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Chronic Urticaria and Irritable Bowel Syndrome: a Cross-Sectional Study of 11,271 Patients

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Keywords: Chronic Urticaria; Irritable Bowel Syndrome.

Abbreviations used:

Chronic urticaria	CU
Clalit Health Services	CHS
Gastrointestinal	GI
Health maintenance organization	HMO
IBS with constipation	IBS-C
Irritable bowel syndrome	IBS
Irritable bowel syndrome with diarrhea	IBS-D

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Mast cells	MC
Thyroid stimulating hormone	TSH

The human body interacts with the environment mainly through three major tissues: the lungs, skin, and gastrointestinal (GI) tract. In each one, an intensive nervous network is present, conjugated with abundant mast cells (MC). While MC-mediated disorders in airways and the skin are extensively discussed, MC-mediated disorders of the GI tract remain relatively uncommon. Since the GI tract is one of the three main environment-interacting tissues, it is reasonable that MC-mediated disorders of the GI may have the same weight and impact as asthma or chronic urticaria (CU).

Irritable bowel syndrome (IBS) is one of the most common GI disorders.¹ The role of allergies and MC in IBS is being increasingly implicated. Recently, Pearson JS et al. and we described two case reports of positive clinical responses to omalizumab in patients with IBS-D and concomitant chronic spontaneous urticaria (CSU)² and asthma.³ Consequently, we hypothesize that MCs' involvement in IBS may lead to a significant epidemiologic association between CU and IBS; the aim of our study was to evaluate this association using a large database.

Clalit Health Services (CHS) is the largest health maintenance organization in Israel—it covers approximately 4.4 million of the country's residents—and its electronic database includes comprehensive information on the insured population, such as demographic data, records of clinical visits, and laboratory tests.

We designed a cross-sectional study of patients with CU and age- and gender-matched controls based on a frequency matching method. To exclude acute urticaria as well as false diagnoses, we used a conservative definition for CU that included eight urticaria diagnoses (with each two diagnoses registered within a period of six weeks). Each urticaria diagnosis was made by a physician in community services, the outpatient clinic, or during hospitalization from January 2002 to December 2013. The control group consisted of age- and gender-matched patients without CU, extracted from the general population of CHS enrollees.

Only IBS diagnoses (ICD-9-CM diagnosis Code 564.1 in the CHS database) made by board-certified gastroenterologists were included, both in cases and controls, extracted in a manual search process. Patients with IBS and concomitant inflammatory bowel disease (IBD), GI malignancy, low hemoglobin (<10 g/dl), albumin (<3.5 g/dl), or abnormal TSH levels (<0.35 ; >5.5 uIU/ml) in laboratory tests were excluded from the study to avoid false IBS diagnoses, as defined by Rome III criteria.

To examine the differences between CU patients and controls, continuous variables were compared using t-tests, and dichotomous variables were compared using Pearson's chi-square. The association between CU and IBS was further tested by a multivariate logistic regression model, adjusting for age, sex, general practitioner clinic visits, dermatologist clinic visits, allergist clinic visits, and hospitalizations. General practitioner clinic visits, dermatologist clinic visits, allergist clinic visits, and hospitalizations were all included in the model as continuous variables. These data were previously reported⁴ and were supposed to best reflect the personal and direct contact of a patient with his or her healthcare provider,

which can impact the probability of being diagnosed with IBS. All statistical tests performed were two-sided; a p -value <0.05 was considered statistically significant.

Demographic and laboratory data regarding the study population are presented in Table 1. The study included 11,271 CU patients and 67,626 controls. Of the patients, 827 had a concomitant IBS diagnosis (1.1%), of which 74 patients were excluded due to concomitant IBD, GI malignancy, or lab results occurring in a time period succeeding their IBS diagnoses: 7 with IBD, 3 with GI malignancy, 27 with low hemoglobin, 8 with low albumin, and 29 with abnormal TSH levels. Thus, a concomitant IBS diagnosis was identified in 188 (1.7%) CU patients and in 565 (0.8 %) controls ($p<0.001$). A sample of 250 medical records were manually reviewed for their CU diagnosis, 228 of which were found to be dermatologist-confirmed, giving a positive predictive value (PPV) of 91.2% to our CU patients. In a multivariate analysis (Table 1), CU was significantly associated with IBS (OR=1.86; 95% CI 1.57–2.19, $p<0.001$).

A pathophysiological explanation is currently lacking of the observed higher prevalence of IBS in CU. The pathophysiological role of MC is being increasingly implicated in the pathophysiology of IBS.^{5,6,7} Therefore, we can only speculate about the hypothetical roles of MC linking these two chronic diseases.

In conclusion, we report a novel finding of an association between CU and IBS. Our observation fits with previous findings that MC are involved in IBS pathogenesis. Future studies should clarify whether anti-IgE treatments, effective for urticaria, can also benefit IBS patients.

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Professor Daniel A. Vardy passed away prematurely during the review process of this manuscript. He spent his successful career by curing thousands of patients as a great clinician, teaching dermatology passionately to many young dermatologists and residents, and researching various clinical aspects of dermatology. He was Chairman and Professor in Dermatology at the Soroka Medical Center and the Ben-Gurion University of the Negev, Beer-sheva, Israel. Not only was Dani an excellent teacher, but also a marvelous team leader who could motivate people and promote excellence. Professor Daniel A. Vardy will never be forgotten.

Guy Shalom and Eli Magen take responsibility for the integrity of the work.

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Table 1. Baseline characteristics of the study population and the association between CU and IBS according to different multivariate models

		Chronic urticaria (n=11,271) n (%)	Control group (n=67,216) n (%)	p-value	Patients without IBS (n=77,734)	IBS patients (n=753)	p-value
Age, mean (SD)		47.4 (22.1)	47.4 (21.9)		47.3 (21.8)	58.1 (18,8)	<0.001
Gender	Male	3,811 (33.8)	22,805 (33.9)	>0.1	26,447 (34.1)	162 (21.5)	<0.001
	Female	7,450 (66.2)	44,411 (66.1)		51,215 (65.9)	591 (78.5)	<0.001
Socioeconomic status	Low	4,600 (40.8)	27,476 (40.9)	<0.001	31,838 (41.7)	217 (29)	<0.001
	Intermediate	4,436 (39.4)	25,270 (37.6)		29,369 (38.4)	312 (41.8)	<0.001
	High	1,889 (16.8)	13,573 (20.2)		15,228 (19.9)	218 (29.2)	<0.001
Ethnicity	Arabs	2,421 (21.5)	14,033 (20.9)	<0.001	16,369 (21.1)	81 (10.8)	<0.001
	General population	8,840 (78.4)	53,183 (79.1)		61,293 (71.9)	672 (89.2)	<0.001
Smokers		1,754 (15.6)	9,987 (14.9)	0.05	11,639 (15)	93 (12.4)	0.047
Obesity		2,544 (22.6)	12,653 (18.8)	<0.001	14,996 (19.3)	184 (24.4)	<0.0001
Asthma		1,215 (10.8)	4,342 (6.5)	<0.001	5,457 (7)	91 (12.1)	<0.0001
Allergic rhinitis		2,238 (19.9)	6,807 (10.1)	<0.001	8,835 (11.4)	195 (25.9)	<0.0001
Atopic dermatitis		1,100 (9.8)	2,471 (3.7)	<0.001	3,517 (4.5)	52 (6.9)	0.003
<i>The association between CU and IBS</i>							

Model of analysis	OR (95% confidence interval)	P value
Univariate model	1.93 (1.61–2.23)	<0.001
Age and sex adjusted	1.98 (1.58–2.23)	<0.001
Age, sex, and general practitioner clinic visits adjusted	1.89 (1.59–2.21)	<0.001
Age, sex, general practitioner, and dermatologist clinic visits adjusted	1.87 (1.58–2.12)	<0.001
Age, sex, general practitioner, dermatologist, and allergist clinic visits adjusted	1.87 (1.59–2.21)	<0.001
Age, sex, general practitioner and dermatologist clinic visits, allergist clinic visits, and hospitalizations adjusted	1.86 (1.57–2.19)	<0.001

IBS – Irritable bowel disease