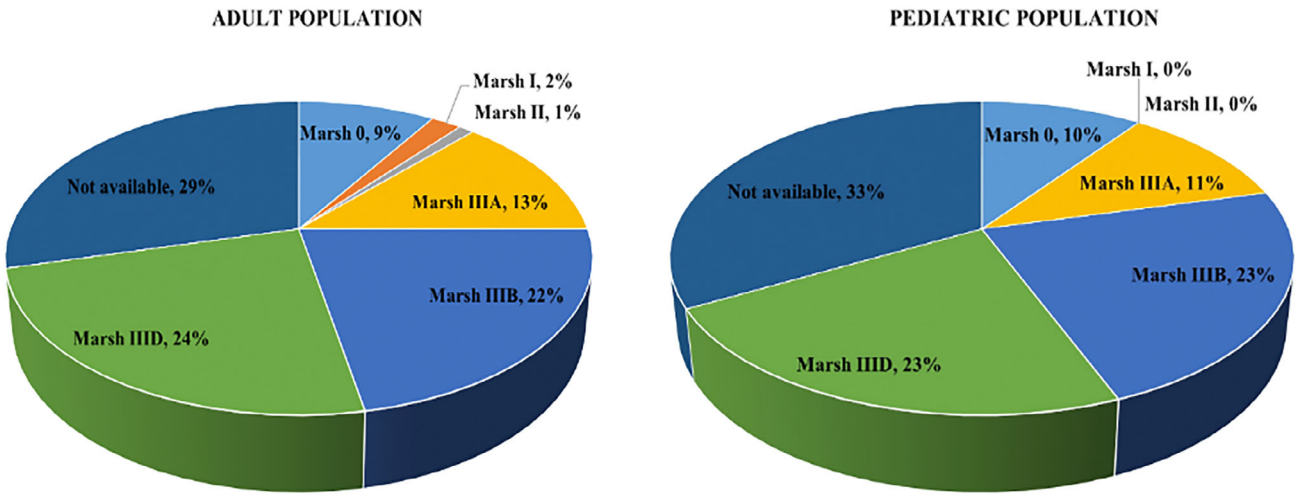

Figure 2 Distribution of adult and pediatric patients based on biopsy findings.

Discussion

The prevalence of CeD in India ranges from 1 in 96 to 1 in 310,[9] but it is still considered a disease of India's northern and western parts. With people in all regions having equal genetic susceptibility, as determined by the population prevalence of HLA-DQ2 and HLA-DQ8, the differences in the prevalence are likely due to the differences in the wheat-eating pattern, with the highest being in the northern part of India (455 g/day) and lowest in the southern part of India (25 g/day).[4] With increasing awareness and diagnostic armamentarium, the absolute number of CeD cases is expected to increase markedly in Asia and India. The present study suggests that CeD is as common in Central India as in the northern and western parts of India, as wheat is a staple food in a significant part of Central India. However, because Central India has not reported it, most physicians remain ignorant about CeD. Young adults and adults, including the elderly, present with various symptoms, including abdominal pain, constipation, asymptomatic transaminitis, neurological abnormalities, and so on. Because of nonspecific symptoms, many patients are labeled with irritable bowel syndrome, and diagnosis is delayed for years. The Canadian Celiac Association's survey reported that over 60% of the respondents, including children and adults, had to consult three or more physicians before the diagnosis was made.[10] A study from North India reported that almost one-half of the adult patients with CeD presenting with atypical manifestations consulted physicians other than gastroenterologists.[11] Another study from Australia revealed that nearly a quarter of new cases of CeD present with atypical symptoms, and half of them have normal duodenal mucosa on UGI endoscopy.[12] A significant increase in the diagnosis of CeD with nonclassical symptoms or without any symptoms is believed to be partly due to an actual increase in autoimmune disease in the general population and partly to increasing awareness and better diagnostic facilities.[13,14]

The estimated prevalence of CeD in individuals between 45 and 76 years of age in the United Kingdom is approximately 1.2%. About 20% of all newly diagnosed celiac cases are over 60 years of age.[15] The average age of diagnosis of CeD in the developed world falls between the fourth and sixth decades of life, with approximately 20% of cases diagnosed in those over 60 years. In the Canadian Celiac Health Survey, the mean age at diagnosis was 46 years.[16] This suggests a clear shift in our understanding, that is, CeD is no longer a disease of children and adolescents. The clinical presentation of CeD has also changed from typical malnutrition to oligosymptomatic cases such as anemia, osteoporosis, and even asymptomatic cases diagnosed by screening high-risk groups.[15] This study highlights that most adult patients in central India (i.e. 55.9%) presented with nonspecific symptoms such as dyspepsia, bloating, and weight loss, while chronic, painless, small-bowel-type diarrhea, which is the classical presentation, was seen only in 41% of patients. The "atypical" forms of the disease are characterized by few or no GI symptoms and predominating extra-intestinal features such as refractory iron deficiency anemia, osteoporosis, nonspecific abdominal pain, weight loss, vomiting, abdominal bloating, abdominal distension, melena, pedal edema, and dysphagia. It further highlights that the majority of newly diagnosed adult CeD patients were females who were from rural backgrounds. This difference in pattern between sexes is consistent with previous data.[17] However, no such predilection for females was seen among pediatric CeD; in fact, more male children were diagnosed with CeD than females in contrast to the adult population, where more female patients had adult CeD. However, no difference was seen in presenting symptoms between males and females among pediatric and adult CeD. This study further highlights that most patients who presented with one or more symptoms had either Grade II or more villous atrophy on duodenal mucosal histopathology. A meta-analysis had shown the pooled prevalence of CeD in first-degree relatives as 7.5%.[18]

However, none of the patients in the present series had any family history of CeD. It is possible that a few of the first-degree relatives may have atypical symptoms and have not been screened. Short stature and neurological manifestations were not seen in the present series, unlike other series which showed 10% of patients

with short stature.[19] Previous studies from India had shown the prevalence of CeD in Type I diabetes ranging from 7 to 14.9%.[20] The current series had only 2.2% of patients with Type I diabetes. This study underlines the need for mass awareness about CeD, especially with nonclassical symptoms or without any symptoms, that too in females from a rural background who are more often ignored in terms of access to health care in India.

Conclusions

The following conclusions could be drawn from our study:

1. CeD is not uncommon in Central India.
2. An increasing number of patients with CeD are diagnosed for the first time after the age of 18 years.
3. Adult CeD presents more often with nonclassical symptoms than typical symptoms; hence, it is often missed in clinical practice. Therefore, it is important to make general physicians and gastroenterologists aware of the possibility of CeD among adults with vague abdominal symptoms.
4. A population-based study is needed to know the exact prevalence of CeD among adults.

Ethics statement

The Institutional Ethics Committee approved the study vide letter no. EC/Dec/2021/17 dated 22 December 2021.

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