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CLINICAL PROFILE OF NON-DIARRHEAL CELIAC DISEASE: SINGLE CENTRE EXPERIENCE FROM CHILDREN'S HOSPITAL SRINAGAR

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Abstract

Background: Celiac Disease (CD) is an immune-mediated systemic disorder elicited by gluten in wheat and related prolamines from rye and barley in genetically susceptible individuals and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD–specific antibodies, human leukocyte Antigen (HLA)-DQ2 or DQ8 haplotypes and enteropathy.

Aim: To study the clinical profile of non-diarrhoeal coeliac disease in children.

Methods: This Observational cross sectional study, was conducted in the Postgraduate Department of Paediatrics, Children Hospital, an associated hospital of Government Medical College Srinagar, which is a referral tertiary care hospital for the children of Kashmir valley. A total of 30 pediatric patients within the age group of 0 to 18 with non classical disease (diagnosed or suspected from 6 months) were enrolled and children from 6 months to 18 years with diagnosed or suspected coeliac disease with diarrhoea as the predominant symptom were excluded. Independent sample t-test was used for comparing the quantitative variables with normal distribution while Mann-Whitney U-test was used for comparing quantitative variables having abnormal distribution. A p-value of less than 0.05 was considered significant.

Results: The most common clinical presentation was anemia 50% (n=15), followed by short stature 23.33% (n=7). 16.67% (n=5) presented with gastrointestinal; bleeding. Out of 30 patients, 66.67% (n=20) were underweight, 2333% (n=7) were of normal weight and 10% (n=3) were overweight. The most common finding on endoscopy was duodenal scalloping 46.6% (n=14) followed by decreased folds 36.6% (n=11). Duodenitis was seen in 20% 9n=6) patients. Out of 30 patients, 43.33% (n=13) had Marsh-Oberhuber grading 3b, 33.33% (n=10) had Marsh-Oberhuber grading 3a and 23.33% (n=7) had Marsh-Oberhuber grading 3c on histopathology examination of duodenal biopsy. On correlating age with various variables in terms of gender, HPE findings, other demographic data and clinical features no statistical significance was seen (P >0.05). However, a significant correlation was seen between age and BMI (P<0.05).

Conclusion: We concluded that, serologic tests are highly recommended for children with failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting and abnormal liver enzyme elevation.

Keywords: Celiac Disease, immune-mediated systemic disorder, anemia, weight loss, Duodenitis, serologic tests.

Introduction:

Celiac Disease (CD) is an immune-mediated systemic disorder elicited by gluten in wheat and related prolamines from rye and barley in genetically susceptible individuals and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD–specific antibodies, human leukocyte Antigen (HLA)-DQ2 or DQ8 haplotypes and enteropathy. CD–specific Antibodies comprise autoantibodies against TG2 including endomysial Antibodies (EMAs), and antibodies against deamidated forms of gliadin peptides. Celiac disease is a condition where the ingestion of gluten causes an immune response in the small intestine. There may be a delay or latent period between gluten intake and the onset of symptoms.[1]

The prevalence of celiac disease in the general population is estimated to be 1% in the world. [2] The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the world is 1.4% and 0.7%, respectively. [3] Its prevalence varies depending on geographical and ethnic variations. The highest prevalence is in Europe (0.8%) and Ocenia (0.8%), and the lowest prevalence is in South America (0.4%). The biopsy-proven prevalence of celiac disease was found to be 1.5 times higher in women than men, and approximately two times higher in children than adults. The reason for this difference may be genetic factors [human leukocyte antigen (HLA) and non-HLA genes], environmental factors such as wheat consumption, age at gluten intake, gastrointestinal infections, proton pump inhibitor and antibiotic use, and the rate of cesarean section. [3,4,5]

Celiac disease can occur at any age from early childhood to old age. It has two peaks; the first peak occurs after gluten intake within the first 2 years of life, the second is seen in the second or third decade of life. The diagnosis of celiac disease is difficult because symptoms vary from patient to patient. [6]

Symptoms typically occur in children between the ages of 4 and 24 months and can include chronic diarrhea, abdominal pain, vomiting, and failure to thrive. [7,8] In recent years, the clinical symptoms of celiac disease in children have shifted from gastrointestinal symptoms to extraintestinal symptoms [9,10], such as short stature and delayed puberty. The reason for this change is not clear, but it may be due to increased awareness and use of sensitive and specific serologic tests.

The only current treatment for CD is a strict, lifelong gluten-free diet. [11] Adherence to this diet reverses malabsorption, nutritional deficiencies, and symptoms and decreases comorbidities. Intestinal mucosa healing begins, and serum antibody levels normalize within a few months of beginning the diet. [12,13]

Untreated or partially treated CD can lead to osteoporosis, kyphoscoliosis, fractures, splenic malfunction, infertility, repeated pregnancy loss, low-birth-weight offspring, ulcerative colitis, neurologic impairment (e.g., cerebellar ataxia, peripheral neuropathy), and intestinal lymphoma. [12] Celiac crisis, a life-threatening syndrome of severe diarrhea and metabolic and electrolyte impairments leading to hypoproteinemia can develop in small children. [12]

Material and Methods:

The present Observational cross sectional study, conducted in the Postgraduate Department of Paediatrics, Children Hospital, an associated hospital of Government Medical College Srinagar, over a period of 18 months on children's of age group between 6 months to 18 years.

METHODS

Informed consent was obtained from the parents and guardians of the children included in the study. The duration of the symptoms was ascertained from a reliable patient‟s relative or attendant, medical records and referring physician‟s note. All patients were managed with standard treatment protocol. Detailed history and physical examination with special reference to anthropometric

assessment was performed in all children at the time of diagnosis. With clinical diagnosis of CD, serological tests were performed besides routine investigations and all base line investigations. The serological tests include Antigliadin antibody Ig G & Ig A (AGA), Endomysial antibody Ig A(EMA), Tissue Transglutaminase (TTG) and in some cases Antireticulin antibodies (ARA). The small intestinal biopsy was performed in all cases for histological study. Children diagnosed as CD were put on Gluten free diet (GFD). The parents were given the list of GFD. They were explained in details regarding the disease, importance of compliance of diet and prognosis. In the follow up, these children were assessed for details of diet (to ascertain the compliance and quality of food intake) and their clinical profile, especially anthropometry.

Anthropometry (weight, height, mid arm circumference) was recorded by standard technique. Informed consent of all the subjects was obtained before collecting samples. The intestinal biopsy was performed by a pediatric gastroenterologist by a pediatric fiber optic endoscope after written consent and appropriate sedation. The biopsies were sent for histopathological examination in a 10% formalin. The histopathological grading was done using Marsh Oberhuber grading.

STATISTICAL METHOD

Data obtained was entered into Microsoft Excel Spreadsheet (2010) and then exported to the data editor of Statistical Package for Social Sciences (SPSS Ver. 23). Qualitative variables like gender, clubbing, abdominal distension, malnutrition and short stature were presented as frequencies and percentages. Chi-square test was used for comparing the frequencies of qualitative variables. Quantitative variables such as age, hemoglobin, and TTG were subjected to normality testing using Shapiro Wilk test. Variables having normal distribution were presented as mean and standard deviation while those having abnormal distribution were presented as median and interquartile range. Independent sample t-test was used for comparing the quantitative variables with normal distribution while Mann-Whitney U-test was used for comparing quantitative variables having abnormal distribution. A p-value of less than 0.05 was considered significant.

Results:

Most of the patients (60%) presented in the age group of 6-10 years with mean age of study population was 6.36 ± 3.84 years. Both males 50% (n=15) and females 505 (n=15) were equally affected in our study. Most of the patients had weight of 3rd to 50 the percentile accounted for 53.33% (n=16) and height for age in 3 rd to 50th percentile accounted for 53.33% (n=16) [Table 1].

Table 1: Demographic profile of the study population

Variables		**Mean±SD (%)**
Age		**6.36 ± 3.84**
Sex M/F		**50/50**
Weight For age (percentile)	**<3**	**23.33**
	3-50	**53.33**
	50-97	**23.33**
Weight for Height (percentile)	**<3**	**23.33**
	3-50	**56.67**
	50-97	**20.00**
Height for Age (percentile)	**<3**	**26.67**
	3-50	**43.33**
	50-97	**30.00**

The most common clinical presentation was anemia 50% (n=15), followed by short stature 23.33% (n=7). 16.67% (n=5) presented with gastrointestinal; bleeding [Table 2].

Table 2: Clinical Presentation

Variables	Opts	%
Clinical Presentation	Anemia	50.00
	Asymptomatic Transaminitis	3.33
	Chylous Ascites	3.33
	Gastrointestinal Bleeding	16.67
	Seizure disorder..Hepatomegaly	3.33
	Short Stature	
		23.33

Out of 30 patients, 66.67% were underweight, 2333% were of normal weight and 10% were overweight [Table 3].

Table 3: BMI of Patients

Variables	Opts	%
BMI	Underweight	66.67
	Normal	23.33
	Overweight	10.00
	Obese	0.00
Mean ± S.D = 18.029 ±4.464		

The most common finding on endoscopy was duodenal scalloping 46.6% followed by decreased folds 36.6%. Duodenitis was seen in 20% patients [Fig 1].

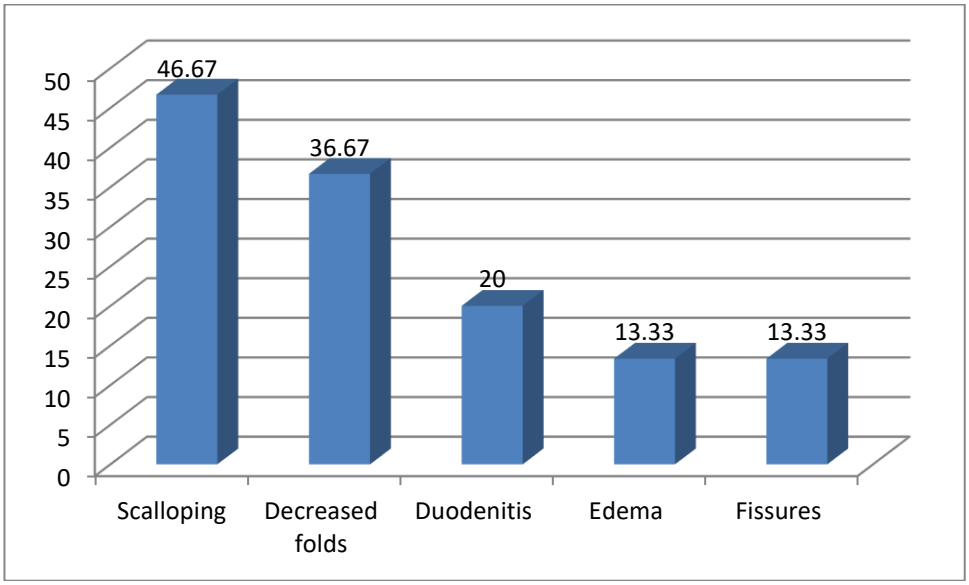

Fig 1.

Out of 30 patients, 43.33% (n=13) had Marsh-Oberhuber grading 3b, 33.33% (n=10) had Marsh-Oberhuber grading 3a and 23.33% (n=7) had Marsh-Oberhuber grading 3c on histopathology examination of duodenal biopsy [Fig 2].

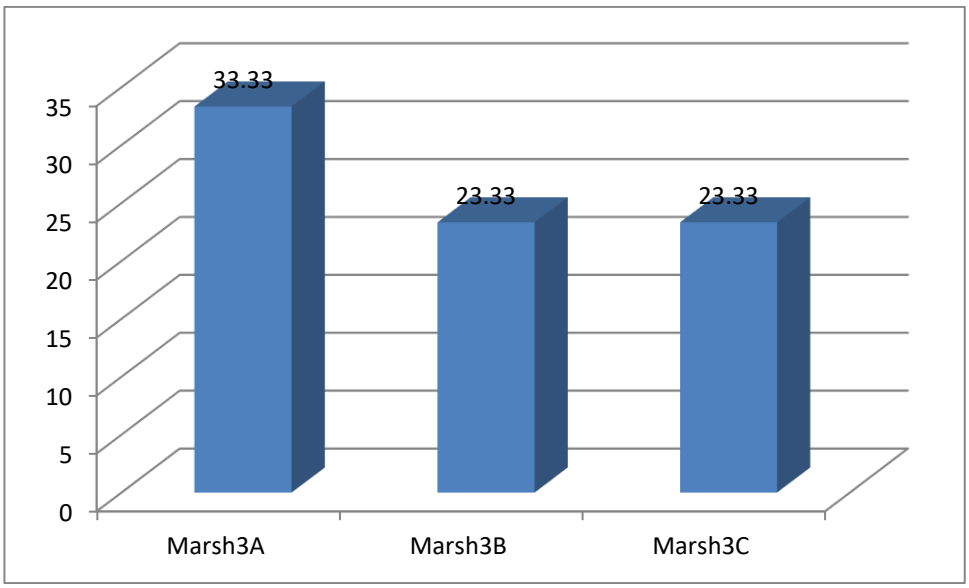

Fig 2.

Discussion:

The prevalence of celiac disease in the general population is estimated to be 1% in the world. [14] The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the word is 1.4% and 0.7% respectively. [15] The prevalence of celiac disease depends on the geographical and ethnic variations. The overall prevalence of celiac disease in Indian is 1.04%. Despite the similar HLA haplotypes DQ2 and DQ8, the prevalence is greater in Punjab region 1.2% and elsewhere in North compared to south is 0.1%. [16] The reason for the differences may be genetic factor, environmental factors, age at gluten intake, gastrointestinal infections and antibiotic use. There is no such data yet on atypical celiac disease from our region. So, the purpose of present study was to determine the clinical profile of non-diarrheal celiac disease in children in at our teaching hospital.

In our study, most of the patients 60 % (n=18) presented in the age group of 6-10 years, followed by age group of 2-5 years accounted for 30% (n=9). 10% (n=3) of patients had age group of less than 2 years. The mean age at presentation was 6.36 ± 3.84 years. Both males and females were equally affected in our study accounted for 50% (n=15) each. Similar finding were reported by **Boskovic A et al, [17]** where he found most of the patients with atypical celiac disease presented in age group of >3 years, both genders affected almost equally. **Imran A et al, [18]** in the study reported maximum number of patients with less than 10 years of age with slight female predominance.

In our study, most of the patients (53.33%) had weight of 3-50 percentile, followed by 50-97 percentile and <3rd percentile, both of which had equal distribution of 23.33%. While as comparing weight for height 56.67% (n=17) were within 3-50 percentile. 23.33% (n=7) in <3rd percentile and 20% (n=6) in 50-97 percentile. On seeing height for age, 43.33% (n=13) were in 3-50 percentile, 30% (n=9) in 50-97 percentile and 26.67% (n=8 in <3rd percentile. The mean weight of patients was 20.93 kilograms and mean height was 105.47 centimeters. Most of the patients (66.67%; n=20) were underweight, 23.33% (n=7) had normal BMI and 10% (n=3) were overweight. The mean BMI was 18.029 ±4.464. In a study by **Pooni PA et al, [19]** aimed to evaluate the clinical and anthropometric profile of 71 children confirmed to have celiac disease reported that all the patients in group III (more than 10 years of age), had weight for age (w/a) <3rd percentile and majority (83 per cent) had short stature, with delayed puberty in all. **Hashmi MA et al, [20]** in their study found 95.5% of children with severe malnutrition in NDCD group. **Agarwal N et al, [21]** observed mean body weight of 18.1kgs in children with non-diarrheal celiac disease. **Dehbozorgi M et al, [22]** in their study on celiac disease in children reported 5.4% of the patients with BMI more than 95th percentile.

In our study, the most common presenting symptom was anemia, accounted for 50% (n=15) followed by short stature 23.33% (n=7) and GI bleeding 16.67% (n=5). Other presenting symptoms

seen were asymptomatic transaminitis, chylous ascites and seizure disorder and hepatomegaly each showed equal distribution of 3.33% (n=1). The findings were comparable with **Imran A et al, [18]** who in their study found short stature, refractory anemia and abdominal pain as the most common presenting symptoms in patients with non-diarrheal celiac disease. **Semwal P et al, [23]** had anemia, short stature, abdominal pain and failure to thrive as the most common presenting symptom in NDCD group. **Agarwal N et al, [21]** observed refractory anemia as the most common presenting symptom in children with NDCD. **Patwari AK et al, [24]** reported anemia as the most common clinical presentation among children with celiac disease. **Sharma A et al, [25]** also reported that the common clinical presentations of atypical CD are short stature, anemia, abdominal distension. **Isa HM et al, [26]** also found that anemia (iron-deficiency) as the most frequent associated disease (69.7%) in patients with celiac disease.

In the present study mean TTG IgA was 314.77 U/mL, mean total IgA was 271.67 U/mL. Mean ALT and AST were 34.47 and 38.70 IU/L. Mean haemoglobin in our study was 8.93 %. Mean serum albumin was 3.44 g/dL and the mean serum iron was 61.13 **ug/dL** (Table 8) (Figure 8). **Boskovic A et al, [17] had** mean tTG antibodies titre of 140.66 U/mL. The mean haemoglobin in a study by **Agarwal N et al, [21]** was 8.1g/dL in children with non-diarrheal celiac disease. **Imran et al, [18]** found TTG-IgA titer>10 times. **Ganji A et al, [27]** found mean TTG IgA titre of >100 among children with atypical CD.

In our study, the most common gross finding on GI endoscopy was duodenal
scalloping 46.6% (n=14) and decreased folds 36.6% (n=11). Other endoscopic finding were duodenitis 20% (n=6), mucosal edema 13.3% (n=4) and mucosal fissures 13.3% (n=4) (Table 9) (Figure 9). **Mateen A et al, [28]** had only 8 out of 12 patients who had gross pathological findings on endoscopy. **Semwal P et al, [23]** in their study mentioned that duodeno-endoscopic features may have considerable practical importance for the diagnosis of celiac disease in children. Scalloping, mosaic pattern, reduced fold height and nodularity are main endoscopic markers of celiac disease in children and endoscopic findings of duodenal mucosa may be important in early diagnosis of celiac disease, inchildren with atypical presentations or indications other than suspected celiac disease.

On histopathological examination, the duodenal biopsy revealed villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes. The most common histopathological grade was marsh 3b in 43.33% (n=13) followed by Marsh 3a in33.3% (n=10). The least histological Marsh grade seen was 3c in 23.4% (n=7). None of the patient had Marsh grade of <3 . **Hashmi MA et al, [20]** found Marsh 3b and 3c in 44.4% and 24.1% in their study among the children with celiac disease. **Imran et al, [18]** in their study that included 90 pediatric patients with celiac disease, found that Marsh grade 3b as most common histological finding in GI biopsies. **Isa HM et a1, [26]** in their study of celiac disease in children 45.7% of patients had histopathological Marsh Oberhuber type III on duodenal biopsy. On correlating age with various variables in terms of gender, HPE findings, other demographic data and clinical features no statistical significance was seen (P >0.05). However, a significant correlation was seen between age and BMI (P<0.05). On correlating gender with various variables in terms of gender, HPE findings, other demographic data and clinical features no statistical significance was seen (P >0.05).

Conclusion:

Celiac disease is a lifelong multi-systemic disease triggered by intake of gluten in genetically susceptible individuals. The presentation of atypical celiac disease is quite tricky and can delay the diagnosis that may lead to the long-term complications such as failure to thrive, osteopenia, short stature, malignancy etc. from our study we observed that, serologic tests are highly recommended for children with failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting and abnormal liver enzyme elevation.

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