ORIGINAL ARTICLE

Prevalence and Predictors of Celiac Disease in Children With Constipation

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ABSTRACT

Objectives: To determine the prevalence of celiac disease and its predictors in children with constipation.

Methods: A hospital-based cross-sectional comparative study was conducted between November, 2018 to April, 2020. Children aged 1-12 years were screened for the presence of constipation as per ROME IV criteria and designated as cases. Age and sex matched healthy children with normal bowel habits were enrolled as comparison group. Participants underwent a detailed history and examination, and were screened for celiac disease by estimating serum anti-tissue transglutaminase IgA antibody levels (tTG-IgA). Upper gastrointestinal endoscopy and duodenal biopsy were performed in all participants who tested positive on screening (serum tTG-IgA ≥ 20 U/mL). The prevalence of celiac disease and associated factors were compared between the two groups.

Results: A total of 460 children (230 in each group) with mean (SD) age 64.08 (37.12) months were enrolled. Twenty-one (4.6%) children screened positive for anti tTG antibodies, among these 15 (75%) children had biopsy features suggestive of celiac disease (Marsh grade III). Children with constipation had significantly higher prevalence of celiac disease (5.65% vs 0.87%, $P = 0.004$) compared to children without constipation. Wasting and stunting were significantly associated with celiac disease in constipated children ($P < 0.001$).

Conclusion: Children with constipation and associated growth failure have a high prevalence of celiac disease.

Keywords: *Gluten enteropathy, Malabsorption, Risk factors, Tissue transglutaminase*

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INTRODUCTION

Constipation is a significant problem during childhood, and its reported prevalence varies between 1-30% worldwide [1]. Pediatric outpatient departments are frequented by children presenting with complaints of abdominal pain and constipation often categorized as a functional gastrointestinal disorder. Previously, constipation has been documented as one of the presenting features in children diagnosed with celiac disease, which is amenable to treatment [2]

Celiac disease (CD) is a chronic immune-mediated entero-pathy caused by ingestion of gluten-containing food, in genetically susceptible individuals resulting in immune-mediated mucosal damage in small intestine. Prevalence of celiac disease varies globally, with a pooled sero-prevalence of 1.4% in general population [3]. In India, the prevalence of celiac disease according to one community-based study is 1.04% [4], which is concordance with seroprevalence of the world population. Presenting symptoms of celiac disease vary according to the age; typical gastrointestinal symptoms and failure to thrive are common in children less than two years of age. While, in older children and adults, atypical, non-specific extra-intestinal symptoms with few or no gastrointestinal symptoms are more common, such as abdominal pain, microcytic hypochromic anemia, osteoporosis, overweight, short stature, fatigue, depression and occasionally there is constipation, bloating, rectal prolapse or intussusception [5]. The timely evaluation of atypical symptoms can help in planning more focused strategies for early identification and timely management of underlying disease and thereby, reducing celiac disease-related morbidity, especially in developing countries [6].

Majority of the studies from India are related to typical manifestations of celiac disease in children. There is a concerning delay in diagnosis due to low awareness about the varied clinical presentation of celiac disease [7]. Recently, studies have reported a rise in the non-diarrheal presentation of celiac disease, and constipation as a presenting complaint has been documented in 1-31% of

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children diagnosed with celiac disease [8-11]. There is a paucity of data on the prevalence of the celiac disease in constipated children in developing countries, including India.

To address this knowledge-gap the current study was undertaken to estimate the prevalence of celiac disease and its predictors in children with constipation.

METHODS

This was a cross-sectional comparative study conducted in the department of pediatrics in a public sector tertiary hospital in Delhi, India, primarily catering to children belonging to urban low-income families of East Delhi and adjoining parts of Uttar Pradesh. An approval from the Institutional Ethics Committee–Human Research was obtained before the commencement of the study. Between November, 2018 and April, 2020, all children aged 1-12 years presenting to the outpatient department or emergency room with complaint of constipation were screened as per ROME IV criteria and enrolled [12]. Exclusion criteria comprised known case of celiac disease, those with a family history of celiac disease, hypothyroidism, those taking drugs causing constipation (antihypertensive drugs, antidepressants, oral iron supplementation, opiates and cannabinoids etc.), enteric myopathies or neuropathies, organic colorectal diseases, spinal cord injury and other central nervous system diseases, any surgical cause of constipation, chromosomal disorders, and chronic systemic illnesses. Age and sex matched healthy children (i.e children visiting outpatient department either with minor illnesses like upper respiratory tract infection, or for vaccination) with regular bowel habits were enrolled as comparison group.

Eligible children were enrolled after obtaining a written informed consent from the parent(s) or the caregiver for participation in the study. A comprehensive bowel history (passage of stools, straining, frequency, consistency, fecal incontinence, large fecal mass, feeling of obstruction etc.), along with relevant demographic and clinical history (including dietary, immunization, family and socio-economic history) was documented in a predesigned performa. Clinical exami-nation findings and baseline anthropometric parameters (weight, length, mid-upper arm circumference and head circumference) were recorded as per standard techniques.

All enrolled participants underwent baseline complete blood count and thyroid function tests. Celiac disease screening was performed by estimating serum anti-tissue transglutaminase IgA (tTG-IgA) antibody levels. Commercially available enzyme-linked immunosorbent assay kits (Xema-medica Co. Ltd., Moscow, Russia) were used for estimation; tTG-IgA levels >20 units/mL were interpreted as positive result of screening for celiac disease. Participants who screened positive, underwent upper gastrointestinal endoscopy (UGIE) followed by a duodenal biopsy [13]. Endoscopic findings such as absence of mucosal folds, scalloped mucosal folds, mosaic pattern of the mucosa between the folds in duodenum were suggestive of celiac disease. Biopsy specimens obtained from the bulb and the second or third part of duodenum were examined by histopathologist blinded to clinical history and graded using the modified Marsh grading [14]. Celiac disease was confirmed on the basis of Marsh grade III histopathological changes.

Children diagnosed with constipation were managed according to the standard guidelines including dietary modifications in the form of increased intake of dietary fiber and plenty of liquids, and medical management using laxatives or stool softeners [15]. Children with biopsy findings of celiac disease were counselled and started on gluten-free diet along with micronutrients supplements and kept in regular follow up. Those found to be anemic during examination were evaluated for type of anemia and started on iron / vitamin B12-folic acid supplementation.

To calculate the sample size, prevalence rate of prior study done by Sadjadei et al [16] was considered. With an estimated celiac disease prevalence of 6% in constipated children and 1% in healthy controls, a sample size of 210 children in each group was determined to be adequate to detect a similar prevalence rate in Indian children with 80% power and 5% levels of significance. To account for 10% potential loss, 230 children were enrolled in each group.

Statistical analysis: Data was analyzed with IBM SPSS Statistics Ver.25. Continuous data were summarized as mean (SD) while categorical data was expressed as in number and percentage. Differences between groups were calculated using an independent samples *t*-test for the normally distributed data and the Mann–Whitney *U*-test for data not normally distributed. Chi-square test was used for the comparisons of qualitative data. A multivariable logistic regression was performed for determining the predictors of celiac disease identified through univariate analysis ($P < 0.3$). $P < 0.05$ was regarded as statistically significant.

RESULTS

A total 460 (230 with constipation, 230 without constipation) children were included in the study; 229 and 230, respectively completed the study **(Fig. 1.)**. The mean (SD) age of the children was 64.08 (37.12) months, more than half of the participants were aged under five.

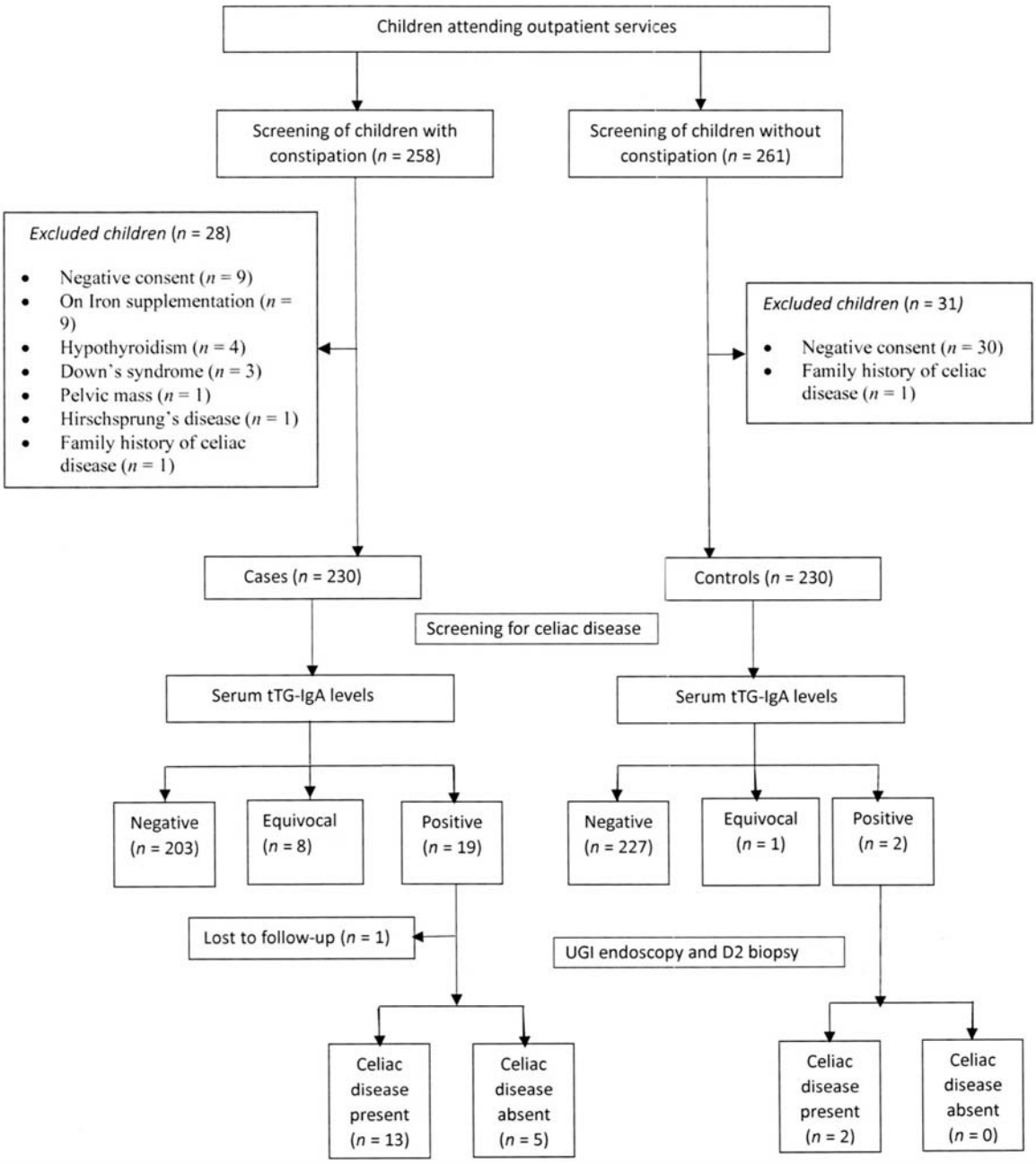

Fig.1 Flow of participants in the study

The children with constipation had a significantly lower weight for age, weight for height, body mass index and BMI z-score values in comparison to children without constipation. **Table I** depicts the comparison of the baseline parameters between two groups. On comparing the constipated children without celiac disease (n = 217) and children without constipation (n = 230), there was no significant difference in mean (SD) weight [16.76 (7.11) vs 17.86 (8.43) kg, P = 0.138] and height [104.85 (19.76) vs 104.93 (20.15) cm, P = 0.964], respectively.

Two hundred seventy (58.7%) children had anemia with mean (SD) hemoglobin level of 10.7 (1.6) g/dL; 7 (1.5%), 191 (41.5%) and 72 (15.7%) children had severe, moderate and mild anemia, respectively as determined using WHO defined cut-offs of hemoglobin for age. Peripheral smear examination for type of anemia showed predominantly normocytic normochromic picture in 381 (82.83%) children, while 77 (16.74%) children showed microcytic hypochromic RBCs, and 2 (0.43%) had a macrocytic blood picture. On comparing the two groups

Table I Comparison of the Baseline Characteristics of Children with Constipation (*n* = 230) and Children Without Constipation (*n* = 230).

Characteristics	*Children with Constipation (n = 230)*	*Children without Constipation (n = 230)*	*P value*
Male[a]	135 (59)	129 (56)	0.57
Age (mo)	63.74 (36.6)	64.43 (37.8)	0.84
Pallor[a]	60 (26.1)	5 (2.1)	< 0.001
Weight (kg)	16.61 (7.1)	17.95 (8.5)	0.07
Height (cm)	104.5 (19.7)	105.1 (20.2)	0.76
WAZ	-1.30 (1.04)	-0.95 (0.87)	< 0.001
HAZ	-1.09 (1.06)	-1.06 (0.55)	0.64
WHZ	-0.96 (1.17)	-0.46 (1.16)	0.001
Body mass index (kg/m^2)	14.65 (1.79)	15.36 (1.90)	< 0.001
BMIZ	-0.97 (1.20)	-0.47 (1.14)	< 0.001
Stunting[a]	25 (10.9)	7 (3)	< 0.001
Severe Stunting[a]	9 (4)	1 (0.4)	< 0.001
Wasting[a]	23 (10)	5 (2.2)	0.001
Severe wasting[a]	5 (2.2)	1 (0.4)	0.001

Values expressed as mean (SD), [a]n (%). BMIZ Body mass index z-score, HAZ Height for age z-score, WAZ Weight for age z-score, WHZ Weight for height z-score, mo Months

according to the severity of anemia there was no significant difference (*P* = 0.76). Results of thyroid function tests revealed a mean (SD) level of thyroid stimulating hormone were 3.34 (1.3) mIU/mL, while hypothyroidism was diagnosed in 1 (0.2%) child.

The mean (SD) value of serum tTG-IgA (U/mL) in the study participants was 8.33 (52.4); ranging from 0.1 - 838.8 U/mL. Twenty-one (4.6%) children screened positive for celiac disease and 9 (1.96%) children had equivocal results. There was a statistically significant difference in the mean (SD) serum tTG-IgA levels between children with constipation and those without constipation 13.2 (68.78) vs 3.5 (26.87), *P*=0.04), though the serum tTG-IgA levels were within the normal range. Out of 21 children who screened positive for tTG-IgA antibodies, 20 children underwent upper gastrointestinal endoscopy and biopsy. Among those undergoing UGIE and duodenal biopsy, 15 children (13 with constipation, 2 without constipation) had biopsy features suggestive of celiac disease (Marsh grade IIIa/ IIIb/ IIIc). There was a significant difference between the two groups, when the biopsy finding of celiac disease was compared the two groups (13 vs 2, *P* = 0.004). In our study, the proportion of celiac disease in constipated children was 5.65%; however, proportion of celiac disease in non-constipated group was 0.87%. In univariate analysis, presence of stunting in children with constipation was significantly associated with celiac disease (**Table II**). A significant association was found between presence of severe wasting, severe stunting and celiac disease among children with constipation (*P* < 0.001) (**Table III**).

DISCUSSION

The findings of present study suggest that there is a significantly high prevalence of celiac disease in children with constipation and growth failure than in children with normal bowel habits and it is more than the estimated prevalence in the population.

Celiac disease is a chronic immune-mediated enteropathy caused by ingestion of gluten-containing food, in genetically susceptible individuals. Mucosal inflammation and villous atrophy results in malabsorption presenting as diarrhea, abdominal distension and failure to thrive in majority of children. Disturbances in the gastrointestinal motility in untreated celiac disease patients

Table II Predictors of Celiac Disease in Children With Constipation (*n* = 230)

Parameters	*Children without celiac disease (n=217)*	*Children with celiac disease (n=13)*	*P value*	*OR (95% CI)*
Male gender	126 (58)	9 (69)	0.57	1.62 (0.48, 5.55)
Breastfeeding	214 (98.6)	13 (100)	0.55	1.00
Exclusive Breastfeeding	187 (86)	12 (92.3)	0.50	1.92 (0.24, 15.5)
Timely initiation complementary feeds at 6 months	176 (81)	9 (69)	0.29	0.52 (0.15, 1.78)
Anemia	130 (60)	8 (61.5)	0.91	1.07 (0.34, 3.38)
Wasting[a]	24 (20)	4 (50)	0.06	4.08 (0.95, 17.51)
Stunting	29 (13.3)	5 (38.5)	0.03	4.05 (1.24, 13.24)
Underweight	23 (23)	2 (40)	0.59	2.20 (0.35, 13.99)

All values in no (%), [a] Children <5 years (n=130)

WHAT THIS STUDY ADDS?

- The prevalence of celiac disease in children with chronic constipation and growth failure is higher than the general population.

Table III Predictors of Celiac Disease in Children With Constipation (*n* = 230)

Parameter	*Children with celiac disease (n =13)*	*Children without celiac disease (n =217)*	*P value*
Anemia	8/13 (61.5)	130/217 (60)	0.30
Moderate wasting[a]	2/8 (25)	21/122 (17.2)	< 0.001
Severe wasting[a]	2/8 (25)	3/122 (0.24)	
Moderate stunting	3/13 (23)	22/217 (10)	< 0.001
Severe stunting	2/13 (15.4)	7/217 (3.2)	

Values expressed as n (%), [a]n = 130 children aged <5 years

compared to controls have been reported. It has been hypothesized that immune mediated mucosal damage and inflammation may affect contractile gut motility through perturbations of the complex interactions among decreased food absorption, hormonal and neuro-immunomodulatory regulation of the intestinal mucosa. It is plausible that disturbed gastrointestinal motility may give rise to constipation in untreated celiac disease patients [17].

Previous studies examining the prevalence of celiac disease in constipated children have yielded diverse and inconsistent results. Studies from different regions have reported tTG-IgA seropositivity ranging from 1% - 50% [18–22]. Studies from Turkey, Iran, Colombia, USA and India have found no significant difference in the prevalence of seropositivity for celiac disease in constipated children as compared to general population [18,20–22]. In one of the largest series from India involving 316 children with constipation celiac disease was not reported as the cause of constipation [23]. In contrast studies by Sadjadei et al [16] (7.2%), Akman et al [19] (3.6%), Pelleboer et al [24] (1.8%) and Navarra et al [25] (51.2%) reported a significantly higher prevalence of celiac disease among constipated children than the general population, and these findings are consistent with the results of the present study.

Variability in participants' ethnicity, age group, inclusion and exclusion criteria, definition of constipation, sample size, cut-off values of tTG-IgA level, and histopathological staging discrepancies may have contributed to these differences. Some studies have included all consecutive children with constipation [22], while others have focussed on children referred to hospitals due to failed laxative therapies [16,23,24], creating discrepancies in participants' profile.

Only a few studies have assessed the anthropometric parameters while evaluating for presence of celiac disease in children with constipation. Similar to our study, Cakir et al [18] documented a significantly high prevalence of underweight and obesity in children with constipation comparison to healthy children (12.1% vs. 7.5%, $P < 0.05$, and 10.2% vs. 2.4%, $P < 0.05$, respectively) and Navarra et al [25] found high incidence of stunting in constipated children.

The main strengths of our study were that it tried to explore the prevalence of atypical symptoms (constipation) of CD among Indian children where childhood malnutrition is also common. Apart from this, presence of robust methodology with adequate sample size, minimal loss to follow up and confirmed diagnosis of CD by histopathology were some of the other strengths of our study. The main limitation was that it was a hospital-based study and hence the result obtained in this study might not be representative of the population in the community. Moreover, we were not able to perform biopsy in one child with constipation who was lost to follow-up Genetic testing was not performed in children diagnosed with CD. Also, we did not follow-up the CD patients after diagnosis to document the response to gluten-free diet and thus, are unable to comment on the effect of gluten-free diet on the requirement of laxatives and the cause-and-effect relationship between constipation and CD.

We conclude that there is a high prevalence of celiac disease in children with constipation, emphasizing the importance of considering atypical symptoms in the diagnosis of CD. Thus, routine serological screening among constipated children with growth failure as evident by the presence of stunting and wasting may help in the early diagnosis and treatment of CD, improving the quality of life, and reducing the long-term mortality and morbidity.

Ethics approval: Institutional Ethics Committee-Human Research (IEC-HR) of University College of Medical Sciences, Delhi, No. IEC-HR/2018/36/112, dated Oct 15, 2018.

Contributors: MN: Conceptualization, supervision of data collection, statistical analysis and interpretation, critical inputs to

manuscript writing; MM: Data collection and writing the initial draft of manuscript; RKM: Statistical analysis and interpretation, writing the initial draft of manuscript and editing the final manuscript; AA: Supervised data collection and its interpretation, critical inputs to manuscript writing. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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