ASSOCIATION OF AUTOIMMUNE DISEASES IN CHILDREN WITH CELIAC DISEASE: A SINGLE-CENTER PROSPECTIVE OBSERVATIONAL STUDY

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KEYWORDS

Celiac Disease, Autoimmune Diseases, Clinical Profile, Type 1 Diabetes Mellitus, Autoimmune thyroiditis.

ABSTRACT

BACKGROUND

Celiac disease is an immune mediated chronic systemic disease characterised by intestinal mucosal damage in response to dietary gluten, among genetically predisposed individuals. There is a recognised association between celiac disease and a variety of other autoimmune diseases (AIDs). There are studies available about association of AIDs with celiac disease in adults, but there is paucity of literature for children. No reports regarding AIDs associated with celiac disease are available in literature for Indian pediatric population.

METHODS - The study included 90 children (aged 1–18 years) with celiac disease who were diagnosed and followed up at our tertiary care center. All AIDs that accompanied celiac disease were recorded and their association was analysed.

RESULTS- Mean age of celiac disease patients was 7.69 ±3.79 years (age range:1-18). Among them, 47 (52.2%) were boys and 43 (47.8%) were girls (male:female ratio-1.09 : 1). Among the 90 patients with celiac disease, 40 (44.4%) were found to have associated AIDs. The common AIDs were Type 1 diabetes mellitus (40%), autoimmune hypothyroidism (12.5%), autoimmune hemolytic anaemia (10%), autoimmune hepatitis (5%) and dermatitis herpeteformis (5%). Other less common diseases were grave's disease (2.5%), rheumatoid arthritis (2.5%) and vitiligo (2.5%). Direct Coombs test was positive in 12.5% of patients with ADs ($p = 0.035$). Laboratory analysis showed DCT positivity , higher HbA1C and high random blood sugar levels in celiac disease patients correlated significantly with presence of AIDs ($p < 0.001$).

CONCLUSION - A better knowledge of clinical profile of celiac disease patients and associated immune mediated disorders will provide a better diagnostic efficacy. This will be helpful in avoiding unnecessary hardships of parents and improving overall well being of children.

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INTRODUCTION

Celiac disease is an immune mediated chronic systemic disease characterized by malabsorption due to damage to intestinal mucosa, in a genetically predisposed individual, in response to dietary gluten and other environmental factors.[1] It is characterized by inflammatory process resulting in flattening of villus and damage to intestinal mucosa, leading to loss of absorptive functions and reduction in digestive enzymes.[2] Celiac disease is closely related to genes
encoding HLADQ2 and HLADQ 8.[1] HLA DQ 2.5 shows strongest association with Celiac Disease.[3] . Earlier it was believed that celiac disease exclusively involves the gastrointestinal tract, but recent studies have proved it to be a systemic disease.[4]

Gastrointestinal symptoms of celiac disease are mainly attributed to intestinal mucosal damage i.e. diarrhoea, steatorrhoea, loss of appetite, abdominal distension, failure to thrive, abdominal pain eight loss etc. Extra intestinal manifestations owing to tissue destruction and autoantibody production also coexist in celiac disease. Common symptoms in children include, growth retardation, short stature, delayed puberty, iron deficiency anemia refractory to oral iron supplementation, bleeding disorders, recurrent stomatitis, liver and biliary disease, dermatitis herpeteformis, arthralgia / arthritis etc[4].

Pathogenesis of the disease involves gluten (composed of gliadin and glutenin) which cause extensive activation of Helper T Cell-1 mediated inflammation.[1] Similar T cell mediated activation of immune responses have been observed in other immune mediated disorders like IDDM (5), autoimmune thyroiditis [6], autoimmune hepatitis (7), sjogren's syndrome [8], SLE[9], Autoimmune

Hemolytic Anaemia(10), ITP[11] , dermatitis herpetiformis(12) etc. The presence of ADs in CD patients can complicate the clinical picture, affecting disease management and prognosis [13]. In pediatric populations, the coexistence of CD and ADs poses unique challenges, as early-onset autoimmune conditions can impact growth, development, and quality of life [14]. There are studies available about association of autoimmune disease with celiac disease in adult population but there is paucity of literature for children. To the best of our knowledge, this will be the first study in India to study the proportion of associated autoimmune diseases in pediatric population with celiac disease. Clearly, a better understanding of celiac disease, with particular reference to other associated autoimmune conditions would be of great benefit. Filling these gaps in our basic knowledge has potential diagnostic and therapeutic importance. This study aims to investigate the association of autoimmune diseases in children with celiac disease, providing insights into the clinical profile and impact of ADs on pediatric CD patients.

MATERIALS AND METHODS

- **Study Design and Participants**
  This hospital-based prospective observational study was conducted from January to December 2023 at the Department of Pediatrics, S.P.I.N.P.H. Hospital, attached to Sawai Man Singh Medical College & Hospital, Jaipur, India. Ninety children aged 1–18 years diagnosed with celiac disease (both newly and previously diagnosed cases) were enrolled after obtaining informed written consent from parents or guardians.
- **Inclusion and Exclusion Criteria**
  Inclusion criteria were children aged 1–18 years with a confirmed diagnosis of CD based on clinical features, positive serology (anti-tissue transglutaminase IgA antibodies), and histopathological findings from duodenal biopsies. Exclusion criteria included children below 1 year or above 18 years, patients with other gastrointestinal disorders, intestinal infections, inflammatory bowel disease, drug-induced enteropathy, patients in celiac crisis, and those who did not provide consent.
- **Data Collection**
  Demographic data, clinical history, and physical examination findings were recorded using a pre-designed proforma. Anthropometric measurements were taken to calculate body mass index (BMI). Clinical symptoms such as diarrhea, abdominal pain, anemia, growth parameters, and signs of ADs were documented.
- **Evaluation for Autoimmune Diseases**
  All patients underwent a comprehensive evaluation for associated AD's based on clinical suspicion. Laboratory investigations included complete blood count, liver and renal function tests, serum electrolytes, blood glucose levels, thyroid function tests (TSH, free T4, free T3), HbA1C, anti-thyroid peroxidase antibodies (anti-TPO), direct Coombs test (DCT), anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA), and immunoglobulin G (IgG) levels. Screening for Type 1 Diabetes Mellitus was done using random blood sugar and

HbA1C levels. Thyroid autoimmunity was assessed with thyroid function tests and antiTPO antibodies.

- **Statistical Analysis**
  Data were compiled using Microsoft Excel and analyzed with Epi Info version 7.2.1.0. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations. Chi-square test was used for comparison of categorical variables, and independent t-test for continuous variables. A p-value ≤ 0.05 was considered statistically significant.
- **Ethical Considerations**
  The study was approved by the Institutional Ethics Committee (approval number (1124/MC/EC/2023). All procedures adhered to the ethical standards of the Helsinki Declaration.

RESULTS

Demographic and Clinical Characteristics

Baseline demographic data of the study Population is dedicated in table-1 which shows Among 90 children with CD enrolled in this study, 47 (52.2%) were males and 43 (47.8%) were females. (Male: female ratio 1.09: 1). 26 (29.9%) were aged below 5 years, 34 (37.8%) were aged 5-10 years, 26 (29.9%) were aged 10-15 years and 4 (4.4%) were aged above 15 years. (Mean age =7.69 ± 3.79 years) (Table 2).

Prevalence and Spectrum of Autoimmune Diseases

Out of the 90 CD patients, 40 (44.4%) had associated autoimmune diseases (table 3) The most common AD was Type 1 Diabetes Mellitus (T1DM), observed in 23 patients (57.5%), followed by autoimmune hypothyroidism in 5 patients (12.5%), autoimmune hemolytic anemia in 4 patients (10%), dermatitis herpetiformis and autoimmune hepatitis each in 2 patients (5%). Less common ADs included nephrotic syndrome (steroid-dependent) (2.5%), rheumatoid arthritis (2.5%), Graves' disease (2.5%), and vitiligo (2.5%) were also found in our study (table 4). The presence/ absence of autoimmune diseases in children with celiac disease was not found to be significantly associated with any age or gender difference. ($p > 0.05$) (table 5, table 6)

Laboratory Findings

Patients with associated ADs had significantly higher mean HbA1C levels ($8.44 \pm 3.32\%$) compared to those without ADs ($4.95 \pm 0.52\%$) ($p < 0.001$). Similarly, the mean random blood

sugar (RBS) levels were higher in patients with ADs (252.23 ± 152.6 mg/dL) compared to those without (109.3 ± 14.65 mg/dL) ($p < 0.001$). The mean thyroid-stimulating hormone (TSH) level was also significantly elevated in patients with ADs (3.22 ± 4.08 µU/mL) versus those without (1.97 ± 1.62 µU/mL) ($p = 0.048$). Direct Coombs test (DCT) positivity was observed in 5 patients (12.5%) with ADs and none without ($p = 0.035$).

Table 1: Gender distribution of study subjects

Gender	**N**	**Percentage**
Male	47	52.2
Female	43	47.8
Total	90	100

Table 2: Age distribution of study subjects

Age group (years)	**N**	**Percentage**
<5	26	28.9
5-10	34	37.8
10-15	26	28.9
15-18	4	4.4
Total	90	100
Mean ± SD	7.69 ± 3.79 years	

Table 3: Distribution of study subjects according to presence / absence of Autoimmune Disease

	N	Percentage
CD with AD	40	44.4
CD without AD	50	55.6
Total	90	100

Table 4: Distribution of study subjects according to type of autoimmune disease presence

Autoimmune disease	N	Percentage
Type 1 Diabetes Mellitus	23	57.5
Autoimmune Hypothyroidism	5	12.5
Autoimmune Hemolytic anaemia	4	10
Dermatitis Herpeteformis	2	5
Autoimmine Hepatitis	2	5
Nephrotic Syndrome SDNS	1	2.5
Rheumatoid Arthritis	1	2.5
Grave's Disease	1	2.5
Vitiligo	1	2.5
Total	40	100

Table 5: Distribution of study subjects according to presence / absence of autoimmune diseases in different age groups

Age group (years)	CD with AD		CD without AD		Total	
	N	%	N	%	N	%
<5	10	25.0	16	32	26	28.9
5-10	15	37.5	19	38	34	37.8

10-15	13	32.5	13	26	26	28.9
15-18	2	5.0	2	4	4	4.4
Total	40	100	50	100	90	100
Mean ± SD	8.30 ± 3.94		7.20 ± 3.63		7.69 ± 3.79	
t = 1.370 with 88 degree of freedom; P = 0.17 4						

Table 6: Gender distribution of study subjects according to the presence/absence of Autoimmune Disease

Gender	**CD with AD**		**CD without AD**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Female	22	55	25	50	47	52.2
Male	18	45	25	50	43	47.8
Total	40	100	50	100	90	100
Chi-square = 0.067 with 1 degree of freedom; ᵖ = 0.795						

DISCUSSION

In this study, we found that 44.4% of children with celiac disease had associated autoimmune diseases. **Kayar et al** (2019), conducted a study in adults (median age 37.1 years), and reported that Hashimoto thyroiditis was the most prevalent (24.1%), followed by type 1 diabetes (5.5%) and psoriasis (2.8%) in patients with CD[1]. In our study in pediatric population, type 1 diabetes (57.5%) was most common followed by autoimmune hypothyroidism (12.5%) and AIHA (10%). This high prevalence of autoimmune diseases underscores the importance of routine screening for ADs in pediatric CD patients to ensure early diagnosis and management.

Similar study by **Yasin Sahin et al (2021)[15]**, also reported that the most common accompanying disease in children with celiac disease was type 1 Diabetes Mellitus. The association between high prevalence of early onset T1DM in children with CD can be attributed to shared HLA-DR3, HLA-DQ2 and other genetic loci that played roles in early disease development. Both diseases share common genetic predispositions and pathophysiological relationships. Our findings align with previous studies demonstrating a significant coexistence of CD and T1DM in children [16]. This was further supported by the observation that patients with celiac disease had much higher HbA1C and RBS in comparison with patients without celiac disease, which both are significant ($p < 0.001$). The shared immune-pathogenesis suggests that gluten exposure may influence the autoimmune response in genetically susceptible individuals [17].

Autoimmune thyroid diseases, including autoimmune hypothyroidism and Graves' disease, were also observed in our cohort, accounting for 15% of the associated ADs. Similar associations have been reported in other studies by **Muhammad R. Khan et al (2019)[18]** and **Stefano Bibbò et al (2017)[19]**, emphasizing the need for thyroid function monitoring in CD patients [20]. The elevated TSH levels in patients with ADs in our study further support this recommendation.

Autoimmune hemolytic anemia (AIHA) was present in 10% of patients with ADs. Autoimmune hemolytic anaemia may represent an extension of immunological disorders linked with coeliac disease, centered on the histocompatibility antigen B8(10). Although the association between CD and AIHA is less commonly reported, some studies suggest that immune dysregulation in CD may predispose to hematological autoimmune conditions [21]. The significant positivity of the direct Coombs test among patients with ADs in our study corroborates this association.

Autoimmune hepatitis was also identified in 5% of patients. The association between CD and autoimmune liver diseases has been established further by **Caterina Anania et al (2015) [22]**, with studies suggesting that CD patients have an increased risk of liver involvement [23]. Early detection is crucial as it may impact treatment decisions and prognosis. dermatitis herpetiformis, a cutaneous manifestation of CD, was observed in 5% of patients. It is characterized by IgA deposits in the dermal papillae and is considered a cutaneous marker of gluten sensitivity [24].

The presence of dermatitis herpetiformis warrants evaluation for CD, even in the absence of gastrointestinal symptoms [25].

Salarian et al (2017) found no (0%) association of vitiligo in a study conducted on 204 children from Iran, while in our study on Indian children , vitiligo was associated in 2.5% of children with celiac disease. This difference could be attributed to gene pool variability between two populations.[4]

Kayar, Y., & Dertli, R. et al (2019) [1] in a study on adult population reported a higher risk of AID with increasing age among celiac patients, whereas in pediatric age group, no significant difference was seen in age of patients in relation to presence / absence of autoimmune diseases (p=0.174). This difference may be attributed to the diagnosis of associated AID even before diagnosis of celiac disease in younger population.

Study conducted by **Kotze et al** (2018) on Brazillian children reported 54.4% of the patients with CD presented with Immune mediated disorders. No significant difference was observed in the total prevalence between females and males (P=0.22). [26] Similarly, our study did not find any significant differences in gender distribution among CD patients with and without ADs, consistent with other reports [27]. This indicates that screening for ADs should be considered in all pediatric CD patients regardless of demographic factors like age and gender.

The limitations of our study include the single-center design and relatively small sample size, which may limit the generalizability of the findings. Additionally, the cross-sectional nature precludes establishing causal relationships.

Future studies with larger, multicenter cohorts are necessary to further elucidate the mechanisms underlying the association between CD and ADs. Understanding these relationships may lead to improved screening strategies and therapeutic interventions.

CONCLUSION

Our study demonstrates a high prevalence of autoimmune diseases among children with celiac disease, with Type 1 Diabetes Mellitus being the most common. Grave's Disease, Juvenile Rheumatoid Arthritis and Vitiligo were other rare associations found in our study which have not been reported in children earlier. Clearly, a high level of suspicion and screening for these autoimmune diseases in children with CD is of paramount importance, irrespective of age or gender. These patients must be timely treated with a multidisciplinary approach so that potentially severe complications can be avoided. This will help in abating unnecessary hardships of parents and improving overall wellbeing of children.

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