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# Changing Spectrum of Celiac Disease in India

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## Abstract

***Objective:*** Celiac disease is an important cause of chronic diarrhea, failure to thrive, and anemia in children. Mode of presentation of celiac disease has changed in last few years. Study was conducted to determine the mode of clinical presentation of a large group of patients with celiac disease and whether there has been a change in the presentation with the time.

***Methods:*** A prospective study was conducted on 134 children diagnosed to be having celiac disease in the Pediatric Gastroenterology, PGIMER, Chandigarh, from July 1st 2006 to December 31st 2007. Their detailed clinical profile was recorded on a pretested proforma and all patients underwent hemogram, liver function tests, IgA anti-tissue transglutaminase (anti tTG), and upper gastro-intestinal endoscopy.

***Findings:*** Major symptoms at presentation were diarrhea (54.5%), failure to thrive (52.2%), abdominal distension (41%), anemia (40%), pain abdomen (19.4%), vomiting (15.7%) and constipation (2.2% of cases). 60.4% of patients had short stature. Anemia was microcytic hypochromic in 79.1% of patients, and dimorphic in 20.9%. Serum transaminases were raised in 38.8 % of cases. The mean serum anti tTG level was 164.24U/ml (Range 0-749 U/ml) and levels correlated with the severity of small intestinal damage on biopsy. 15 patients were negative for the serology but 8 out of them had IgA deficiency and all had histopathology suggestive of celiac disease.

***Conclusion:*** Classical presentation of celiac disease is less commonly encountered these days probably related to the more widespread use of serologic testing and early recognition of atypical manifestations of celiac disease.

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***Key Words:*** Celiac disease; Gluten enteropathy; Sprue, celiac; Tissue-type transglutaminase; IgA

## Introduction

Celiac sprue, also termed as celiac disease is characterized by small intestinal malabsorption of nutrients after ingestion of wheat gluten or related proteins from rye and barley a characteristic, though not specific villous atrophy of the small intestinal mucosa; prompt

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clinical and histological improvement after adherence to strict gluten free diet and clinical relapse when gluten is reintroduced[1].

Celiac disease is an important cause of chronic diarrhea, failure to thrive, and anemia in children. This triad of symptoms was classical of celiac disease reported earlier. Over the time early recognition and suspicion has changed the scenario. Introduction of serology for screening of celiac disease has enabled to recognize celiac disease in asymptomatic patients, its atypical manifestations and in its latent form.

Diverse problems such as dental anomalies, osteopenic bone disorders, lactose intolerance, infertility, refractory anemia may sometimes be the presenting manifestations of celiac disease[2]. At least, 10% of children with celiac disease have associated conditions[3] including selective IgA deficiency[4], dermatitis herpetiformis[5], diabetes mellitus type 1[6,7] and Down's Syndrome[8]. Study was conducted to determine the mode of clinical presentation of a large group of patients with celiac disease and whether there has been a change in the presentation with the time.

## Subjects and Methods

**Study population and design:** All the prospective patients coming to **C**eliac **D**isease **C**linic in division of Pediatric Gastroenterology, Post Graduate Institute Medical Education and Research, Chandigarh, India were enrolled for study, starting from July 1st 2006 to December 31st 2007. Inclusion criteria were pediatric patients of celiac disease as diagnosed by revised ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) criteria[9]. Inability to provide the informed consent by legal guardian was taken as exclusion criterion.

Ethical clearance was obtained from Institute Ethical Committee. A verbal assent was taken from the children and a written informed consent was obtained from legal guardian of each subject. All the subjects were studied for baseline demographic and social profile. Their detailed history, physical examination was recorded on pretested proforma. All patients underwent hemoglobin, total leucocytes count, differential leukocytes count, platelet count, reticulocyte count and peripheral smear for the type of anemia, liver function test including serum bilirubin, SGOT/SGPT, serum alkaline phosphatase, serum proteins, serum calcium, serum phosphorus, IgA anti-tissue transglutaminase (anti-tTG) and serum zinc levels.

Anti tTG levels were done using DRG tTG-A ELISA REF EIA-10503 kit. This test is based on recombinant human tTG as antigen. This is an indirect non-competitive enzyme immunoassay for determination of tTG antibodies in human sera or plasma. Reference cut off of anti-tTG IgA by above kit was 15 U/ml. In case of clinical setting but serology negative, immunoglobulin A levels were done.

Upper GI endoscopic biopsy was performed using GIF 160 Olympus endoscope. Patients received injection ketamine 1 mg/kg of body weight as premedication. Endoscopic markers were evaluated for grooving/scalloping of the duodenal folds, mosaic pattern of the mucosa, nodularity, and reduction and thinning in the numbers (no more than three folds in straight line on endoscopic vision or absence of Kerkring folds at maximum insufflations).

Biopsy specimens comprising of at least three fragments with a forceps (open cup ~ 6mm) were taken. Samples were carefully oriented on filter paper and fixed in 10% formalin. Biopsies were embedded in paraffin wax, cut in sections and stained with hematoxylin and eosin. Histopathology was expressed according to the Marsh classification 1992[10].

**Statistical analysis:** Statistical analysis was performed with Statistical Package for the Social Sciences software (SPSS version 13.0, Chicago, Illinois, USA). In total study group, for continuous data mean, standard deviation and range were calculated. For categorical data, number and percentages were calculated.

## Findings

One hundred and thirty four children diagnosed as having celiac disease who came for regular

follow up were included in the study group.

**Age and sex distribution of the study group:** The number of cases present in age group of <5 years were 60 (45%), followed by 55 cases (41%) in 5-10 years of age group and 19 cases (14%) in more than 10 years of age group. There was male predominance with M:F ratio being 3:2. Mean age of onset of symptoms was 3.4 years (6 months-11.5 years) and patients presented at a mean age of 6.2 years (1-14) with mean period of delay in diagnosis of 33.4 months (0-132.0).

Mean age at cereal introduction was 7.2 (2-29) months (Table 1). In 77% of patients, symptoms appeared early i.e. below 5 years of age (mean age 3.36 years) but 55.2% presented to the hospital late i.e. after 5 years of age (mean age 6.19 years) with mean delay in diagnosis of 33.4 months.

**Rural and urban distribution of study group:** Distribution noted in the study group was urban 57% and rural 43%. The urban group presented early (59.6% of patients <5 years of age) than rural patients (40.4% of patients <5 years of age).

**Presenting symptoms of study group:** Diarrhea was presenting symptoms in 54.5%, failure to thrive in 52.2%, features suggestive of anemia were seen in 40.3%, short stature in 20.9%, abdominal pain in 19.4%, vomiting in 15.7% and constipation in 2.2% of cases. Abdominal distension was the presenting feature in 41% of cases. Features suggestive of liver disease were observed in 2 cases.

History of seizures was elicited in 2 cases but in one case these were post traumatic and in other they were related to past history of tuberculous meningitis. One patient had features suggestive of Down's syndrome and one was already a known case of juvenile rheumatoid arthritis.

Family history of celiac disease was noted in 7 cases out of which 5 were siblings and 2 were paternal aunts. Family history of asthma was there in 1 case.

**Physical examination of study group:** Pallor was present in 100% of cases, short stature in 60.4%, clubbing and edema in 15.7% and 3% of cases at the time of diagnosis, respectively. Evidence of rickets, B complex group of vitamin deficiency and vitamin A deficiency was seen in 23, 9 and 1 case respectively.

Hepatomegaly was noted in 9 cases and splenomegaly in 1 case. No abnormality was seen in any case with regards to respiratory, cardiovascular and nervous system examination.

**Weight and height at presentation:** At presentation, the mean weight was 14.6±5.5 kg. The mean length/height at the time of presentation was 102.6±17.2cm. 14.2% of the patients had weight >80% of 50$^{th}$ percentile of NCHS for that age and sex at the time of diagnosis. 24.6% of patients had weight for age less than 60% of normal (Grade III and IV or severe PEM according to the IAP classification). 60.4% of patients had length/height below 3$^{rd}$ percentile of NCHS for that age and sex.

**Laboratory investigations:** Mean hemoglobin was 8.81±1.9 gm/dl. Anemia was microcytic hypochromic in 60.4% of patients, dimorphic in 20.9% and normocytic normochromic in rest of patients (Table 2).

Forty nine patients (36.6%) had thrombocytosis at the time of diagnosis. Serum albumin

**Table 1:** Demographic profile of the study group (n=134)

| Variables | Mean ± SD | Range |
|---|---|---|
| **Age (years)** | 6.2 ± 3.2 | 1.3- 14.0 |
| **Age of onset ( years)** | 3.4 ± 2.6 | 0.5- 11.5 |
| **Age at presentation (years)** | 6.2 ± 3.2 | 1- 14.0 |
| **Delay in diagnosis (months)** | 33.4 ± 30.6 | 0- 132.0 |
| **Weight (kgs)** | 14.7 ± 5.6 | 6- 37.2 |
| **Height (cms)** | 102.6 ±17.1 | 70- 156 |
| **Breast feeding (months)** | 13.6 ±10.1 | 0- 48 |
| **Cereal introduction (months)** | 7.2 ± 2.9 | 2- 29 |

**Table 2:** Laboratory investigations in the study group (Data expressed as Mean ±SD; n=134)

| Parameters | Normal | Cases (Mean ± SD) | Range |
|---|---|---|---|
| **Hemoglobin (g/dl)** | 12-18 | 8.81 ± 1.9 | 4-12 |
| **Total leucocyte count /µl** | 4000-11000 | 8738.1 ± 2752.2 | 2300-19000 |
| **Platelets (1000)/µl** | 150-400 | 395.9 ± 220.8 | 52-1120 |
| **Total Protein (g/dl)** | 6.4-7.8 | 6.9 ± 0.9 | 4-9 |
| **Albumin (g/dl)** | 3-5 | 3.6 ± 0.7 | 1-5 |
| **Globulin (g/dl)** | 2.5-3.5 | 3.3 ± 0.6 | 1-5 |
| **Bilirubin (mg/dl)** | 0-1 | 0.7 ± 0.1 | 1-2 |
| **SGOT (IU)** | 2-40 | 65.3 ± 70.1 | 30-328 |
| **SGPT (IU)** | 2-41 | 49.5 ± 33.5 | 18-304 |
| **Serum alkaline phosphatase (IU)** | 40-129 | 215 ± 88.1 | 88-528 |
| **Calcium (mg/dl)** | 9-11 | 8.9 ± .6 | 7.2-10.3 |
| **Phosphorus (mg/dl)** | 3-5 | 4.3 ± 1.01 | 1.0-7.0 |
| **Baseline serum Zinc levels (µg/dl)** | 70-110 | 67.2 ± 37.4 | 1- 292 |

SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase, SAP:

of <2.5 g/dl was present in 9% of patients. Serum trans- aminases were raised in 38.8 % of cases but rise was mild in all (<3 times the normal) except those with associated liver disease (Table 2).

**Anti tissue transglutaminase IgA (tTG) levels in study group:** The mean serum anti tTG level of study group at presentation was 164.24U/ml (Ranging from 0 to 749 U/ml). 15 patients were negative for the serology but 8 out of them had IgA deficiency and all of these had histopathology suggestive of celiac disease. Sensitivity of anti tTG was 94.7%.

**Histological categorization of small intestinal biopsy in study group:** 86 patients (64.2%) had subtotal villous atrophy (Marsh IIIb), 30 (22.4%) had partial villous atrophy (Marsh IIIa) and only one patient had evidence of total villous atrophy on small intestinal biopsy. Levels of IgA anti tTG correlated with the severity of small intestinal damage on biopsy (Table 3).

## Discussion

This prospective study was undertaken to study the clinical and investigative patterns of presentation in patients of celiac disease. Mean age at onset of symptoms, mean age at diagnosis, mean period of delay in diagnosis and mean age at cereal introduction correlates with other Indian studies as reported earlier[11-14]. In majority of studies, conducted in western countries, the classical age of presentation is 9-18 months and the diagnosis is usually made within 6 months of onset of symptoms[15-17]. In

**Table 3:** Correlation of serology and biopsy in the study group (n=134)

| Biopsy | Serology | | | | | *P* value |
|---|---|---|---|---|---|---|
| | <15 | 15-50 | 51-100 | 101-300 | >300 | |
| **Subtotal VA** | 3(3.5) | 5(5.8) | 19(22.1) | 31(36.0) | 28(32.6) | 0.0001 |
| **Partial VA** | 3(10.0) | 5(16.7) | 7(23.3) | 11(36.7) | 4(13.3) | |
| **Crypt hyperplasia** | 9(64.3) | 3(21.4) | 1(7.10 | 1(7.1) | 0(.0) | |
| **Intraepithelial lymphocytes** | 1(33.3) | 1(33.3) | 0(.0) | 1(33.3) | 0(.0) | |
| **Total VA** | 0(0) | 0(0) | 0(0) | 0(0) | 1(100) | |

VA: Villous Atrophy

the study conducted by Baudon et al[15] in France, the first symptoms/signs occurred before one year of age in 73% of the cases, during the second year of life in 20.5% and after 3 in only 6.5%. The diagnosis was made before 2 years of age in 77% of the cases and after 3 in only 23%. In contrast to this, in the present study, no patient presented before one year of age though symptom onset occurred in 23.8%.

Symptom onset during the second year of life occurred in 19% and in 35% of patients the symptoms occurred in 2-5 years of age. No patient was diagnosed before one year of age and only 5.2% between 1-2 years of age and more than half of cases (55.2%) were diagnosed after 5 years of age. The higher mean age of onset of symptoms in our patients may be attributed to prolonged breast feeding practices, delayed weaning and late introduction of gluten in the diet. The delay in diagnosis is probably because in developing countries like India, infection as a cause of chronic diarrhea is very common and there is lack of awareness about celiac disease. In the present study, the disease distribution is slightly higher in urban population. Early diagnosis in urban patients may be because of their direct presentation to tertiary care hospitals while delayed diagnosis in rural population shows that celiac disease is still not being diagnosed at primary health care centers.

In the present study, the major symptoms at presentation were diarrhea, failure to thrive, abdominal distension, while pain abdomen, vomiting and constipation were relatively less common symptoms**.** The main differences in the clinical features of celiac disease as highlighted by the present study and other studies from northern India[11-14] as compared to west[18] are the higher incidence of failure to thrive and anemia in India (Table 4). These two clinical manifestations are features of more severe disease and correlate with delay in diagnosis in our country. With increasing awareness about the varied manifestations of CD and with the availability of reliable noninvasive markers (celiac serology) of the disease, it is now being recognized in the atypical form with early diagnosis as compared to earlier studies (Table 4).

The mean IgA anti tTG level at time of presentation was 164.24 U/ml which was higher than the study conducted by Tursi et al[19].

Sensitivity of anti tTG was 94.7% which correlates with previous studies[1]. IgA deficiency was confirmed on investigation in 6% of cases which is higher than previously noted[1,20]. Tursi et al showed that the mean serum value of anti tTG ranged from 3.6 U/ml in Marsh I lesions to 74.95 U/ml in Marsh IIIc lesions, respectively[19].

The higher mean anti tTG levels in our study correspond with severe intestinal damage (Marsh IIIb-c lesions).

The majority of patients had subtotal villous atrophy (Marsh IIIb). 22.4% had partial villous atrophy (Marsh IIIa) and only one patient had evidence of total villous atrophy on small intestinal biopsy at the time of presentation. Young et al reported total villous atrophy in all

**Table 4:** Comparison of clinical features of children with celiac disease at presentation in various studies

| | Walker Smith et al[18] (%) | Thapa et al[11] (%) | Patwari et al[13] (%) | Poddar et al[14] (%) | Present study (%) |
|---|---|---|---|---|---|
| **Failure to thrive** | 14.0 | 100.0 | 100.0 | 91 | 52.2 |
| **Pallor/anemia** | 13.5 | 100.0 | 100.0 | 84 | 100.0 |
| **Diarrhea** | 86.5 | 93.3 | 93.8 | 84 | 54.5 |
| **Abdominal distension** | 44.2 | 73.3 | 70.8 | 48 | 41.0 |
| **Pain abdomen** | 44.2 | 20.0 | 50.8 | 31 | 19.4 |
| **Vomiting** | 61.5 | 20.0 | 9.2 | 17 | 15.7 |
| **Edema** | 13.5 | 10.0 | 7.7 | 6 | 3.0 |
| **Constipation** | 5.8 | 2.0 | 3.1 | 3 | 5.2 |
| **Rectal prolapse** | 3.8 | 1.3 | 3.1 | 0 | 0 |

his patients at the time of presentation[21].

Anemia is a frequent feature of celiac disease and present in all the cases at the time of presentation. Iron deficiency, microcytic hypochromic anemia was the most common type of anemia recorded in our study which is in conformity with the results of other studies[18].

Thrombocytosis was detected in 37% of our patients at diagnosis. In the study done by Patwari et al, thrombocytosis was present in 60% of the cases at the time of diagnosis[13]. Ogrady et al documented evidence of hyposplenism of unknown cause with thrombocytosis and splenic atrophy in 50% of adults with celiac disease. In most of the cases the evidence of hyposplenism disappeared with elimination of gluten from the diet[23].

Serum transaminases were raised in 38.8 % of our cases but rise was mild in all (<3 times the normal) except those with associated liver disease. Chronically elevated transaminases levels in the range of 1.5 to twice normal values have been reported in 9-40% of patients with untreated celiac sprue[1]. In our study associated liver disease was present in 2 cases; Down's syndrome in one case, nephrotic syndrome in one and juvenile rheumatoid arthritis in one case. Polanco described associated disorders in a series of 440 children with celiac disease. Out of these selective IgA deficiency was present in 3% of children, dermatitis herpetiformis and diabetes mellitus type I each in 2% of cases; chronic active hepatitis, psoriasis, cardio-vascular disease and Down's syndrome each in 1% of children with celiac disease. Vitiligo, cystic fibrosis, fibrosing alveolitis, renal tubular defects, $\alpha_1$ anti-trypsin deficiency, Henoch-Schönlein purpura were also noted as associated disorder in children with celiac disease[3].

There are some limitations of this study related to follow up of the patients. There was some referral bias also as the study center is a tertiary care referral center.

## Conclusion

Classical presentation of celiac disease is less commonly encountered these days in India in accordance to apparent changing trend worldwide. Appreciation of the more occult presentations of celiac disease together with the more widespread use of serologic testing will probably result in an increase in the rate of diagnosis of celiac disease in India.

***Conflict of Interest:*** None

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