Celiac disease: variations of presentations in adults
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Background: Patients with celiac disease, who remain undiagnosed or asymptomatic in childhood, may present in adulthood with either typical or atypical features. Methods: In a retrospective analysis, we reviewed the case records of 45 consecutive patients with celiac disease diagnosed in adulthood. The diagnosis of celiac disease was made on the basis of the modified European Society of Pediatric Gastroenterology, Hepatology and Nutrition criteria. The modes of presentation, clinical manifestations, endoscopic features and histological features were analyzed. Results: The mean age of these patients at diagnosis was 28.7 (11.2) years. The median duration of symptoms before diagnosis was 2.5 years (range: 6 months to 40 years). 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%). Intestinal mucosal folds were scalloped in 31 (69%), attenuated in 34 (76%) and normal looking in 11 (24%) of them. Mild, moderate and severe villous abnormalities on intestinal mucosal biopsies were present in 10 (22.2%), 15 (33.3%) and 19 (42.2%) patients, respectively. Conclusions: More than half of adult patients with celiac disease present with atypical manifestations. A high index of suspicion is required for diagnosing variant forms of celiac disease in adults. [Indian J Gastroenterol 2007;26:162-166]

Methods
In a retrospective analysis, we reviewed the case records of adult patients (age >18 years) who were diagnosed as having celiac disease in our Department during the period, January 2000 - December 2005. The mode of presentation, clinical features, biochemical tests, serological tests, endoscopic features and histological features of these patients were recorded. The diagnosis of celiac disease was made on the basis of the modified European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria.5

All patients had a complete hemogram, biochemical tests which included liver function tests, renal function tests, serum calcium and serum phosphorus. After an overnight fast, a five-hour urinary D-xylose test was done after ingestion of 5 g of D-xylose to study the status of mucosal absorption. Microscopic examination of three stool specimens for ova and cysts was done to exclude any parasitic infection. Esophago-gastro
duodenoscopy (EGD) and/or enteroscopy were done in all of them and endoscopic appearance of duodenal mucosa and folds were noted for scalloping, attenuation of folds, and cobblestoning of the mucosa. Four pieces of mucosa were obtained from the third part of the duodenum or the proximal jejunum. The mucosal biopsies were collected on filter paper and oriented using a hand lens. A modification of the Marsh classification was used to grade the mucosal changes: 0 – normal histology; 1 – mild increase in intraepithelial lymphocytes (IEL), crypt-villous (CV) ratio 1:1; 2 – moderate villous atrophy with CV ratio more than 1; 3 – flat mucosa with no recognizable villi. In the initial part of our study period, IgA anti-endomysial antibody (AEA) was obtained at our institution using monkey esophagus whereas in the later stages of the study period, serum anti tissue transglutaminase (anti-TTG) antibody was obtained from standard commercial laboratories. Serum immunoglobulin levels (IgA, IgG, and IgM) were obtained in patients whose clinical profiles were consistent with celiac disease but had negative serological test for celiac disease.

Patients were evaluated by a nutritionist and counseled about the need for adherence to gluten free diet. Supplemental iron and calcium were added after 2 to 4 weeks of gluten free diet. Follow up visit was done every 2 weeks initially and then every 3 months.

Results

Forty-five adult patients were diagnosed to have celiac disease during the period January 2000 to December 2005. Their demographic characteristics are shown in Table. Eight (17.7%) patients presented for the first time in the fifth decade and beyond. In three patients, there was a positive family history of celiac disease. While a sibling was affected in two patients, in another both of her sons had celiac disease.

Presenting manifestations

Chronic diarrhea was the presenting manifestation in 20 (44%) patients whereas 25 (55%) presented with other symptoms such as refractory anemia in 10 (22.2%), short stature in 6 (13.3%), secondary infertility or delayed menarche in 4 (8.8%), chronic liver disease in 3 (6.6%) and metabolic bone disease in 2 (4.4%). Chronic diarrhea was present in 32 (71%) patients. A history of childhood diarrhea was present in 13 (29%) patients but that was followed by a long asymptomatic period. Twenty (44.4%) patients complained of postprandial bloating and 12 (27%) patients had mild abdominal discomfort.

Anemia was present in 95% of patients; 10 (22%) were referred to us by hematologists with
refractory iron deficiency anemia despite prolonged oral iron and folic acid supplementation. The mean hemoglobin in them was 8.5 g/dL and most of them had microcytic hypochromic anemia. Three of these patients had associated thalassemia—thalassemia intermedia in one and thalassemia minor variant in two of them. The diagnosis of thalassemia minor was made prior to the diagnosis of celiac disease in one as this patient had disproportionately low hemoglobin. In two of them, the diagnosis of thalassemia was made once their hemoglobin failed to rise despite normalization of intestinal mucosa with gluten free diet. One patient had macrocytic anemia, which responded to parenteral administration of vitamin B12.

Endocrinological manifestations were the third most common mode of presentation. While short stature was present in 14 (31%), in 6 (13.3%) patients short stature was the main presenting manifestation. The mean age of patients who presented with short stature was 15 years, which was a decade earlier than that of other patients. There was a response to gluten free diet and their height increased by 0.8 cm per year over a 30-month follow up. Five (11%) had delayed puberty, 2 (4.4%) had secondary infertility. Both patients with secondary infertility conceived on gluten free diet; one had a full term normal delivery, the second patient had a stillbirth at 32 weeks of gestation. Three (6.6%) and 3 (6.6%) patients, respectively had type 1 diabetes mellitus (DM) and hypothyroidism associated with celiac disease. Of them, two patients had both diabetes mellitus and hypothyroidism.

Nine (20%) patients had evidence of liver disease. While 5 (11.1%) patients had isolated elevated (more than 2 times upper limit of normal) transaminases, 4 (12.6%) patients had evidence of portal hypertension (non cirrhotic portal hypertension in 1, cirrhosis of the liver in 3). Three patients had associated renal disease; two of them had history of nephrotic syndrome in childhood, and another patient had active albuminuria (2.8 g/24 hours) and renal biopsy showed IgA nephropathy. Serological tests for celiac disease were available in 39 of 45 patients and were positive in 34 (76%) patients (IgA anti-endomysial antibody in 10, IgA anti-human tissue transglutaminase antibody in 23 and IgG anti-gliadin antibody in 1). Three of five patients with negative serological tests for celiac disease were IgA deficient. In the remaining 2 patients, the serum levels of IgA, IgG and IgM were within normal limits. Of these 5 patients with negative serological tests, two had moderate and three severe villous abnormalities. Scalloping of duodenal and/or jejunal mucosal folds were present in 31 patients (69%) while the folds were attenuated in 34 (76%) and normal looking in 11 (24%) patients on endoscopic examination. Villous atrophy on histological examination of the mucosal biopsies was present in all but one patient. Mild, moderate and severe villous abnormalities on intestinal mucosal biopsies were present in 10 (22.2%), 15 (33.3%), 19 (42.2%) patients, respectively. The single patient with a normal crypt villous ratio presented with severe iron deficiency anemia, and a diagnosis of celiac disease was made in him on the basis of a positive serological test and a response to gluten free diet. While an increase in intraepithelial lymphocytes was present in 42 (93%) patients, excessive lympho-plasmacytotic infiltrates in the lamina was present in 43 (96%) patients.

**Discussion**

In the present report, almost half the adult patients with celiac disease presented with atypical manifestations to physicians other than gastroenterologists and one fourth of them had only mild villous abnormality at histological examination.

An unequivocal response to gluten free diet is an essential criterion for the definitive diagnosis of disease. While most of the manifestations of celiac disease are modifiable by the treatment, some of them such as short stature may not improve especially if GFD is instituted after the fusion of the epiphysis. Therefore, the presently used revised ESPGHAN criteria for diagnosis of celiac disease may not be applicable to some of the patients with suspected celiac disease who have atypical manifestations. Although post treatment histology is not required for the confirmation of the diagnosis of celiac disease, demonstration of histological improvement strengthen the diagnosis especially in those where there are no modifiable symptoms such as short stature in adults. In the present study, all those patients who presented with short stature as their main manifestation also had either chronic diarrhea or anemia. A response in these modifiable symptoms in them may suggest a response to gluten free diet. Furthermore, a positive serological test such as anti-TTG antibody and anti-EMA antibody strengthen the diagnosis of celiac disease in those with atypical manifestations both in children and adults.
The small intestinal mucosal lesion in patients with celiac disease remains in the stage of evolution; patients may thus present to a clinician at various stages of histological evolution. Therefore, at presentation the histological lesions of celiac disease may vary from a normal crypt-villus ratio with increased intra-epithelial lymphocytes at one end of the spectrum to severe villous abnormality at the other. Recent data from our institution have shown that among Indian children with chronic diarrhea confirmed to have celiac disease, classical severe villous abnormality and moderate villous abnormality were present in one third each. Interestingly among children in whom the mucosal changes were limited to mild blunting of villi, at least a third were confirmed to have celiac disease by the presence of serological antibodies, clinical response to gluten free diet and a positive gluten challenge. It appears that celiac disease in India has a heterogeneous histological presentation; the diagnosis may be missed or delayed if it is based only on severe mucosal changes, or serology is not considered when moderate or mild mucosal changes are present. Even in the present study, 25.4% adult patients with celiac disease had only mild villous abnormality.

The rarity of celiac disease in Asia may not be real. A low index of suspicion and reliance on classic symptoms may result in significant under-diagnosis of celiac disease. In recent years, celiac disease is recognized more frequently in India not only in children but in also adults. The under-diagnosis of celiac disease presenting with atypical manifestations is also supported by the results of the Canadian Celiac Association’s Survey conducted in 1989-91. Fewer than 75% of the 1294 respondents with biopsy-confirmed celiac disease had presented with classic symptoms. The average duration of symptoms in adults before diagnosis was 7 years for fatigue, diarrhea, bloating and abdominal pain. For headache or neuro-psychiatric symptoms, main duration before diagnosis was 14 years. In over a third of pediatric cases, symptoms were present for 1 year or longer. Over 60% of the respondents, whether children or adults, had to consult 3 or more physicians before the diagnosis was made, and 15% had to consult 5 or more physicians.

The present study has a few limitations. There is a lack of demonstration of histological improvement in all those who presented with atypical manifestations. In view of the long delay in diagnosis; there may be an error in estimation of the median duration of disease. In conclusion, more than half of adult patients with celiac disease present to a clinician other than gastroenterologists or internists with atypical manifestations. A high index of suspicion is required for a diagnosis of variant forms of celiac disease in adults.

References


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Image

Esophageal pseudo-tattoo from ingested capsule

A 66-year-old lady with moderate aortic stenosis, mild aortic regurgitation, trivial tricuspid regurgitation and ejection fraction of 65%, presented with vague abdominal discomfort of 1-month duration. She was given oral amoxycillin as prophylaxis 30 minutes prior to upper GI endoscopy. During endoscopy the lower esophageal mucosa showed capsule debris. On flushing with water the letters “Am” were seen on the esophageal mucosa just above the gastroesophageal junction (Fig). With continued washing the letters disappeared.

Knowing the history of amoxycillin capsule ingestion, a diagnosis of esophageal pseudo-tattoo from ingested capsule was made. The outer sheath of the capsule was stuck to the mucosa, giving a picture of a tattoo. Only one earlier report of esophageal tattoo was found.1

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