SHORT COMMUNICATION

Prevalence of Urticarial Diseases in Patients with Coeliac Disease

Eli MAGEN[1,2], Eugene MERZON[1,3], Ilan GREEN[1], Shlomo VINKER[1,4] and Ariel ISRAEL[1,4]
*[1]Leumit Health Services, Tel Aviv-Yafo, [2]Medicine A Department, Assuta Ashdod University Hospital Faculty of Health Sciences, Ben-Gurion University, Beer-Sheba, [3]Adelson School of Medicine, Ariel University, Ariel, and [4]Department of Family Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel. *E-mail: allergologycom@gmail.com*
Submitted Aug 31, 2024. Accepted after revision Nov 21, 2024
Published Jan 26, 2025. DOI: 10.2340/actadv.v105.41918. Acta Derm Venereol 2025; 105: adv41918

Coeliac disease (CD) is an autoimmune disorder triggered by gluten ingestion in genetically susceptible individuals. Previous studies have suggested a potential association between CD and chronic spontaneous urticaria (CSU) (1–3). This study aimed to investigate the prevalence of all types of urticarial diseases in CD patients and explore potential associations between these conditions.

MATERIALS AND METHODS

We conducted a retrospective observational study using electronic health records from Leumit Health Services (LHS), a nationwide healthcare organization in Israel. This was approved by the Leumit Health Services Institutional Ethics Committee. Data were collected through custom scripts developed by LHS in Python and SQL. Data were extracted from January 2001 to August 2023 and reflect the population of active insurees and diagnoses that were recorded up to this date. Case individuals were the patients who had a recorded diagnosis of CD (ICD-9 code 579.0). Control individuals were randomly selected among LHS members with no diagnosis of CD, which exactly matched case individuals on gender, age category (1–2, 2–3, 3–5, 5–18, 18–30, 30–40, 40–50, 50–60, 60–70, 70–80, >80), geographic region, ethnic group, and socioeconomic category, with a ratio of 10 control individuals for each case individual. The date of first CD diagnosis was taken as index date for the case group, and this date was taken for corresponding controls. All the clinical diagnoses of urticarial diseases were based on ICD-9 codes 708, 708.0, 708.2, 708.3, 757.331, 708, 708.5, 708.8, 708.9, and 995.1. Two recorded diagnoses of urticaria (ICD-9-CM codes 708.1, 708.8, or 708.9) separated by at least 6 weeks were classified as one observation of chronic spontaneous urticaria (CSU). Additionally, cases with a combination of 1 diagnosis from these codes and one diagnosis of angioedema (995.1) at least 6 weeks apart were also counted as one CSU observation. For patients with more than 2 observations of urticaria >6 weeks apart, each observation separated by at least 6 weeks was considered as a separate episode of CSU.

A diagnosis of CD was identified by ICD-9 579.0 recorded in the patient's electronic health record by gastroenterologists after the clinical and laboratory investigation confirmed the presence of CD. The study included 3,389 CD patients and 33,890 matched controls.

Statistical analysis

Differences between groups were analysed using independent sample *t*-tests for continuous variables and Fisher's exact test for categorical variables. Odds ratios (OR) with 95% confidence intervals were calculated. All analyses were conducted using R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

CD patients and controls had similar median ages (15 vs 16 years) and gender distribution (64.0% female). CD patients had a lower mean BMI (19.7 vs 21.3 kg/m^2, $p<0.001$) and more frequent allergology (7.61% vs 5.02%, $p<0.001$) and dermatology visits (42.37% vs 37.99%, $p<0.001$). Laboratory tests revealed lower TSH, haemoglobin, WBC, CRP, iron, and ferritin levels in CD patients ($p<0.001$). CD patients also showed higher eosinophil and platelet counts ($p<0.001$) and lower basophil counts ($p=0.046$) in peripheral blood (**Table I**). CD patients had a higher prevalence of acute urticaria (ICD-9 code 708.0) with an OR of 1.23 ($p=0.005$), and CSU with an OR of 1.34 ($p=0.002$). There were no statistically significant differences in prevalence between CD patients and controls for other specific subtypes of urticarial diseases (708.1 to 708.9 and 995.1) (**Table II**).

DISCUSSION

Our findings align with previous research, confirming an association between CD and urticaria (3–5). CD patients in our study exhibited a higher prevalence of various urticarial diseases, including acute allergic urticaria, acute spontaneous urticaria, and CSU, than the control group. These findings are also consistent with the growing body of evidence suggesting that CD patients have a higher occurrence of IgE-mediated allergy, including allergic urticaria (6, 7). CD patients had more frequent visits to allergology and dermatology departments, suggesting a higher prevalence of allergic and dermatological manifestations in this population. This may have resulted in an inflated prevalence of urticaria in CD patients compared with the control group. However, our matching process was intended to mitigate potential biases related to healthcare access and demographic factors. Despite these efforts, we acknowledge that the observational nature of the study limits our ability to fully eliminate selection bias.

It is important to note that urticaria, especially acute urticaria, is a common diagnosis in children, often triggered by airway infections. However, healthcare professionals should maintain awareness of the potential association between urticaria and CD, as well as other autoimmune diseases. This is particularly relevant for patients with relapsing spontaneous urticaria or CSU, where CD may

Table I. Clinical characteristics of the coeliac disease subjects with coeliac disease and matched controls

Factor	Case $n = 3,389$	Control $n = 33,890$	p-value	OR [95% CI]
Age (years) at cohort extraction, median [IQR]	15 [8–33]	16 [8–33]	0.591	
Age (years) at index date (CD diagnosis for cases), median [IQR]	10 [5–27]	12 [5–27]	0.564	
Age category				
1–2 years	61 (1.80)	610 (1.80)	0.999	
2–3 years	87 (2.57)	870 (2.57)	0.999	
3–5 years	208 (6.14)	2,080 (6.14)	0.999	
5–18 years	1,503 (44.35)	15,030 (44.35)	0.999	
18–30 years	523 (15.43)	5,230 (15.43)	0.999	
30–40 years	270 (7.97)	2,700 (7.97)	0.999	
40–50 years	271 (8.00)	2,710 (8.00)	0.999	
50–60 years	192 (5.67)	1,920 (5.67)	0.999	
60–70 years	142 (4.19)	1,420 (4.19)	0.999	
70–80 years	62 (1.83)	620 (1.83)	0.999	
> 80 years	70 (2.07)	700 (2.07)	0.999	
Sex, *n* (%)				
Female	2,168 (64.0)	21,680 (64.0)	0.999	1.00 [0.93–1.08]
Socioeconomic status	8.06 ± 3.98	8.03 ± 3.86	0.762	
Ethnic group, *n* (%)				
Arab	357 (10.5)	3,594 (10.6)	0.930	0.99 [0.88–1.11]
General	1,786 (52.7)	17,915 (52.9)	0.857	0.99 [0.93–1.07]
Jewish Ultra-orthodox	1,246 (36.8)	12,381 (36.5)	0.793	1.01 [0.94–1.09]
Smoker, *n* (%)	62 (11.59)	839 (15.72)	0.012	0.73 [0.56–0.95]
BMI (kg/m^2), mean±SD	19.7 ± 5.6	21.3 ± 6.3	< 0.001	
Allergology visits, *n* (%)	258 (7.61 %)	1,702 (5.02)	< 0.001	1.56 [1.35–1.79]
Dermatology visits, *n* (%)	1,436 (42.37)	12,876 (37.99)	< 0.001	1.20 [1.12–1.29]

SD: standard deviation; OR: odds ratio; CI: confidence interval; BMI: body mass index; IQR: interquartile range.

be an underlying condition. Identifying CD in such cases could improve outcomes, especially when other clinical indicators, such as gastrointestinal symptoms or nutritional deficiencies, are present (8). However, this study was not designed to assess the timing of urticaria episodes in relation to diagnosis of CD.

Several cases have been documented where individuals with CSU experienced relief from their skin symptoms upon adopting a gluten-free diet, which is the cornerstone of CD management (9, 10). In such cases, timely recognition and management of CD could improve outcomes for both CD and CSU. Previously, Gallo et al. identified histological evidence of CD in a subset of CSU patients, suggesting a potential association (11). However, not all cases of CD-associated CSU present with gastrointestinal symptoms suggestive of CD (12). This highlights the need for clinicians to consider the possibility of CD in CSU cases, even in the absence of typical gastrointestinal symptoms (12). Nevertheless, the resolution of urticarial diseases with a gluten-free diet may not be absolute (10), which raises questions concerning the potential involvement of additional pathophysiological factors in these autoimmune comorbidities (13). Previous research has identified the increased numbers and proinflammatory phenotype of mast cells (MC) in patients with CD (14). Moreover, gliadin fragment p31–43 can bind specifically to MC surfaces, inducing their degranulation and the selective release of histamine and proinflammatory cytokines (13). While the precise mechanisms of MC activation by p31–43 require further investigation, it suggests a common immunological mechanism of MC activation connected to the symptoms and pathogenesis of both CD and urticaria. Further investigations could explore the mechanisms underlying the association between CD and urticaria and elucidate whether a gluten-free diet may have a role in managing urticarial symptoms in CD patients, as suggested by previous research (15).

Table II. Prevalence of urticarial diseases in subjects with and without coeliac disease

Factor	Patients with coeliac disease $n = 3,389$ *n* (%)	Control group $n = 33,890$ *n* (%)	OR [95%CI]	p
Acute urticaria				
Acute spontaneous urticaria	334 (9.85)	2,660 (7.85)	1.28 [1.14–1.45]	< 0.001
Acute urticaria, allergic	232 (6.85)	1,917 (5.66)	1.23 [1.06–1.41]	0.005
Acute urticaria, other specified	15 (0.44)	125 (0.37)	1.20 [0.65–2.06]	0.462
Physical (inducible) urticaria				
Urticaria, due to cold and heat	2 (0.06)	19 (0.06)	1.05 [0.12–4.37]	0.999
Urticaria, dermatographic	5 (0.15)	11 (0.03)	4.55 [1.24–14.22]	0.012
Urticaria, vibratory	1 (0.03)	2 (0.01)	5.00 [0.08–96.20]	0.249
Urticaria, cholinergic	3 (0.09)	9 (0.03)	3.34 [0.58–13.37]	0.089
Angioneurotic oedema, mast cell mediated	11 (0.33)	70 (0.21)	1.57 [0.75–2.99]	0.172
Chronic spontaneous urticaria	134 (3.95)	1,012 (2.99)	1.34 [1.11–1.61]	0.002

OR: odds ratio; CI confidence interval.

This study has limitations, including its retrospective nature and reliance on electronic health records. Nevertheless, our study provides valuable insights into the prevalence of urticarial diseases in CD patients, warranting increased awareness among healthcare professionals of this association.

REFERENCES

1. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev 2017; 16: 1196–1208. https://doi.org/10.1016/j.autrev.2017.10.003
2. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol 2012; 129: 1307–1313. https://doi.org/10.1016/j.jaci.2012.01.043
3. Ludvigsson JF, Lindelöf B, Rashtak S, Rubio-Tapia A, Murray JA. Does urticaria risk increase in patients with celiac disease? A large population-based cohort study. Eur J Dermatol 2013; 23: 681–687. https://doi.org/10.1684/ejd.2013.2158
4. Haussmann J, Sekar A. Chronic urticaria: a cutaneous manifestation of celiac disease. Can J Gastroenterol 2006; 20: 291–293. https://doi.org/10.1155/2006/871987
5. Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. Pediatr Allergy Immunol 2005; 16: 428–432. https://doi.org/10.1111/j.1399-3038.2005.00309.x
6. Majsiak E, Choina M, Knyziak-Mędrzycka I, Bierła JB, Janeczek K, Wykrota J, et al. IgE-dependent allergy in patients with celiac disease: a systematic review. Nutrients 2023; 15: 995. https://doi.org/10.3390/nu15040995
7. Kårhus LL, Skaaby T, Madsen AL, Thuesen BH, Schwarz P, Rumessen JJ, et al. The association of celiac disease and allergic disease in a general adult population. United European Gastroenterol J 2019; 7: 78–89. https://doi.org/10.1177/2050640618811485
8. Hautekeete ML, DeClerck LS, Stevens WJ. Chronic urticaria associated with coeliac disease. Lancet 1987; 1: 157. https://doi.org/10.1016/S0140-6736(87)91986-6
9. Ohlsen BA. Acupuncture and a gluten-free diet relieve urticaria and eczema in a case of undiagnosed dermatitis herpetiformis and atypical or extraintestinal celiac disease: a case report. J Chiropr Med 2011; 10: 294–300. https://doi.org/10.1016/j.jcm.2011.06.003
10. Levine A, Dalal I, Bujanover Y. Celiac disease associated with familial chronic urticaria and thyroid autoimmunity in a child. Pediatrics 1999; 104: e25. https://doi.org/10.1542/peds.104.2.e25
11. Gallo C, Vighi G, Schroeder J, Strozzi M, Scibilia J, Colafrancesco M, et al. Chronic urticaria atopic dermatitis and celiac disease. Am J Gastroenterol 1992; 87: 1684.
12. Scala E, Giani M, Pirrotta L, Guerra EC, De Pità O, Puddu P. Urticaria and adult celiac disease. Allergy 1999; 54: 1008–1009. https://doi.org/10.1034/j.1398-9995.1999.00216.x
13. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. Arch Dermatol 1983; 119: 636–640. https://doi.org/10.1001/archderm.1983.01650320010007
14. Frossi B, Tripodo C, Guarnotta C, Carroccio A, De Carli M, De Carli S, et al. Mast cells are associated with the onset and progression of celiac disease. J Allergy Clin Immunol 2017; 139: 1266–1274.e1. https://doi.org/10.1016/j.jaci.2016.08.011
15. Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. Am J Clin Dermatol 2003; 4: 13–20. https://doi.org/10.2165/00128071-200304010-00002