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Spectrum of Autoimmune Diseases in Children with Celiac Disease: A Single Center Cross-Sectional Study from A Tertiary Childcare Facility of South Punjab, Pakistan

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ABSTRACT

Celiac disease (CD), an autoimmune disorder triggered by gluten ingestion, is increasingly recognized for its association with a higher prevalence of other autoimmune conditions in children, underscoring the need for more exploration. **Objectives:** To evaluate the spectrum of autoimmune diseases (AIDs) in children with CD. **Methods:** This cross-sectional study was performed at the Department of Gastroenterology, Hepatology and Nutrition, The Children's Hospital and The Institute of Child Health, Multan, Pakistan, from September 2023 to December 2024. Children aged between 1-12 years and having CD were analyzed. The presence of AIDs was explored utilizing physical and clinical examination, along with relevant laboratory and radiographic studies. **Results:** In a total of 167 children with CD, 95 (56.9%) were male. The mean age was 6.01 ± 3.31 years. The most frequent presenting complaints were abdominal pain, diarrhea, and weight loss, noted in 70 (41.9%), 65 (38.9%), and 53 (31.7%) children, respectively. AIDs were diagnosed in 38 (22.8%) children, while the most common AIDs were autoimmune thyroiditis, type-1 diabetes mellitus (T1DM), asthma, and autoimmune hepatitis, found in 11 (6.6%), 7 (4.2%), 4 (2.4%), and 4 (2.4%) children, respectively. Low monthly family income (p=0.013), or severe CD type (p=0.010), were found to have a significant association with AIDs. **Conclusions:** Children with CD have a high prevalence of associated AIDs, with autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis being the most commonly observed conditions. The severity of CD appears to be a contributing factor to the development of AIDs.

INTRODUCTION

Celiac disease (CD) is a common autoimmune disorder triggered by the ingestion of gluten proteins found in wheat, barley, and rye [1]. CD is marked by the presence of anti-transglutaminase autoantibodies and damage to the intestinal villi. In children with other autoimmune diseases (AIDs), such as type 1 diabetes mellitus (T1DM), or thyroiditis, screening frequently uncovers previously undiagnosed CD, affecting approximately 5% to 10% of these pediatric patients [2, 3]. The prevalence of AIDs is significantly higher in children with CD [4, 5]. The interplay between CD and other autoimmune disorders appears to be bidirectional, with studies indicating an increased prevalence of AIDs in CD patients. However, the relationship remains largely associative rather than causal, as no definitive mechanistic link has been established. Prolonged gluten exposure in pediatric CD patients has been suggested as a potential contributor to the development of additional AIDs, though it remains unclear

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whether gluten directly triggers these conditions or if underlying genetic and immunological factors predispose CD patients to autoimmunity [6]. Contemporary epidemiological evidence has indicated a significant rise in the prevalence of AIDs among CD patients [7]. Ventura et al. analyzing 909 patients of CD reported a 34% prevalence of AIDs, and proposed that prolonged gluten exposure may have contributed to factors influencing AIDs [8]. A study from Finland by Viljamaa et al. evaluating 703 CD patients revealed the prevalence of AIDs as 31%, while a French study analyzing 924 patients reported that to be 19.3% [9, 10]. These findings suggest a strong association, but they do not establish a direct causal relationship. Several potential mechanisms have been proposed to explain the coexistence of CD and AIDs, including shared genetic predisposition (such as HLA-DQ2 and HLA-DQ8 alleles), environmental triggers, dysregulated immune responses, impaired intestinal barrier function, and increased intestinal permeability. While these mechanisms support an immunopathological overlap, further research is needed to determine whether CD actively drives the onset of other AIDs or if both conditions arise independently due to common risk factors. Despite the well-documented association between CD and AIDs, there is a significant lack of regional data from South Punjab, Pakistan, where CD remains underdiagnosed and often presents late with complications. Most studies on this relationship come from Western populations, limiting their applicability to South Asian children due to genetic, environmental, and dietary differences. There are no region-specific screening guidelines for AIDs in CD patients, making it unclear which AIDs are most prevalent locally. The role of prolonged gluten exposure in AID development also remains debated, with limited pediatric-specific data exploring whether early diagnosis and strict dietary adherence influence AID risk. Given the increasing recognition of AIDs in CD, this study aims to address these gaps by determining the spectrum and prevalence of AIDs in children with CD, providing critical insights for early screening, targeted management, and localized clinical guidelines.

This study aims to evaluate the spectrum of AIDs in children with CD.

METHODS

This cross-sectional study was conducted at the Department of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital, and The Institute of Child Health, Multan, Pakistan, from September 2023 to December 2024. Children of either gender, aged between 1-12 years, and having CD were included. A sample size of 167 was calculated based on an estimated 19.3% prevalence of AIDs in CD, as reported in a French study [10]. This estimate was selected due to the lack of region-specific data from South Punjab, Pakistan, and was considered relevant based on available international literature. A 6% margin of error was chosen to balance statistical precision with feasibility, ensuring adequate power to detect a meaningful prevalence estimate within the constraints of a single-center study. This approach allows for a robust yet practical sample size while maintaining a 95% confidence level for reliable estimates. The sample size was calculated using the online Open EPI sample size calculator. Children with acute on chronic liver disease (ALT > 40 IU/L), irrespective of the cause, were excluded. Children diagnosed with intestinal tuberculosis were also excluded. The CD was confirmed through small intestinal biopsy exhibiting mucosal alterations as per "Modified March Criteria" that involved partial to complete villous atrophy, crypt elongation with or without a rise in intraepithelial lymphocytes [11]. Approval for this study was obtained from the Institutional Ethical Committee (IEC) (letter number: ERC/2023/1644) of The Children's Hospital and The Institute of Child Health, Multan, Pakistan. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant institutional guidelines for research involving human subjects. Written informed consent was obtained from parents or legal guardians of all participating children before data collection. Participant confidentiality was ensured by anonymizing all data, using unique identification codes instead of personal identifiers, and restricting access to study records to authorized personnel only. Non-probability, consecutive sampling technique was utilized. Gender, age, residential status, family history of CD or AIDs, along with related gastrointestinal (GI) symptoms, were documented. The CD was labeled as mild to moderate between type 2 to 3a, while it was named severe if above type 3b to 4 [12]. Anemia was designated as hemoglobin below 11 g/dl [13]. Monthly family income was termed high if above PKR 65,000, middle if between 35,000 to 65,000, or low if below 35,000 [14]. The diagnosis of AIDs was made utilizing physical and clinical examination along with relevant laboratory and radiographic studies. Data were analyzed using IBM-SPSS Statistics, version 26.0. For age, the mean and standard deviation were calculated. Frequency and percentages were shown for gender, residence, socio-economic status, CD staging, family history of CD or AIDs, GI-related symptoms, and AIDs. Comparison of categorical data was made using the chi-square test, considering $p<0.05$ as significant.

RESULTS

In a total of 167 children with CD, 95 (56.9%) were male and 72 (43.1%) female. The mean age was 6.01 ± 3.31 years,

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ranging between 1 to 12 years. The residential status of 107 (64.1%) children was rural. The monthly family income was low in 95 (56.9%) children. The CD stage evaluation revealed that 116 children belonged to mild to moderate disease. Family history of CD and AIDs was reported in 24 (14.4%) and 63 (37.7%) children, respectively. The most frequent presenting complaints were abdominal pain, diarrhea, and weight loss, noted in 70 (41.9%), 65 (38.9%), and 53 (31.7%) children, respectively (Table 1).

Table 1: Demographics and Clinical Characteristics (n=167)

Characteristics		n (%)
Gender	Male	95 (56.9%)
	Female	72 (43.1%)
Age (Years)	1-5	91 (54.5%)
	6-12	76 (45.5%)
Residence	Urban	60 (35.9%)
	Rural	107 (64.1%)
Monthly Family Income	Low	95 (56.9%)
	Middle	49 (29.3%)
	High	23 (13.8%)
Celiac Disease Staging	Mild to Moderate	116 (69.5%)
	Severe	51 (30.5%)
Family History of Celiac Disease		24 (14.4%)
Family History of Autoimmune Disease		63 (37.7%)
Anemia		31 (18.6%)
Frequency of Presenting Symptoms/Complaints	Abdominal pain	70 (41.9%)
	Diarrhea	65 (38.9%)
	Weight loss	53 (31.7%)
	Nausea and/or Vomiting	45 (26.9%)
	Reflux	39 (23.4%)
	Constipation	26 (15.6%)
	Dyspepsia	26 (15.6%)
	Joint Pain	24 (14.4%)
	Fever	21 (12.6%)

AIDs were diagnosed in 38 (22.8%) children with CD, while the most common autoimmune diseases were autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis, found in 11 (6.6%), 7 (4.2%), 4 (2.4%), and 4 (2.4%) children, respectively. Findings are showing the details about the types of AIDs diagnosed among children with CD (Figure 1).

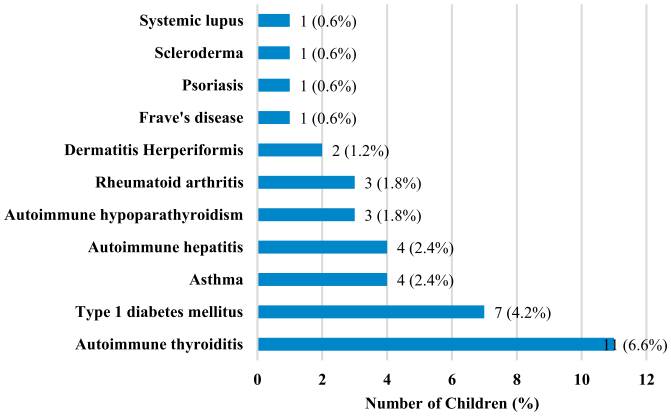

Figure 1: Types of Autoimmune Diseases Noted among Children with Celiac Disease (n=167)

No association of presence of AIDs was found with gender (p=0.886), age (p=0.081), residential status (p=0.198), family history of CD (0.195), or family history of AIDs (0.898). Low monthly family income (p=0.013), or severe CD type (p=0.010) were found to have a significant association with AIDs (Table 2).

Table 2: Association of Autoimmune Diseases with Demographic and Clinical Characteristics of Children with Celiac Disease (n=167)

Characteristics		Autoimmune disease		p-Value
		Yes (n=38)	No (n=129)	
Gender	Male	22 (57.9%)	73 (56.6%)	0.886
	Female	16 (42.1%)	56 (43.4%)	
Age (Years)	1-5	16 (42.1%)	75 (58.1%)	0.081
	6-12	22 (57.9%)	54 (41.9%)	
Residence	Urban	17 (44.7%)	43 (33.3%)	0.198
	Rural	21 (55.3%)	86 (66.7%)	
Monthly Family Income	Low	22 (57.9%)	73 (56.6%)	0.013
	Middle	6 (15.8%)	43 (33.3%)	
	High	10 (26.3%)	13 (10.1%)	
Celiac Disease Staging	Mild to Moderate	20 (52.6%)	96 (74.4%)	0.010
	Severe	18 (47.4%)	33 (25.6%)	
Family History of Celiac Disease		3 (7.9%)	21 (16.3%)	0.195
Family History of Autoimmune Disease		14 (36.8%)	49 (38.0%)	0.898
Anemia		8 (21.1%)	23 (17.8%)	0.653
Frequency of Presenting Symptoms/ Complaints	Abdominal pain	15 (39.5%)	55 (42.6%)	0.728
	Diarrhea	12 (31.6%)	53 (41.1%)	0.291
	Weight loss	12 (31.6%)	41 (31.8%)	0.981
	Nausea and/ Vomiting	14 (36.8%)	31 (24.0%)	0.118
	Reflux	8 (21.1%)	31 (24.0%)	0.703
	Constipation	10 (26.3%)	16 (12.4%)	0.038
	Dyspepsia	4 (10.5%)	22 (17.1%)	0.329
	Joint Pain	11 (28.9%)	13 (10.1%)	0.004
	Fever	6 (15.8%)	15 (11.6%)	0.496

DISCUSSION

In the present study, 22.8% children with CD had some kinds of AIDs, which means that nearly 1 in 5 children with

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CD are exposed to other AIDs as well. Literature highlights some reports from Europe indicating a co-occurrence of CD with other autoimmune conditions. Contemporary data have consistently shown a distinct pattern exhibiting high prevalence rates of various AIDs in CD in comparison to controls [15-18]. As the risk of diverse AIDs is increasing worldwide, it is also anticipated to rise among CD patients as well [19]. The underlying cause for these associations could be the shared pathogenic autoimmune mechanisms or genetic defects in the same responsible genes. A study from Turkey analyzing patients with CD revealed that 31.3% patients had AIDs [12]. In a recently published study by Hajaj *et al.* from Morocco, analyzing 60 children with CD, found that 13% children had associated AIDs [20]. Khan *et al.* showed that 5% of CD patients after 5 years had de novo AIDs diagnosis versus 1.3% controls (p=0.01) [21]. A hallmark of active CD is the presence of anti-transglutaminase antibodies, which often disappear when the patient adheres to a gluten-free diet. The underlying mechanisms linking CD and AIDs remain multifactorial, involving shared genetic predisposition (HLA-DQ2/DQ8), immune dysregulation, environmental triggers, and impaired intestinal barrier function. While molecular mimicry has been proposed as a mechanism where infectious agents trigger autoimmunity through cross-reactivity with self-antigens, other potential contributors include chronic immune activation due to gut permeability, persistent systemic inflammation, and dysbiosis-driven immune modulation [22]. Further research is required to elucidate these pathways and their role in AID development in CD patients. In this study, autoimmune thyroiditis, T1DM, autoimmune hepatitis, and asthma were the most frequent AIDs. Kayar and Dertli documented that autoimmune thyroiditis, asthma, and T1DM were the most common AIDs among patients with CD [12]. Hajaj *et al.* found T1DM to be the most common AID among children with CD [20]. Cosnes *et al.* from France reported T1DM, autoimmune thyroiditis, and psoriasis to be the most frequent autoimmune diseases in patients with CD [10]. Dermatitis herpetiforms is considered to be the most common dermatological disorder in CD, and we found that it was found in 1.2% children with CD in this study [23]. A range of hepatobiliary disorders has been documented in individuals with CD. The first recognition of liver changes in CD patients and subsequent studies have confirmed these findings, showing that abnormal liver enzyme tests are present in 9-25% CD cases [24-26]. Mild liver enzyme abnormalities are frequently seen in individuals with CD and tend to improve or normalize when the patient adheres to a strict gluten-free diet. In cases where CD is accompanied by autoimmune liver diseases, the liver's histological findings are typically indicative of the specific liver condition involved, such as autoimmune hepatitis or primary biliary cholangitis, each with distinct pathological features [27]. This association underscores the importance of considering CD in the differential diagnosis of unexplained liver enzyme elevations, as timely diagnosis and dietary management can lead to significant improvements in liver function. While some studies suggest that a gluten-free diet may reduce the risk or severity of AIDs, particularly autoimmune thyroiditis and autoimmune hepatitis, the impact of dietary adherence on long-term AID prevalence remains controversial [28, 29]. Further studies are needed to establish whether strict gluten avoidance can prevent or mitigate AID onset in pediatric CD patients. The present study is the first one from the region showing the details of AIDs among children and may pave the way towards further research.

CONCLUSIONS

Children with CD have a high prevalence of associated AIDs, with autoimmune thyroiditis, T1DM, asthma, and autoimmune hepatitis being the most commonly observed conditions. The severity of CD appears to be a contributing factor to the development of AIDs. Future studies should focus on the long-term impact of CD severity and early intervention strategies to mitigate the risk of autoimmune comorbidities.

Authors Contribution

Conceptualization: AT
Methodology: SI, IA, GK, AS, SZ
Formal analysis: GK, AS, SZ
Writing review and editing: SI, AT

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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