Background and Aims: Non-diarrheal presentation of celiac disease (CD) is being increasingly recognized. Data on this form of CD from India are limited.

Methods: Consecutive patients with CD presenting to a tertiary referral center in northern India over a 3-year period were studied, with special emphasis on non-diarrheal celiac disease (NDCD). Diagnosis was based on the presence of autoantibodies typical of CD (IgA anti-tissue transglutaminase antibodies and/or IgA endomysial antibodies), abnormal duodenal biopsy and response to gluten-free diet (GFD). Clinical, hematological and histological responses were assessed over a one-year period after instituting GFD.

Results: Of 86 patients with CD, 31 (16 children, 15 adult) had NDCD. Mean (SD) age of these children (12 boys) and adults (4 male) was 10.2 (4.2) y and 35.3 (12.0) y, respectively. Failure to thrive was the most common (11/16) presentation in children, as was refractory anemia in adults (10/15). Malabsorption was found in 8 adults (54%) and 10 children (64%) with NCCD. The duration from onset of symptoms to diagnosis was 2.9 (1.5) y in children and 3.3 (0.3) y in adults. There was significant improvement in body weight (children – baseline 18.9 [5.8] Kg, follow up 27.4 [12.4] Kg; adults – baseline 47.6 [18.2] Kg, follow up 54.9 [5.1] Kg) and hemoglobin (children – 8.1 [2.0] g/dL to 11.2 [1.4] g/dL; adults – 7.3 [2.3] g/dL to 9.7 [1.7] g/dL) in both groups after one year of GFD; duodenal biopsy also improved, with a majority of patients attaining normal to IIIa Marsh grading. Five adults and all children had evidence of metabolic bone disease at presentation, which did not revert completely with GFD. Eight adults and nine children showed dietary transgression 6 weeks after starting GFD. Conclusion: NDCD accounted for nearly one-third of all cases with CD at our center, with ‘failure to thrive’ and refractory anemia being the most common presentations in children and adults, respectively. [Indian J Gastroenterol 2007;26:122-126]

Based on clinical presentation, celiac disease (CD) is broadly classified as diarrheal and non-diarrheal celiac disease (NDCD).1,2 Because of its protean and subtle symptoms, NDCD can remain undiagnosed for a long period. Use of serologic tests for the diagnosis of CD has further widened the spectrum of NCCD by recognizing silent cases, referred to as potential and latent CD.1,3 Thus, in a recent study from the US, only 55% of patients with CD had diarrhea at presentation.4

Clinical features associated with NDCD are variable. Children often have growth retardation with or without refractory anemia.5,6,7 In adults, refractory anemia, usually iron-deficiency type, and metabolic bone disease are common.8,9,10 Other extraintestinal manifestations include peripheral neuropathy, seizures, ataxia, amenorrhea, infertility, autism, dermatitis herpetiformis, and growth hormone deficiency, and less commonly, epilepsy, Plummer-Vinson syndrome, and recurrent oral ulcerations.11-15 This report looks at the clinical presentation of NDCD in adults and children at a tertiary referral center in northern India.

Methods

In this prospective study, consecutive patients with CD seen at our institution over a 3-year period (December 2003 to December 2006) were analyzed. Diagnosis of CD was based on the revised ESPGHAN criteria (abnormal villous structure and response to gluten-free diet [GFD] are main components of these criteria).16 Marsh classification was used for grading duodenal histological abnormalities.17 Patients and their first-degree relatives were tested for the presence of IgA antibodies against tissue transglutaminase (TTG) and/or endomysium (EMA). Cut-off value for TTG was taken as 12 IU/L. IgA levels were measured in patients in whom IgA antibodies were negative but severe villous abnormality was present. Potential CD was defined as positive serology on two occasions at least 6 months apart detected during targeted screening, with normal or minimally abnormal (Marsh I) duodenal mucosa.

At enrolment, detailed history, physical examination, and routine biochemical and hematological evaluation was done. In children (age <15 y), anthropometric assessment was also done. Skeletal X-rays of limbs, pelvis and spine were
obtained. Serum intact parathyroid hormone (iPTH) levels were measured at baseline and at 6-12 months later if abnormal. Bone mineral density (BMD) was measured when possible at the lumbar spine and femur neck using dual-energy X-ray absorptiometry (DEXA). Results were expressed as Z scores for children and as T scores for adults, using the WHO criteria. Standard tests for malabsorption (urine D-xylose using 5 g D-xylose and 72-hour fecal fat estimation) were done in all patients.

Patients with CD who did not present with diarrhea were diagnosed to have NCCD. Refractory anemia was defined as unexplained anemia (hemoglobin <10 g/dL) for at least 6 months and not responding to oral iron and folic acid therapy. Anemia was categorized as severe if hemoglobin was <8 g/dL. Children were labeled to have short stature if their height was less than the 3rd percentile of the expected height for age, in the presence of normal height of both parents. Malabsorption was defined as abnormal D-xylose and/or fecal fat tests. Hypocalcemia was defined as serum calcium levels <8.5 mg/dL, and secondary hyperparathyroidism as elevated levels of iPTH in the presence of hypocalcemia, normal kidney function tests and no other possible explanation.

Patients were advised to take GFD and counseled about need for strict adherence. Calcium and vitamin D₃ supplementation was given to patients with hypocalcemia, and iron and folic acid supplementation to those with anemia. Patients were followed up every month for at least three months to assess clinical response to GFD; body weight, height (only children), body mass index (BMI) and hemoglobin were recorded at each visit.

Values are expressed as mean (SD) or median (range); differences between baseline and follow-up values were compared using appropriate tests.

**Results**

Of the 86 patients (48 adults) diagnosed to have CD during the study period, 31 (36%) had NCCD. This included 16 children (12 boys) with mean age of 10.2 (SD 4.2) y and 15 adults (4 male) with mean age of 35.3 (12.0) y. The mean duration of symptoms prior to diagnosis was 2.9 (1.5) y in children and 3.3 (2.6) y in adults.

**Children with NCCD**

Failure to thrive was the dominant manifestation (11 of 16 children); two children presented with refractory anemia. Two others had transudative ascites, in the absence of evidence of chronic hepatitis, Wilson’s disease, autoimmune hepatitis or metabolic liver disease. One patient presented with bone pains. Four other patients gave history of bone pains on questioning during the course of their illness, and three of these had history of fractures on insignificant trauma. The baseline and post-GFD anthropometric data of these 16 children are shown in Table 1.

Ten (62.5%) children had evidence of malabsorption. Only 2 children had radiographic features of rickets. BMD showed abnormal Z scores in all 5 children (range -3.3 to -1.6) in whom it was done (Table 2). EMA and TTG were positive in 13 (81.5%) and 14 (87.5%) children, respectively. Two children had selective IgA deficiency. Most children had Marsh IIIc histological abnormalities (Table 3). iPTH was measured in 9 children before starting GFD and in 5 after GFD.
Baseline secondary hyperparathyroidism was found in 5/9 (55.5%) children and in 1/5 (20%) on follow up. The mean follow-up period in children was 1.7 (0.5) years. During this period, there was significant gain in height, weight and hemoglobin (Table 1). Nine children (56.2%) showed evidence of dietary non-compliance 6 weeks after starting GFD. However, on repeated counseling, 7 of these 9 were adherent to GFD as assessed at one year. Therefore, 14 children had good compliance at one year. Duodenal histology showed considerable improvement in all children with good compliance (Table 3). A majority with good compliance (14/15) revealed normal histology on follow up; one patient with lack of compliance at one year showed no improvement in histology. IgA TTG declined from initial values of median 147 (range, 56-825) IU to 34 (range, 5-114) IU. EMA (indirect immunofluorescence) was initially positive in 4 of 5 cases and was negative in all 3 cases on follow up in whom it was done. Baseline and follow up (at 1 year after GFD) TTG value in the only child with poor dietary compliance was 301 IU/L and 286 IU/L, respectively.

**Table 3: Baseline and follow-up histological severity of duodenal changes in patients with NCCD**

<table>
<thead>
<tr>
<th>Children</th>
<th>Follow up</th>
<th>Adults</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh I</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Marsh II</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Marsh IIIa</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Marsh IIIb</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Marsh IIIc</td>
<td>12</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

Marsh criteria (1999)²²

Baseline secondary hyperparathyroidism was found in 5/9 (55.5%) children and in 1/5 (20%) on follow up.

The mean follow-up period in children was 1.7 (0.5) years. During this period, there was significant gain in height, weight and hemoglobin (Table 1). Nine children (56.2%) showed evidence of dietary non-compliance 6 weeks after starting GFD. However, on repeated counseling, 7 of these 9 were adherent to GFD as assessed at one year. Therefore, 14 children had good compliance at one year. Duodenal histology showed considerable improvement in all children with good compliance (Table 3). A majority with good compliance (14/15) revealed normal histology on follow up; one patient with lack of compliance at one year showed no improvement in histology. IgA TTG declined from initial values of median 147 (range, 56-825) IU to 34 (range, 5-114) IU. EMA (indirect immunofluorescence) was initially positive in 4 of 5 cases and was negative in all 3 cases on follow up in whom it was done. Baseline and follow up (at 1 year after GFD) TTG value in the only child with poor dietary compliance was 301 IU/L and 286 IU/L, respectively.

**Adults with NDCD**

Refractory anemia, with associated lethargy and breathlessness, was the dominant presentation (10 of 15 patients) of NDCD. Two presented with transudative ascites. One patient had dysphagia due to an esophageal web associated with Plummer-Vinson syndrome and another had unexplained weight loss. One patient was detected to have potential CD during family screening. Hemoglobin and MCV levels increased significantly after GFD (Table 1). All adults with NDCD had normal serum calcium and alkaline phosphatase levels (Table 2); iPTH could be measured in 5 adults before starting GFD and 3 after GFD. Secondary hyperparathyroidism was found in all those in whom iPTH was measured. iPTH levels did not return to normal even after up to one year of GFD (Table 2). BMD was abnormal in 2 of 6 patients; both had osteopenia. Antibodies to TTG and EMA were present in 12/14 and 4/5 adults with NDCD, respectively. Median TTG titers at baseline were 134 (range, 20-800) IU/L and follow up were 28 (range, 5-192) IU/L, respectively. One patient had selective IgA deficiency. Duodenal histology findings are shown in Table 3.

On a mean follow up of 1.2 years, all 15 adults had an increase in weight, BMI and hemoglobin (Table 1). Patients with dysphagia and ascites showed improvement of symptoms within 3-6 months. At 6 weeks after starting GFD, eight adults had evidence of dietary transgression. On follow-up duodenal histology at one year, only 3 patients had Marsh grade IIIb versus 13 patients who had grade IIIb-IIIc lesions prior to starting GFD (Table 3). These three patients had poor dietary adherence at 1-year follow up. Median (range) TTG at follow up in compliant cases was 5 (1-8) IU/L vs. 145 (60-180) IU/L.

**Discussion**

In our series, 16 of 38 (42.1%) children and 15 of 48 adults (31.2%) had NDCD. A majority of children (11/16) presented with failure to thrive, and a majority of adults (10/15) with anemia. Metabolic bone disease was an important extraintestinal manifestation in our series. GFD led to marked improvement in most parameters.

In the last few years, NDCD has been recognized in a substantial proportion of patients in the West. In a recent study from the US only 55% had diarrhea at presentation.¹ However, in India, 84%-93% of children have been reported to present with classical disease.⁶ In our study, 36% of all CD patients had NCCD. This high proportion in our study was possibly because our institution is a tertiary referral center. The increased proportion of NCCD in the West has been attributed to the introduction of serological testing and increased awareness of CD among practicing physicians. In our study, the former factor did not seem to be operative.

Previous studies have reported an average delay of 5.9 (range, 1-13.5) years in making the diagnosis of CD.¹⁸,¹⁹ With the sole exception of our earlier report on atypical CD in children, all reports from India cover mainly diarrheal CD.⁶ In our current study, this period was 2.9 years in children and 3.3 years in adults.

Whilst diarrhea is a common presenting feature of CD in northern Indian children, it needs
to be emphasized that diarrheal CD and NDCD have some degree of overlap. In our study, eight patients developed diarrhea long after other symptoms like failure to thrive, often leading to their seeking medical help.

We found that NDCD most often presented as refractory anemia in adults and as failure to thrive in children. Most children with failure to thrive also had anemia. Anemia was almost always due to iron deficiency. Megaloblastic anemia in the setting of CD is very uncommon in Asian patients, unlike data from the West. The high prevalence of iron deficiency may be due to a poor iron nutritional status of the Indian population. Improvement in diarrhea is easily assessed by either the patient or parents in the case of small children. On the contrary, when the presenting features are short stature or refractory anemia, response to GFD may be slow and subjective, and objective assessment of improvement can be considerably delayed. In our experience, response of extraintestinal symptoms like short stature and anemia-related symptoms is considerably less dramatic than diarrhea.

After a mean follow up more than 1 year, there was significant gain in body weight, height (in children) and BMI. However normalization of hemoglobin did not occur despite improvement of symptoms and anthropometric data. When we analyzed the causes of failure to normalize hemoglobin, we found that there were dietary transgressions in such patients. We confirmed this by follow-up questionnaires, serology and biopsy. Patients having maximum dietary transgression had highest follow-up serological titers and abnormal biopsy.

Another common extraintestinal feature that we studied was metabolic bone disease (MBD). The incidence of MBD in various series from the West varies from 33% to 50%. In our study, hyperparathyroidism was present in all 5 adults and 5 of 9 children prior to starting GFD. In adults secondary hyperparathyroidism was seen in all 5 patients in whom the test was done. After one year of GFD, secondary hyperparathyroidism was documented in 1 of 5 children (20%) and 2 of 3 (66%) adults. Low dietary calcium intake in the Indian population with lactose intolerance could be other features responsible for the high prevalence of MBD in our study. However, abnormal bone density has been documented in about 27% of the general population in India.

In conclusion, nearly one-third of Indian patients with CD present with non-diarrheal forms of the disease, including failure to thrive in children and anemia in adults. Treating physicians should have a high index of suspicion for CD in patients with these clinical presentations.

References


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**News and Notices**

**Mid-term Conference of Indian Society of Gastroenterology on Dilemmas in Clinical Practice and Preventive Gastroenterology: Stepping outside the Clinics, organized by Department of Gastroenterology, SGPGI, Lucknow from 1st to 2nd September 2007.**

For further information contact: Uday C Ghoshal, ghoshal@sgpgi.ac.in and G Choudhuri, gc@sgpgi.ac.in and visit www.sgpgigeclinics.org

**International Therapeutic Endoscopy Workshop will be held at All India Institute of Medical Sciences, New Delhi on September 8-9, 2007.**

For further details, please contact: Dr Pramod Garg, Course Director, Tel: +91-11-26588769; e-mail: pgarg10@gmail.com or visit: www.aiimsendoscopy.com

**Second National Bioethics Conference is being organized by the Indian Journal of Medical Ethics in collaboration with 38 institutions across India from December 6 to 8, 2007, at National Institute for Mental Health and Neuro Sciences (NIMHANS) Convention Centre, Bangalore, Karnataka, India**

The theme is Moral and Ethical Imperatives of Health Care Technologies: Scientific, legal and socio-economic perspectives on use and misuse

For further information visit the website: http://nbc.ijme.in/

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Applications are invited from medical teachers working in India for the CMCL-FAIMER Regional Institute Fellowship 2008. This program is uniquely designed for medical school faculties. It is a distance learning program, with two contact sessions of one week each (January 2008 and January 2009). Limited funding is available to support travel, course fee and stay at Ludhiana. Sixteen fellowships are on offer for 2008. Applications are open from June 1st, 2007 to October 15th, 2007

For details visit http://cmcl.faimer.googlepages.com/home or contact Dr Tejinder Singh, Vice principal and Program Director at 141008. cmcl.faimer@gmail.com

**The 8th National Congress and Workshop on Minimal Access Surgery, organized by the Indian Association of Gastrointestinal Endo-Surgeons, will be held in Jaipur February 14-17, 2008.**

For details, contact: Dr K M Bhandari, Organizing Secretary, Bhandari Hospital and Laparoscopic Center, 395 Vasundhara Colony, Gopalpura Bypass, Tonk Road, Jaipur 302 018, Rajasthan

Phone: (141) 270 9044, 270 3851. Mobile: 98290 51047

Website: www.iages2008.com

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