Original Article

Clinicolaboratory profile of children with celiac disease in North India

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ABSTRACT

Background: Prevalence of celiac disease (CD) has increased worldwide, but there are only few studies reporting clinicolaboratory profile of children with CD. **Aim:** To study the current clinicolaboratory profile of celiac disease in North Indian children. **Methods:** This retrospective study was done in pediatric gastroenterology clinic of a tertiary care center of North India. The primary objective was to study clinical and laboratory profile in children with CD. Secondary objective was to find correlation between duodenal biopsy Marsh stage and IgA tissue with tissue transglutaminase antibody (tTG) titers and also with serum hemoglobin, serum iron levels, and severity of anemia. A total of the 54 children fulfilling the diagnostic criteria of CD were included, and details were reviewed and analyzed. **Results:** Average age of onset of symptoms was 4.7±2.5 years, 80% had onset of symptoms after 2 years of age. Chronic diarrhea (70.3%), pain abdomen (62.9%), and abdomen distention (53.7%) were the most common manifestations. Wasting (38.4% - <5 years, 41.4% in >5 years), stunting (46.3%), rickets (22%), and anemia (90.7%) were common. Serum hemoglobin levels and serum iron levels were inversely correlated to the serum tTG levels and Marsh biopsy staging; though, not significant. Correlation of hemoglobin levels between Marsh stage 3A and 3C was statistically significant (p=0.036). There was no correlation between serum tTG levels and Marsh biopsy staging with anemia and its severity. **Conclusion:** Gastrointestinal symptoms still remain the most common presentation in children with celiac disease. Malnourishment, anemia, and rickets require special attention in these children.

Key words: *Celiac disease, Children, Duodenal biopsy, Iron deficiency, Profile*

Prevalence of celiac disease (CD) in children is reported to be approximately 1% in both India and western world [1-4]. Recent increase in prevalence of CD has been reported, which may be attributed to growing awareness among parents and clinicians, ease and accessibility to serological testing and endoscopic facilities [5-7]. Besides common gastrointestinal symptoms, failure to thrive, short stature and refractory anemia are the common atypical manifestations reported in children. Till date, only few Indian studies have reported clinical and laboratory profile in children with CD [8-12]. We evaluated clinical and laboratory profile of North Indian children with CD and also correlated duodenal biopsy Marsh stage and IgA tissue transglutaminase antibody (tTG) titers with serum hemoglobin, serum iron levels, and severity of anemia.

METHODS

This retrospective study was done in pediatric gastroenterology clinic of a tertiary care center in North India. Ethical clearance from the Ethical Committee of the institute was taken. Hospital records of the children aged 0-18 years, who attended the pediatric gastroenterology clinic between July 2014 and December 2015, were screened for those with presumptive diagnosis of CD. The diagnosis of CD was made as per the diagnostic criteria by the World Gastroenterology Organization 2012, i.e., symptomatic children or asymptomatic with positive family history, with positive serology (IgA tTG >10 U/ml) and biopsy suggestive of villous atrophy (Marsh staging 3) [13]. Records of 60 children with presumptive CD were reviewed and analyzed. Of these, 6 patients were excluded due to incomplete records (2) or not meeting the diagnostic criteria (4). 54 children were finally enrolled.

The following data were recorded age, sex, age of onset, duration of disease, gastrointestinal symptoms (chronic diarrhea, vomiting, pain abdomen, abdomen distention, anorexia, and constipation) and non-gastrointestinal manifestations (failure to thrive, short stature, anemia, features of rickets, other vitamin deficiencies, and skin lesions) and anthropometry (Z scores for height for age, weight for height [<5 year] and body mass index [BMI] [>5 years]). WHO growth charts were used as standard reference for anthropometry [14]. Details of laboratory parameters (hemoglobin, severity of anemia, serum iron levels, serum calcium, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), IgA levels, IgA anti tTG antibodies, and duodenal biopsy findings (Marsh staging) were also noted. The cutoff for various laboratory parameters mentioned were taken from standard references used in pediatric population [15,16]. A note was also made of associated disorders.

Statistical analysis was performed by the Stata version 14.1 software. Quantitative variables were represented by means and qualitative variables by percentages. Correlation of tTG levels and duodenal biopsy (Marsh staging) with serum hemoglobin, serum iron, severity of anemia, and iron deficiency was determined using regression analysis. p≤0.05 was considered as significant.

RESULTS

A total of 54 children were diagnosed with CD between July 2014 and December 2015. Table 1 shows the clinical and laboratory details of the enrolled children. The mean age of enrolled children was 8±3.6 years (range: 20 months-17 years), and most children were >5 years (75.8%) with a female predominance (Male:Female ratio - 2:3). Average age of onset of symptoms was 4.7±2.5 years (range: 8 months - 11 year). 81% (44/54) of children had onset of symptoms after 2 years with earliest child presenting at 8 months. Most children (52/54) presented with gastrointestinal symptoms except 2 patients, who presented with failure to thrive and anorexia. Chronic diarrhea (70.3%), pain abdomen (62.9%), and abdomen distention (53.7%) were the most common manifestations. Other presenting features included vomiting, constipation, weight loss, rectal prolapse, anorexia, and not gaining weight. Family history of CD was present in 16.7% of children (siblings - 8, father - 1). Anthropometry showed wasting in 38.4% (5/13) and undernourishment (BMI score <2z score) in 41.4% (17/41) of children ≤5 years of age and >5 years age, respectively. Stunting was present in half (46.3%) of the children (height/age <2z score) of which 18.5% were severely stunted (<3z score). On clinical examination, main manifestations were pallor (62.9%) and rickets (22%). Other findings included edema, ascites, dermatitis, and oral ulcers.

Laboratory Parameters

Mean hemoglobin was 8.11±2.32 g/dl (range 3.1-12.8 g/dl) with anemia in 90.7% cases (48.1% severe anemia). Iron deficiency anemia (serum iron <60 mcg/dl) was seen in 77.8% children. Mean serum iron levels were 37.25±23.14 µg/dL (range 5-97 µg/dL). Hypocalcemia (48%) and raised liver enzymes (SGOT, SGPT) (45%) were commonly seen (Table 1). Other associated systemic disorders were hypothyroidism (n=2), diabetes mellitus type 1 (n=1), and autoimmune hepatitis (n=1). Most of the children enrolled in the study had tTG IgA levels between 100 and 500 U/ml (85%) and duodenal biopsy conclusive of 3b Marsh staging (52%). Most of the children in the enrolled group 39/54 (72.2%) were on gluten free diet for the last 6 months.

Children were grouped according to Biopsy Marsh stages. Correlation analysis between Marsh staging and serum tTG with mean hemoglobin, mean serum iron, presence of iron deficiency, and severity of anemia was done (Table 2). The results showed that mean serum iron and mean hemoglobin levels decreased with increasing serum tTG levels and biopsy staging, but the correlation was not significant (p>0.05). However, on logistic regression analysis, the decrease in hemoglobin levels from Marsh stage 3A to 3C was statistically significant (p=0.036) (Table 2).

There was no significant correlation between iron deficiency and Marsh staging (odds ratio of 3A vs. 3B=2.47, p=0.241 and 3A vs. 3C=6.66, p=0.123). Furthermore, no significant correlation was found between iron deficiency and serum tTG levels (Odds

Table 1: Clinical and laboratory details of enrolled children with celiac disease

Parameter	Number of children	Percentage of children
Age (years)		
≤2	2	3.7
>2-≤5	11	20.3
>5-≤10	26	48.2
>10	15	27.8
Sex		
Males	21	
Females	33	
Age at onset of symptoms (year)		
≤2	10	18.5
>2-≤5	23	42.6
>5	21	38.9
Symptoms and signs		
Chronic diarrhea	38	70.3
Vomiting	21	38.8
Abdomen distention	29	53.7
Pain abdomen	34	62.9
Rectal prolapse	3	5.5
Constipation	8	14.8
Anorexia	20	37.0
Not gaining weight	25	46.2
Oral ulcer	5	9.2
Pallor	34	62.9
Rickets	12	22
Others (edema, ascites, skin changes)	8	14.8
<5 year: Wasting, severe wasting	5/13, 2/13	38.4, 15.3
>5 year: BMI<2 SD	17/41	41.4
Stunting (severe stunting)	25/54 (10/54)	46.3 (18.5)
Anemia	49/54	90.7
Severe/moderate/mild	26/16/7	48.1/29.6/12.9
Iron deficiency	42/54	77.8
Hypocalcemia (<8.8 mg/dl)	24/50	48
Raised transaminases	24/54	45
tTG values (U/ml)		
>10-<100	7	12.9
100-<200	24	44.4
≥200	23	41.5
Duodenal biopsy (Marsh staging)		
3A	10	18.5
3B	33	61.1
3C	11	20.3

BMI: Body mass index, SD: Standard deviation

Table 2: Logistic regression analysis for correlation between biopsy staging and tTG levels versus mean serum hemoglobin and mean serum iron serum levels

Biopsy staging (Marsh)	Hemoglobin mean±SD	95% CI	Co-efficient	p value	Iron levels mean±SD	95% CI	Co-efficient	p value
3A	9.38±1.7	7.93, 10.82	#		46±28	31.34, 60.65	#	
3B	8.01±2.4	−3.00, 0.28	−1.36	0.10	36.6±23	−26.03, 7.42	−15	0.27
3C	7.24±2.2	−4.12, 0.14	−2.13	0.04*	31±17	−35.24, 0.52	−9.3	0.14
tTG levels								
10-100	8.5±2.9	6.7, 10.3	#		42.7±27	25.11, 60.32	#	
>100-200	8.23±2.1	−2.3, 1.7	−0.27	0.8	40.1±25.8	−30.2, 9.9	−2.54	0.32
>200	7.86±2.4	−2.7, 1.4	−0.63	0.54	32.5±18.8	−22.55, 17.5	−10.15	0.8

#3A and serum tTG levels 10-100 were taken as constant, *Correlation of hemoglobin levels in 3A v/s 3C is significant. CI: Confidence interval, SD: Standard deviation

Table 3: Distribution of percentage of children in each category of anemia according to marsh staging and serum tTG titers

Category of anemia	Biopsy stage (MARSH)			Serum tTG titers (U/ml)		
	3A	3B	3C	10-100	>100-200	>200
No anemia	20	9.09	0	28.57	4.17	8.7
Mild anemia	10	15.15	9.09	0	16.67	13.04
Moderate anemia	40	27.27	27.27	14.29	33.33	30.43
Severe anemia	30	48.48	63.64	57.14	45.83	47.83

ratio of 3A vs. 3B=2.25, p=0.366 and 3A vs. 3C=5, p=0.102). The percentage of children with severe anemia increased with increase in Marsh stage. However, correlation of severity of anemia with Marsh staging or with serum tTG levels was not significant (p=0.641 and p=0.484, respectively) (Table 3). There was no significant correlation between serum tTG levels with Marsh staging (p=0.19).

DISCUSSION

In this study of 54 children with CD, the mean age of children was 8±3.6 years with female predominance and onset of symptoms after 2 years in 80% children. The common symptoms were chronic diarrhea (70.3%), pain abdomen (62.9%), and abdomen distention (53.7%). Stunting (46.3%), wasting (38.4%), anemia (85.1%), rickets (22%), and raised liver enzymes (45%) were commonly observed. Other associated disorders found were hypothyroidism (n=2), diabetes mellitus type 1 (n=1), and autoimmune hepatitis (n=1).

The mean age of enrolled children in the previous studies ranged from 6 to 8 years and was similar to our study (8 years) [9-11]. The age of onset of symptoms in our study 4.7±2.56 years was only slightly higher as compared to Poddar et al. (3.2±1.9 years) and Rawal et al. (3.4±2.6 years) [10,11]. The duration of symptoms before diagnosis was much lower in our study group (2.68±2.26 years) than Patwari et al. (5.2±3 years), indicating early diagnosis, which could be because of better diagnostic techniques and higher suspicion of disease in recent years [9]. Chronic diarrhea still remains the most common presentation of CD (70.5% in our study vs. 54-94% in past reports). As compared to previous Indian studies higher percentage of children in our study had abdomen pain, vomiting, and constipation [8-11]. This may be due to tendency of clinicians to evaluate only cases of diarrhea for CD in past.

We found only 2 patients (2/54) with atypical CD, similar to Mohindra et al. [12]. Few western studies have shown higher number of atypical CD [6,17-20] compared to Indian studies which might be because of under diagnosis of cases with non-gastrointesinal symptoms in our country. Incidence of pallor and short stature was similar to past studies. However, we found higher number of rickets patients 12/54 (22%) in our study. Increased incidence of rickets in CD may be associated with decreased duodenal absorption of calcium (absorbed mainly from duodenum) and fat malabsorption which affects serum vitamin D levels [21]. The increase in incidence of rickets in our study may be attributed to growing subclinical vitamin D deficiency in general population.

Among laboratory parameters mean hemoglobin in our study (8.1 mg/dl) was comparable to previous studies (range 7.7-8.8 mg/dl) [9,11]. Similar to our study high incidence of anemia (90.7%) was also documented by Rawal et al. (100%), Poddar et al. (84%), and Thappa et al. (100%) [8,10,11]. Mean serum iron levels in our study were 37.25 µg/dl, similar to those reported by Sherwani et al. and Qari of 29.2 µg/dl and 38.2 µg/dl, respectively [22,23]. Pathophysiology of anemia in CD is multifactorial including impaired duodenal iron absorption, occult gastrointestinal blood loss, intravascular hemolysis due to other autoimmune disorder and co-existent chronic inflammatory disease, anemia of chronic disease, low erythropoietin for degree of anemia, etc., in CD patients. Iron deficiency anemia in CD patients is refractory to iron therapy alone and responds after gluten free diet [24-26]. Inverse correlation of serum iron and serum hemoglobin with duodenal biopsy Marsh stage and serum tTG levels have been previously reported by Kalhan et al. [27]. He found significant linear association in both percentage of patients with iron deficiency anemia and mean baseline hemoglobin levels from Marsh staging of duodenal biopsy Stage 1 and 2 to 3C and 4 (p<0.001) [27]. In our study, we enrolled children with biopsy Stage 3 only. This may be the possible cause of absence of any significant correlation with increasing severity of duodenal biopsy stages. However, the correlation of 3A vs. 3C biopsy stage and hemoglobin levels was significant in our study. Liver

enzymes were slightly raised in our CD children, which was also found, by Rawal et al. and Poddar et al. [10,11]. Marsh stage 3B was found to be the most common (60.4%) finding on duodenal biopsy of these patients as found by Rawal et al. (64.2%) [11].

The main limitation of our study was fewer numbers of children and absence of control group. Furthermore, we could not evaluate dietary patterns and age of introduction of gluten these children. Serum vitamin D levels, other causes of anemia like serum B12 and folic acid deficiency were not done in our study due to financial constraints. With growing evidence of accelerated atherosclerosis in children with CD related to hyperhomocysteinemia, vitamin B12 deficiency, vitamin D deficiency, deranged lipid profile further studies are suggested in future.

CONCLUSION

We conclude that the gastrointestinal manifestations, anemia, rickets and short stature still remain common presentations of CD in children. Atypical presentation is still uncommon in Indian children. Although not significant, serum hemoglobin levels and serum iron levels are inversely correlated to the serum tTG levels and Marsh biopsy staging (3).

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