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Original Article

Extra-Intestinal Manifestations of Celiac Disease in Pediatric Population of a Tertiary Care Hospital in Rawalpindi, Pakistan - an Observational Study

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ABSTRACT

Objective: To determine the frequency and types of extra-intestinal manifestations (EIMs) in children with celiac disease.
Study Design: Observational study.
Place and Duration of Study: Department of Pediatric Gastroenterology, Combined Military Hospital, Rawalpindi, Pakistan from Jan to Jun 2025.
Methodology: The study included 233 children aged 1–15 years diagnosed with celiac disease based on ESPGHAN guidelines. Children with celiac crisis or other autoimmune/chronic illnesses were excluded. Data were collected through clinical examination and laboratory investigations. EIMs were identified using standard definitions. Statistical associations were analyzed using chi-square or Fisher's exact test (p<0.05 significant).
Results: The median (IQR) of age was 7(4-11) years; 60.1% were male. Common EIMs included iron deficiency anemia (60.5%), short stature (48.9%), eczema (40.8%), and fatigue. Anemia was more frequent in females (69.9%, p=0.02), whereas males had higher rates of behavioral changes (40.0%, p<0.001), headaches (30.0%, p=0.04), and delayed puberty (7.1%, p=0.01). Dental enamel hypoplasia (39.1%, p<0.001), eczema (p<0.001), and fatigue (62.3% in Marsh 3a, p<0.001) varied with Marsh grade. Anemia was frequent in younger children (72.6%, p<0.001), while older children had more failure to thrive (44.9%, p<0.001) and liver dysfunction (20.3%, p<0.001). Recurrent stomatitis (55.6%), fatigue (100%), and psychiatric disorders (55.6%) significantly associated with normal endoscopic findings (all p<0.001).
Conclusion: Extra-Intestinal manifestations (EIMs) are common in pediatric celiac disease, varying significantly with age, sex, histological stage, and endoscopic appearance. Early recognition of EIMs can facilitate timely diagnosis and management.

Keywords: Celiac disease, Extra-intestinal manifestations, Pediatric.

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INTRODUCTION

Celiac disease (CD) is an autoimmune condition that develops in genetically predisposed individuals upon the intake of gluten, a key protein found in wheat, rye, and barley.[1] This immune response results in the production of specific autoantibodies and causes inflammation of the small intestine, presenting with a diverse range of gastrointestinal and extra-intestinal symptoms.[2] Celiac disease affects approximately 1% of children worldwide with higher rates observed in at-risk populations.[3] An estimated 42,000 deaths annually in children under five were attributed to undiagnosed celiac disease in a global model.[4] Celiac disease in children typically presents with chronic diarrhea, abdominal distension, failure to thrive and poor weight gain. Other symptoms include anorexia, irritability and vomiting. Diagnosis is confirmed through serology and intestinal biopsy.[5] Once viewed as a gut-limited disorder, celiac disease is now identified as a systemic condition with varied extra-intestinal symptoms.[6] Common extra-intestinal manifestations of celiac disease in children include iron-deficiency anemia, short stature, delayed puberty, dental enamel defects, recurrent stomatitis, dermatitis herpetiformis, liver issues, joint pain, headaches, neurological and psychiatric disorders, behavioral changes and hair loss.[7] Extra-intestinal manifestations (EIMs) of celiac disease affect 60% of children and 62% of adults with differences in type and resolution.[8] In children, EIMs arise from chronic inflammation and malabsorption of iron, calcium and vitamin D. Gluten-induced autoimmunity may involve the skin, liver, joints and nervous system with systemic immune dysregulation contributing to neuropsychiatric symptoms.[9] Children presenting with EIMs often exhibit more severe villous atrophy than those with GI symptoms or screen-detected cases.[10]

Early identification of CD helps to prevent long-term complications. However, in developing regions the frequent absence of specialized testing and limited clinical recognition often result in delayed

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identification of celiac disease, particularly in children who present without classic digestive complaints. A prospective study on EIMs in pediatric CD patients will offer valuable insights into their frequency, types and correlation with disease severity. This can enhance early diagnosis by pediatricians to help reduce disease complications.

The study aimed to determine the frequency and types of extra-intestinal manifestations in children with celiac disease.

METHODOLOGY

This observational study was conducted at the Pediatric Gastroenterology Department CMH Rawalpindi, Pakistan from January to June 2025 using non-probability convenient sampling. Informed consent was obtained from all parents, and ethical approval was granted by the IRB (serial no. 895, dated: 19/12/2024). Data were recorded on a predesigned proforma.

A sample size of 233 was calculated using OpenEpi, based on a frequency of 18.6% for eczema among children with celiac disease reported in a previous study,[9] with a 95% confidence interval and a 5% margin of error.

Inclusion Criteria: Children aged 1–15 years with confirmed celiac disease based on ESPGHAN guidelines were included. A positive celiac serology was considered as anti-tTG IgA levels above the laboratory-specific upper limit of normal (ULN). Although ESPGHAN permits a biopsy-sparing diagnosis in selected patients with markedly elevated serology (anti-tTG ≥10× ULN with EMA positivity), our study included children who had undergone duodenal biopsy. Biopsy findings of Marsh grade ≥2 were considered diagnostic.

Exclusion Criteria: Children were excluded from the study if they had any other autoimmune or chronic illnesses such as type 1 diabetes, autoimmune thyroiditis. Those presenting with celiac crisis were also excluded, as this could interfere with clinical assessment and raise ethical concerns regarding study participation.

Clinical evaluation included history, examination and tests (anti-tTG, iron profile, thyroid, vitamin D, liver enzymes). Iron deficiency anemia was defined by low iron, ferritin, and high TIBC. Short stature and failure to thrive were defined using the appropriate growth charts for age and sex as recommended by the Centers for Disease Control and Prevention (CDC) with short stature defined as height-for-age below the 3rd percentile, while failure to thrive defined as weight-for-age below the 5th percentile. Delayed puberty was absence of secondary traits by age 13 (girls) or 14 (boys). Dental enamel hypoplasia, eczema, and dermatitis herpetiformis were diagnosed clinically. Recurrent stomatitis meant ≥3 episodes/year. Headaches, fatigue, arthralgia, liver dysfunction and behavioral or psychiatric symptoms were noted via complaints, labs and/or caregiver report.

Data were analyzed using R version 4.3.2. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as median (IQR) if skewed according to the Shapiro–Wilk test or as Mean±SD otherwise. The associations of EIMs with gender, age, Marsh classification, and endoscopic findings were assessed using the Chi-square test. Fisher's exact test was used in cases where more than 20% of the cells in a contingency table had an expected count less than 5 with $p<0.05$ as significant.

RESULTS

The total participants were 233. The median age at diagnosis was 7(4, 11) years, with males (n=140, 60.1%) being more common. Mean anti-tTG was 123.75± 43.76 U/mL. Marsh 3b (n=64, 27.5%) and 3a (n=61, 26.18%) were the most frequent biopsy findings (Table-I). Fissuring (n=151, 64.81%) and nodularity (n=73, 31.33%) were common endoscopic features (Figure-1). Iron deficiency anemia (n=141, 60.52%) was the most common extra-intestinal manifestation, followed by short stature (n=114, 48.93%), eczema (n=95, 40.77%), fatigue (n=94, 40.34%) and failure to thrive (n=84, 36.05%). Less frequent were behavioral changes (n=68, 29.18%), headaches (n=59, 25.32%), enamel hypoplasia (n=52, 22.32%), and stomatitis (n=37, 15.88%).

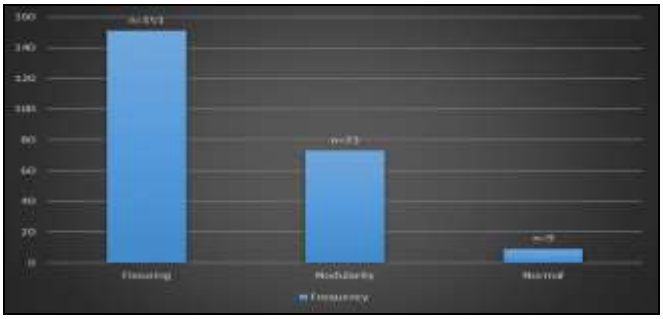

Figure-1: Pattern of Endoscopic Findings Among Celiac Affected Children (n=233)

Iron deficiency anemia was more frequent in females (69.89%) than males (54.29%) (p=0.02). Delayed puberty occurred only in males (7.14%) (p=0.01). Headaches (30.00% vs. 18.28%, p=0.04) and behavioral changes (40.00% vs. 12.90%, p<0.001) were more common in males, while arthralgia/arthritis was higher in females (9.68% vs. 2.86%, p=0.03). Delayed puberty was seen only in Marsh 2(10.42%) and 3a (8.20%) (p<0.001). Enamel hypoplasia peaked in Marsh 3b (39.06%) (p<0.001). Eczema was absent in Marsh 2 but frequent in 3a–3c (p<0.001). Fatigue varied significantly, highest in Marsh 3a (62.30%) and lowest in 3b (23.44%) (p<0.001). Behavioral changes were most common in Marsh 2(43.75%) and 3c(38.33%), least in 3b (7.81%) (p<0.001). Psychiatric disorders were more frequent in Marsh 3c (23.33%) (p=0.01). Dermatitis herpetiformis occurred only in Marsh 3a (8.20%) (p<0.001) and arthralgia/arthritis was limited to Marsh 2(16.67%) and 3b(7.81%) (p<0.001) (Table-II).

Table-I: Demographic, Serological and Histopathological Characteristics of Pediatric Celiac Disease Patients (n=233)

Variable(s)	n= 233
Age (years), median(IQR)	7(4, 11)
Gender, n(%)	
Female	93 (39.91)
Male	140 (60.09)
Anti-tTG Antibody Level (U/mL), Mean ± SD	123.75 ± 43.76
Duodenal Biopsy (Marsh Classification), n (%)	
Marsh 2	48 (20.60)
Marsh 3a	61 (26.18)
Marsh 3b	64 (27.47)
Marsh 3c	60 (25.75)

Iron deficiency anemia was more common in children aged 1–5 years (72.63%) vs. 6–15 years (52.17%) (p<0.001), while failure to thrive (44.93% vs. 23.16%, p<0.001), delayed puberty (7.25%, p=0.01), headaches (30.43%, p=0.03), liver dysfunction (20.29% vs. 4.21%, p<0.001) and behavioral changes (34.06%, p=0.05) were more frequent in older children. Arthralgia/arthritis was more common in younger children (9.47%, p=0.03). Other findings showed no significant age-related differences (Table-III).

Iron deficiency anemia was highest in the nodularity group (75.34%) (p=0.01), while failure to thrive was more common with fissuring (41.06%) and normal findings (44.44%) (p=0.05). Recurrent stomatitis (55.56%) and fatigue (100%) were most frequent in the normal group (p<0.001). Liver dysfunction was more common in normal (44.44%) and nodularity (17.81%) groups (p=0.01). Dermatitis herpetiformis appeared only in the nodularity group (6.85%) (p=0.01). Arthralgia (100%) and psychiatric disorders (55.56%) were exclusive to the normal group (p<0.001). No significant differences were found for short stature, delayed puberty, enamel hypoplasia, eczema, headaches or behavioral changes (Table-IV).

Table-II: Extra-intestinal manifestations among Celiac Children by Duodenal Biopsy/Marsh Classification (n=233)

Characteristic(s)	Marsh 2, n= 48,n(%)	Marsh 3a, n=61,n(%)	Marsh 3b, n=64,n(%)	Marsh 3c, n= 60,n(%)	*p*-value
Iron Deficiency Anemia	23(47.92)	37(60.66)	44(68.75)	37(61.67)	0.17
Short Stature	29(60.42)	23(37.70)	34(53.13)	28(46.67)	0.10
Failure to Thrive	17(35.42)	24(39.34)	25(39.06)	18(30.00)	0.68
Delayed Puberty	5 (10.42)	5 (8.20)	0 (0.00)	0 (0.00)	<0.001
Dental Enamel Hypoplasia	10(20.83)	9 (14.75)	25(39.06)	8(13.33)	<0.001
Eczema	0 (0.00)	33(54.10)	34(53.13)	28(46.67)	<0.001
Recurrent Stomatitis	8 (16.67)	5 (8.20)	15(23.44)	9 (15.00)	0.14
Headaches	13(27.08)	14(22.95)	14(21.88)	18(30.00)	0.72
Fatigue	17(35.42)	38(62.30)	15(23.44)	24(40.00)	<0.001
Liver Dysfunction	4 (8.33)	10(16.39)	10(15.63)	8 (13.33)	0.63
Dermatitis Herpetiformis	0 (0.00)	5 (8.20)	0 (0.00)	0 (0.00)	<0.001
Arthralgia or Arthritis	8 (16.67)	0 (0.00)	5 (7.81)	0 (0.00)	<0.001
Behavioral Changes	21(43.75)	19(31.15)	5 (7.81)	23(38.33)	<0.001
Psychiatric Disorders	0 (0.00)	10(16.39)	10(15.63)	14(23.33)	0.01

Pearson's Chi-squared test; Fisher's exact test

Table-III: Extra-Intestinal Manifestation Among Children with Celiac Disease by Age Groups (n=233)

Characteristic	6-15 years, n=138 n(%)	1-5 years, n= 9 n(%)	*p*-value
Iron Deficiency Anemia	72(52.17)	69(72.63)	<0.001
Short Stature	68(49.28)	46(48.42)	0.90
Failure to Thrive	62(44.93)	22(23.16)	<0.001
Delayed Puberty	10(7.25)	0(0.00)	0.01
Dental Enamel Hypoplasia	30(21.74)	22(23.16)	0.80
Eczema	50(36.23)	45(47.37)	0.09
Recurrent Stomatitis	18(13.04)	19(20.00)	0.15
Headaches	42(30.43)	17(17.89)	0.03
Fatigue	57(41.30)	37(38.95)	0.72
Liver Dysfunction	28(20.29)	4(4.21)	<0.001
Dermatitis Herpetiformis	5(3.62)	0(0.00)	0.08
Arthralgia or Arthritis	4(2.90)	9(9.47)	0.03
Behavioral Changes	47(34.06)	21(22.11)	0.05
Psychiatric Disorders	20(14.49)	14(14.74)	0.96

Pearson's Chi-squared test; Fisher's exact test

DISCUSSION

Our study found that extra-intestinal manifestations followed distinct clinical patterns

across different patient subgroups. The predominance of iron deficiency anemia, short stature and fatigue in CD is a direct consequence of chronic malabsorption caused by villous atrophy, which primarily affects the duodenum which is the key site for the absorption of iron, calcium and other essential micronutrients.[11] Fatigue and behavioral alterations may reflect underlying systemic inflammation or disruptions in the gut-brain axis, both of which have been postulated in existing literature as contributing mechanisms for extra-intestinal manifestations.[12] Behavioral disturbances were more frequently observed in males, whereas arthralgia and iron deficiency anemias were more prevalent in females, suggesting potential sex-related pathophysiological differences.

Table-IV: Extra-intestinal Manifestation Among celiac Children by Endoscopic Findings (n=233)

Characteristic	Fissuring (n= 151)	Nodularity (n= 73)	Normal (n= 9)	*p*-value
Iron Deficiency Anemia	81 (53.64)	55 (75.34)	5 (55.56)	0.01
Short Stature	75 (49.67)	35 (47.95)	4 (44.44)	0.97
Failure to Thrive	62 (41.06)	18 (24.66)	4 (44.44)	0.05
Delayed Puberty	10 (6.62)	0 (0.00)	0 (0.00)	0.06
Dental Enamel Hypoplasia	38 (25.17)	14 (19.18)	0 (0.00)	0.17
Eczema	63 (41.72)	27 (36.99)	5 (55.56)	0.51
Recurrent Stomatitis	14 (9.27)	18 (24.66)	5 (55.56)	<0.001
Headaches	38 (25.17)	16 (21.92)	5 (55.56)	0.51
Fatigue	61 (40.40)	24 (32.88)	9 (100.00)	<0.001
Liver Dysfunction	15 (9.93)	13 (17.81)	4 (44.44)	0.01
Dermatitis Herpetiformis	0 (0.00)	5 (6.85)	0 (0.00)	0.01
Arthralgia or Arthritis	4 (2.65)	0 (0.00)	9 (100.00)	<0.001
Behavioral Changes	46 (30.46)	22 (30.14)	0 (0.00)	0.14
Psychiatric Disorders	29(19.21)	0(0.00)	5(55.56)	<0.001

Pearson's Chi-squared test; Fisher's exact test

Our findings aligned with Salarian *et al.*,[10] on common EIMs like failure to thrive, IDA and short stature though we observed higher IDA rates (60.5%). Unlike their study we found significant associations between EIMs, Marsh types and sex e.g., behavioral issues with Marsh 2/3c, eczema with 3a, and enamel defects with 3b possibly due to sample size or regional differences.

In contrast to the results of Bharo *et al.*,[13] in Sindh, where chronic diarrhea and short stature were most common, our cohort showed a broader range of extra-intestinal manifestations including neuropsychiatric and mucocutaneous symptoms.

In this study younger children had more IDA while older ones showed growth issues, liver dysfunction and headaches. Delayed puberty appeared only in boys with Marsh 2/3a. Enamel defects and stomatitis were linked to Marsh severity supporting oral screening in CD evaluation.The lack of visible changes on the mucosa can indicate the early stages of celiac disease. The study by Repo *et al.*[11] revealed a high prevalence of anemia and iron deficiency anemia (IDA) even when the mucosa appeared macroscopically normal. Other also found similar high anemia in among celiac children.[14] A study by Elbek-Cubukcu *et al.*,[15] involving 62 pediatric patients with celiac disease reported significant associations between Marsh stage 2 lesions, molar-incisor hypo mineralization and recurrent aphthous ulcers. A pediatric study reported no major gender differences in overall EIMs,[16] our results show only minor variations with headaches and behavioral changes slightly more common in males and iron deficiency anemia was more frequent in females. This distinction highlights small gender-related trends without suggesting major differences in EIMs prevalence.

A systematic review showed a strong link between celiac disease and dental enamel defects and aphthous stomatitis in children with higher prevalence in Marsh 2/3a lesions, reaching up to 60% in some cases.[17] Extra-intestinal manifestations are frequently observed in pediatric celiac disease, with variation according to age, sex, and histopathological severity. Behavioral and psychiatric manifestations show associations with specific Marsh classifications. Early recognition of these features facilitates timely diagnosis and may reduce disease-related complications.[18]

LIMITATIONS OF STUDY

This single-center, cross-sectional study may limit national generalizability, though patients were from diverse regions. It identifies associations rather than causation. Some symptom data were based on parental recall, confirmed where possible through clinical records. A multicenter prospective study on EIMs in pediatric CD patients will offer valuable insights into their frequency, types, and correlation with disease severity.

CONCLUSION

Extra-intestinal symptoms like anemia, short stature, fatigue, and eczema are common in pediatric celiac disease varying by age, sex, and biopsy findings. Behavioral and psychiatric issues were linked to specific Marsh types. Early recognition aids timely diagnosis and reduces disease complications.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

A & HU: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SH & IS: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

HK: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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