Rome IV Criteria-Defined Irritable Bowel Syndrome in Atopic Patients and the Effect of Anxiety and Depression: A Case–Control Study

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ABSTRACT

Background: *Numerous studies report an increased prevalence of irritable bowel syndrome in patients with atopic diseases such as allergic rhinitis, allergic asthma, and chronic urticaria. Both disease groups have a higher incidence of psychological disorders. In this study, we aimed to examine the relationship of irritable bowel syndrome with the presence and severity of allergic diseases and accompanying anxiety and depression.*

Methods: *One hundred sixty-two patients (56 with AR, 34 with AA, and 72 with CU) and 43 healthy volunteers were included in the study. Demographic and clinical data, along with disease duration and severity, was analyzed. Irritable bowel syndrome was diagnosed using Rome IV criteria. Hospital Anxiety and Depression Scale was used to evaluate anxiety and depression. All statistical analyses were performed using Statistic Program for Social Sciences 23.0.*

Results: *Irritable bowel syndrome prevalence in the control group was 9.3% and 56% in atopic patients ($P < .0001$). Hospital Anxiety and Depression Scale anxiety scores of 11 and above increased the odds of IBS approximately 14 times, and independently, the presence of allergic disease increased the odds 10 times. In the allergic patient subgroup, Hospital Anxiety and Depression Scale anxiety scores of 11 and above increased the risk of irritable bowel syndrome approximately 18 times.*

Conclusion: *In this first study using Rome IV criteria to examine the relationship of irritable bowel syndrome, allergic diseases, and anxiety and depression, irritable bowel syndrome was more frequent in allergic patients, especially in patients with anxiety. Awareness of a disease cluster where these 3 disease groups intersect will guide clinicians from different disciplines involved in patients' treatment and follow-up.*

Keywords: *Allergy, anxiety, atopy, depression, irritable bowel syndrome*

INTRODUCTION

Irritable bowel syndrome (IBS), one of the most common forms of chronic functional bowel disorders, is characterized by chronic abdominal discomfort and altered bowel habits. Diagnosing a patient with IBS can be challenging. Rome IV criteria have been the current standard for IBS diagnosis since 2016.[1] Irritable bowel syndrome prevalence in Turkey was reported as 9.8% according to Rome III and 3.9% according to Rome IV criteria; however, prevalence can vary in different countries and populations.[2] Although Rome III criteria are shown to diagnose more people with IBS, Rome IV was shown to diagnose more severe symptoms and psychological comorbidity burden.[3,4]

Allergic rhinitis (AR), allergic asthma (AA), chronic urticaria (CU), atopic dermatitis, and food allergy affect approximately 20% of the population.[5] Numerous studies report an increased prevalence of functional bowel diseases in patients with atopic diseases; however, the relationship remains controversial. Although there are population-based evidence and case-control studies, data regarding basic biological mechanisms are scarce.[6]

A common link partially explains the synchrony between allergic diseases and functional bowel disorders: increased psychological disorders in both disease groups.[7] There are several reports in the literature that anxiety, depression, and inability to cope with stress are more common in allergic diseases and are associated with disease severity in these diseases.[8] However, there are no studies in the literature regarding the association between anxiety and depression levels of allergic patients with an IBS diagnosis using Rome IV criteria.

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In this study, we aimed to (i) determine the prevalence of IBS in patients with AR, AA, and CU and compare it with controls and (ii) examine the relationship of IBS with the presence and severity of allergic diseases and accompanying anxiety and depression.

MATERIALS AND METHODS

Study Design, Place, and Time

This cross-sectional case-control study was conducted per the Declaration of Helsinki. Approval for this study was obtained from the local University Medical School Non-Interventional Studies Ethics Committee (Date: January 16, 2020, Approval number: 01/19). Additional approval to carry out the study was gained from the local Provincial Health Directorate Scientific Studies Review Commission. All patients and healthy volunteers provided written informed consent for participation in the study.

Subjects

A total of 200 consecutive patients over 18 with AR, AA, or CU were included in this study. Diagnostic criteria used for AR, AA, and CU were International Consensus Statement on Allergy and Rhinology (ICAR),[9] Global Initiative for Asthma (GINA),[10] and EAACI/GA2LEN/EDF/WAO guidelines,[11] respectively. Patients with a diagnosis or suspicion of an organic bowel disease other than IBS such as malignancy (n = 2), inflammatory bowel disease (n = 2), infectious diarrhea (n = 7), celiac disease (n = 3), and other malabsorption syndromes (n = 1); patients with alarm signs and symptoms such as unexplained involuntary weight loss, fever, or night sweats (n = 2), family history of colon cancer or inflammatory bowel disease (n = 2), ascites, organomegaly or lymphadenopathy on physical examination (n = 4), presence of profound anemia (n = 3); being illiterate in Turkish enough to complete the questionnaire (n = 9) and history of psychiatric disease and antipsychotic or antidepressant medication use (n = 3) were used as exclusion criteria for the study. One hundred sixty-two patients (56 with AR, 34 with AA, and 72 with CU) were included in the final analysis. Forty-three healthy volunteers with no evidence of allergic diseases were used as a control group.

Assessment Instruments

Demographic and clinical data, age, gender, marital status (single or married), education level (primary, high school or university), income level (low, moderate or high), disease duration (months), disease severity, and information on current medications have been recorded for all participants. Total anti-immunoglobulin E (IgE) levels and skin prick test results were accessed from medical records. Allergic rhinitis symptom burden was quantified by total nasal symptom score (TNSS),[12] and severity was classified into 4 as mild intermittent, mild persistent, moderate-to-severe intermittent, and moderate-to-severe persistent.[13] According to GINA guidelines based on symptomatology and pulmonary function, AA severity was classified as mild, moderate, and severe.[10] Chronic urticarial symptom burden was quantified by urticaria activity score (UAS7),[14] and severity was classified as mild, moderate, and severe, according to the recommendations of EAACI/GA2LEN/EDF/WAO guidelines.[11]

Hospital Anxiety and Depression Scale was used to evaluate the participants' anxiety and depression levels. The reliability and validity of the Turkish version questionnaire were examined before.[15] Hospital Anxiety and Depression Scale is a Likert-type self-assessment questionnaire consisting of 14 questions, each consisting of 7-item anxiety (HADS-A) and depression (HADS-D) subscales. Subscale scores are between 0 and 21, with higher scores meaning higher anxiety or depression.[15] Anxiety and depression subscale cut-off points of 8 and 11 were both used since previous publications underline different sensitivities and specificities.[16,17]

Rome IV IBS diagnostic criteria, revised in 2016, were used to evaluate IBS, and Bristol stool scale was used to determine IBS subtype as IBS with predominant diarrhea (IBS-D), predominant constipation (IBS-C), mixed bowel habits (IBS-M), and unclassified (IBS-U).[18]

Statistical Analysis

All statistical analyses were performed using IBM Statistic Program for Social Sciences (SPSS) Statistics for Windows version 23 (IBM Corp., Armonk, NY, USA). Skewness, kurtosis, critical value, analytical normality test methods (Kolmogorov–Smirnov/Shapiro–Wilk tests), and histogram plots were used to examine/evaluate whether continuous variables fit in the normal distribution. Demographic and clinical data were presented as median and range, or in number and percentage values. For inter-group analysis, the chi-square test of independence was used to analyze the relationship between categorical variables. Mann–Whitney *U* tests were used for the comparison of continuous data. Univariate and multivariate logistic regression analyses (with Backwards Wald method) were used to evaluate the relationship between categorical and continuous variables and categorical results. Odds ratios (OR) were presented with 95% CI. A *P*-value of less than .05 was considered statistically significant.

RESULTS

Demographic, Clinical, and Laboratory Data of the Study Group

Two hundred five participants, 56 with AR, 34 with AA, 72 with CU, and 43 in the control group, were included in the study. The demographic data of the participants are presented in Table 1. Allergic rhinitis and chronic urticarial were similar in age with the control group, but the AA group was median 12 years older than the control group (P = .002, Mann–Whitney U test). The AR group was 10 years younger than the CU group and 16 years younger than the AA group (both comparisons, P = .001, Mann–Whitney U test). Groups were similar in terms of gender, marital status, education, and income.

Clinical and laboratory parameters of patients with AR, AA, and CU are presented in Table 2. The most prolonged disease duration was in the AA, then AR, and CU group (all comparisons, P = .001, Mann–Whitney U test). Total IgE values were similar between groups. Skin prick test (SPT) positivity was lower in patients with CU than AR and AA (P = .001, chi-square test). The most common allergen in SPT was house dust mite. Treatments were planned according to current guidelines and patients' symptoms. The most common treatment modality in AR and CU was antihistaminics, montelukast, and inhaled corticosteroids ± beta-agonists in AA.

Table 1. Demographic Data of Patients with Allergic Diseases and Controls

	Control (n = 43)	AR (n = 56)	AA (n = 34)	CU (n = 72)
Age	37 (18-55)	29 (18-61)	45 (19-67)	39 (18-66)
Gender				
Female	25 (58.1%)	35 (62.5%)	20 (58.8%)	45 (62.5%)
Male	18 (41.9%)	21 (37.5%)	14 (41.2%)	27 (37.5%)
Marital status				
Single	14 (32.6%)	20 (35.7%)	7 (20.6%)	20 (27.8%)
Married	29 (67.4%)	36 (64.3%)	27 (79.4%)	52 (72.2%)
Education status				
Primary school	19 (44.2%)	25 (44.6%)	21 (61.8%)	39 (54.2%)
High school	16 (37.2%)	20 (35.7%)	10 (29.4%)	22 (30.6%)
University	8 (18.6%)	11 (19.6%)	3 (8.8%)	11 (15.3%)
Income				
Low	2 (4.7%)	7 (12.5%)	9 (26.5%)	11 (15.3%)
Moderate	36 (83.7%)	41 (73.2%)	22 (64.7%)	53 (73.6%)
High	5 (11.6%)	8 (14.3%)	3 (8.8%)	8 (11.1%)

Data were presented as frequency (percentage) for categorical variables. AR, allergic rhinitis; AA, allergic asthma; CU, chronic urticaria.

IBS, Anxiety, and Depression Prevalence of the Study Group

Irritable bowel syndrome prevalence in the control group was 9.3% (n = 4). In contrast, 55.4% of the AR group (n = 31), 58.8% of the AA group (n = 20), and 55.6% of the CU group (n = 40) had IBS according to Rome IV criteria (Figure 1). Although IBS-C was the most common subtype, the distribution of IBS subtypes was similar among allergic diseases.

Hospital Anxiety and Depression Scale scores data of the participants are presented in Table 3. Both anxiety and depression subscale scores were higher in patients with allergic diseases than controls (both tests, P = .001, Mann–Whitney U test). For both anxiety and depression subscale score cut-offs of 8 and above, anxiety was twice and depression was 5 times more frequent in allergic diseases than control (both tests, P = .001, chi-square test). In comparison, for anxiety and depression subscale score cut-offs of 11 and above, anxiety and depression can be seen 3 times more frequently in patients with allergic diseases than controls (P = .004 and .04, respectively, chi-square test).

Factors Associated with the Presence of Irritable Bowel Syndrome in All Participants

The association between gender, anxiety, depression, and the presence of allergic disease with IBS was analyzed using univariate and multivariate binary logistic regression analysis. In the multivariate analysis including all study population, we observed that HADS anxiety scores of 11 and above increased the odds of IBS approximately 14 times, and independently, the presence of allergic disease increased the odds 10 times. Gender and depression were not associated with IBS (Table 4).

Factors Associated with the Presence of Irritable Bowel Syndrome in Allergic Patients

There were 91 allergic patients with IBS and 71 allergic patients without IBS. Patients with and without IBS were similar in terms of age, marital status, education level, income level, disease duration, total IgE level, SPT results, and treatments used. IBS was 2.6 times (95% CI,

Table 2. Clinical and Laboratory Parameters of Patients with Allergic Rhinitis, Allergic Asthma, and Chronic Urticaria

		AR (n = 56)	AA (n = 34)	CU (n = 72)
Disease Duration	Months	30 (2-240)	96 (4-276)	6 (2-120)
Disease Severity	TNSS	8 (4-12)	-	-
	Mild intermittent	6 (10.8%)	-	-
	Mild persistent	22 (39.3%)	-	-
	Moderate-to-severe intermittent	10 (17.8%)	-	-
	Moderate-to-severe persistent	18 (32.1%)	-	-
	Mild	-	9 (26.4%)	-
	Moderate	-	14 (41.2%)	-
	Severe	-	11 (32.4%)	-
	UAS7	-	-	28 (7-42)
	Mild	-	-	15 (20.8%)
	Moderate	-	-	11 (15.3%)
	Severe	-	-	46 (63.9%)
Total IgE		131 (4-2500)	296 (9-2500)	164 (11-2500)
SPT	Positive	36 (64.2%)	22 (64.8%)	6 (8.3%)
	Mites	27 (48.2%)	17 (50%)	3 (4.1%)
	Grass	7 (12.5%)	3 (8.8%)	2 (2.7%)
	Parietaria	3 (5.3%)	3 (8.8%)	0 (0%)
	Olive	2 (3.5%)	0 (0%)	0 (0%)
	Cockroach mix	1 (1.7%)	0 (0%)	0 (0%)
	Alternaria	1 (1.7%)	0 (0%)	0 (0%)
	Animal danders	1 (1.7%)	0 (0%)	1 (1.3%)
Treatment	Antihistaminics	47 (83.9%)	20 (58.8%)	52 (72.2%)
	Montelukast	26 (46.4%)	34 (100%)	4 (5.5%)
	Glucocorticoids	1 (1.7%)	8 (23.5%)	20 (27.7%)
	Subcutaneous immunotherapy	17 (30.3%)	-	-
	Inhaled corticosteroids ± Beta-agonists	-	30 (88.2%)	-

Data were presented as frequency (percentage) for categorical and median (minimum-maximum) for continious variables. AR, allergic rhinitis; AA, allergic asthma; CU, chronic urticaria; TNSS, total nasal symptom score; UAS7, urticaria activity score; SPT, skin prick test.

1.3-4.9) more common in females with allergic diseases than males (P = .004, chi-square test). When anxiety and depression subscales were evaluated with their association with IBS presence in allergic diseases, we have observed that anxiety cut-off point of 11 and depression cut-off point of 8, respectively, are better associated with the presence of IBS (Both tests, P = .001, chi-square test). A HADS anxiety score of 11 or above increased the odds of IBS by 17.7-fold (95% CI, 7.5-41.9). A HADS depression score of 8 or above increased the odds of IBS by 5.8-fold (95% CI 2.9-11.6). Severe AR increased the odds of IBS by 6.8-fold (95% CI 1.7-27.7) and severe CU increased the odds by 3.9-fold (1.4-10.8) (P = .015 and .001, respectively, chi-square test). In contrast, there is no association between disease severity for AA and the presence of IBS (P = .123, chi-square test). In the final multivariate analysis, we demonstrated that the HADS anxiety scores of 11 and above increased the odds of IBS approximately 18 times, and gender did not have an effect in the multivariate analysis. In disease-specific subgroup analyses, disease severity was only included in the final model in patients with CU: severe CU increases the odds of IBS approximately 8 times, independent of the effect of anxiety, while a HADS anxiety score of 11 and above increases the odds of IBS 14.5 times (Tables 5 and 6).

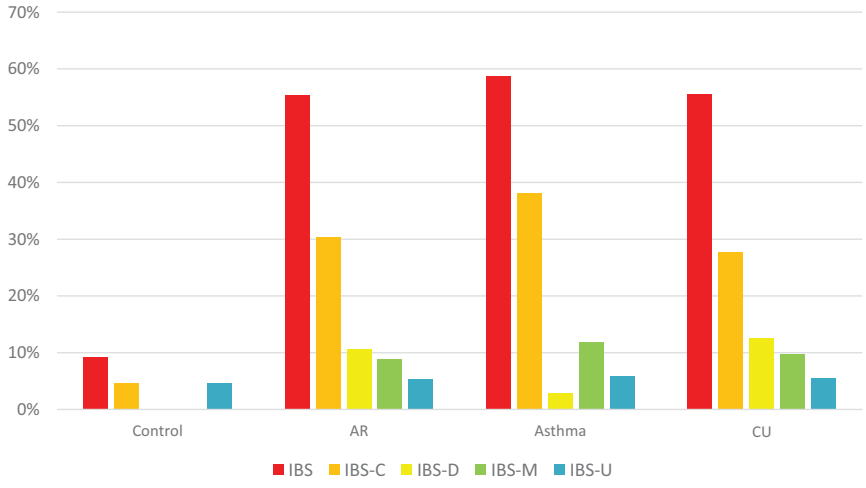

Figure 1. Frequency of IBS and IBS subtypes in the study population (percentage). IBS, irritable bowel syndrome; IBS-C, predominant constipation; IBS-D, predominant diarrhea; IBS-M, mixed bowel habits; IBS-U, unclassified.

Table 3. Hospital Anxiety and Depression Scale Scores of Patients with Allergic Diseases and Controls

		Control (n = 43)	AR (n = 56)	AA (n = 34)	CU (n = 72)
HADS	Anxiety subscale	6 (0-15)	9 (0-18)	8.5 (0-18)	9 (0-19)
	0-7	29 (67.4%)	18 (32.1%)	16 (47.1%)	23 (31.9%)
	≥8	14 (32.6%)	38 (67.9%)	18 (52.9%)	49 (68.1%)
	≥11	6 (14%)	24 (42.9%)	14 (41.2%)	33 (45.8%)
	Depression subscale	4 (0-13)	8 (0-14)	7.5 (0-16)	8 (0-16)
	0-7	38 (88.4%)	27 (48.2%)	17 (50%)	30 (41.7%)
	≥8	5 (11.6%)	29 (51.8%)	17 (50%)	42 (58.3%)
	≥11	3 (7%)	11 (19.6%)	8 (23.5%)	21 (29.2%)

Data were presented as frequency (percentage) for categorical and median (minimum-maximum) for continuous variables. HADS, Hospital anxiety depression scale; AR, allergic rhinitis; AA, allergic asthma; CU, chronic urticaria.

Table 4. Summary of Binary Logistic Regression Analysis Predicting the Presence of Irritable Bowel Syndrome in the Study Group

		Univariate		Multivariate	
		OR (95% CI)	*P*	OR (95% CI)	*P*
HADS	Gender (Female)	2.34 (1.3-4.2)	.004	-	-
	Presence of allergic disease	12.5 (4.2-36.6)	.0001	10.2 (3.1-33.8)	.0001
	Anxiety subscale ≥8	9.7 (4.9-19.1)	.0001	-	-
	Anxiety subscale ≥11	15.4 (7.49-31.6)	.0001	13.8 (6.4-29.8)	.0001
	Depression subscale ≥8	7.7 (4.1-14.4)	.0001	-	-
	Depression subscale ≥11	4.5 (2.1-9.7)	.0001	-	-

Data were presented as odds ratio (OR) (95% CI) for all variables. Univariate and multivariate logistic regression analyses were used to evaluate the relationship between categorical and continuous variables and categorical results. HADS, Hospital anxiety depression scale.

Table 5. Association of Gender, Disease Severity, and Hospital Anxiety and Depression Scale Scores of Allergic Patients With Irritable Bowel Syndrome

	IBS Absent (n = 71)	IBS Present (n = 91)	*P* (x^2 Test)
Gender			
Female	35 (49.3%)	65 (71.4%)	
Male	36 (50.7%)	26 (28.6%)	.004
HADS			
Anxiety subscale			
0-7	43 (60.6%)	14 (15.4%)	
≥8	28 (39.4%)	77 (84.6%)	.0001
0-10	63 (88.7%)	28 (30.8%)	
≥11	8 (11.3%)	63 (69.2%)	.0001
Depression subscale			
0-7	49 (69%)	25 (27.5%)	
≥8	22 (31%)	66 (72.5%)	.0001
0-10	62 (87.3%)	60 (65.9%)	
≥11	9 (12.7%)	31 (34.1%)	.002
Disease severity			
AR (n = 56)			
Mild intermittent	4 (16%)	2 (6.6%)	
Mild persistent	12 (48%)	6 (19.3%)	
Moderate-to-severe intermittent	6 (24%)	8 (25.8%)	
Moderate-to-severe persistent	3 (12%)	15 (48.3%)	.015
AA (n = 34)			
Mild	6 (42.9%)	2 (10%)	
Moderate	3 (21.4%)	11 (55%)	
Severe	5 (35.7%)	7 (35%)	.168
CU (n = 72)			
Mild	13 (40.6%)	2 (5%)	
Moderate	4 (12.5%)	7 (17.5%)	
Severe	15 (46.9%)	31 (77.5%)	.001

Data were presented as frequency (percentage) for categorical variables. The chi-square test of independennce was used to analyze the relationship between categorical variables.
IBS, irritable bowel syndrome; χ^2, chi-square test; HADS, Hospital Anxiety Depression Scale; AR: allergic rhinitis; AA, allergic asthma; CU, chronic urticaria.

DISCUSSION

In this study, we aimed to determine the prevalence of Rome IV criteria-defined IBS in patients with AR, AA, and CU and to compare it with controls. We have shown that the prevalence of IBS was increased by 10 times in the presence of allergic diseases, independent from the presence of anxiety, which increased the odds of IBS approximately 14 times. Our second aim was to examine the relationship of IBS with the presence and severity of allergic diseases and accompanying anxiety and depression. We have demonstrated that in all patients and the allergic patient subgroup, HADS anxiety subscale scores of 11 or above were associated with an increase in IBS presence.

Allergic Reactions, Gastrointestinal Diseases, and Irritable Bowel Syndrome

The gastrointestinal system plays a crucial role in immunoregulation. Gut-associated lymphoid tissue (GALT) is a vital part of mucosal-associated lymphoid tissue (MALT), represents most of the entire immune system, and hosts the majority of plasma cells. Several diseases have been identified and defined as gastrointestinal allergy. These diseases include but are not limited to: gastrointestinal anaphylaxis, allergic eosinophilic esophagitis and/or gastroenteritis, food-protein induced enterocolitis and/or proctitis, and oral allergy syndrome. Usually, the underlying pathophysiology is caused by a dysregulation of Treg and Th2 cell subsets, and mainly IgE-mediated, a cell-mediated reaction seldom occurs.[19]

Although epidemiological data show an association between IBS and allergic diseases, data on the basic biological mechanisms are scarce.[6] Current information suggests that the pathogenesis of IBS is complex. Recent studies support the idea that T helper-2 (Th2) lymphocytes, Immunoglobulin E (IgE), and IgE-producing plasma cells and mast cells, which are the effector elements of allergic diseases, play a crucial role in IBS. The increase in mast cells in the ileum and colon and mediators such as histamine and serotonin released from mast cells in IBS may explain the increase in bowel movements and other symptoms.[20-23] In particular, the effect of serotonin on intestinal motility and secretion in the pathogenesis of IBS is well known.[24] Although the pathophysiological role of histamine in IBS is not fully clear, both mediators have been hypothesized to contribute to IBS symptoms by increasing mucosal permeability while affecting both intestinal smooth muscles and enteric neuronal networks. Besides mast cell and mast cell mediators, IgE-mediated reactions may also be associated with IBS in allergic patients. IgE-bearing cells in the gut mucosa were shown to be increased after seasonal inhalant allergen exposure.[25] Furthermore, Fang et al[26] demonstrated that total IgE and house dust mite IgE levels were associated with abdominal bloating

Table 6. Summary of Binary Logistic Regression Analysis Predicting the Presence of Irritable Bowel Syndrome in Allergic Patient Subgroups

		Univariate		Multivariate (all)		Multivariate (AR)		Multivariate (Asthma)		Multivariate (CU)	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
	Gender (female)	2.63 (1.34-5.12)	.004	2.2 (0.62-3.3)	.45	3.84 (0.93-16.6)	.063	-	-		
HADS	Anxiety subscale ≥ 8	8.44 (4.02-17.7)	.0001	-	-	-	-	-	-		
	Anxiety subscale ≥ 11	17.7 (7.49-41.8)	.0001	17.7 (7.49-41.8)	.0001	14.6 (3.3-64.8)	.0001	24.1 (2.5-224.9)	.005	14.5 (3.9-54.5)	.0001
	Depression subscale ≥ 8	5.8 (2.97-11.6)	.0001	1.8 (0.7-4.26)	.17	-	-	-	-	-	-
	Depression subscale ≥ 11	3.55 (1.56-8.1)	.002	-	-	-	-	-	-	-	-
Disease severity	AR (moderate-to-severe persistent)	20 (1.6-247.9)	.02	-	-	-	-	-	-	-	-
	AA (severe)	3 (0.39-22.7)	.28	-	-	-	-	-	-	-	-
	CU (severe)	13.4 (2.68-67.2)	.002	-	-	-	-	-	-	7.9 (1.26-49.3)	.027

Data were presented as odds ratio (OR) (95% CI) for all variables. Univariate and multivariate logistic regression analyses were used to evaluate the relationship between categorical and continuous variables and categorical results. AR, allergic rhinitis, AA, allergic asthma; CU, chronic urticaria; HADS, Hospital Anxiety Depression Scale.

in IBS.[26] Another study also confirmed that an increased level of serum total IgE is associated with a positive relationship with functional gastrointestinal disorder complaints.[27] Pearson et al[28] reported a patient with severe asthma and IBS, which almost entirely disappeared after the administration of IgE monoclonal antibody (omalizumab).[28] Similarly, another case report was published of a patient with chronic urticaria with IBS positively responding to omalizumab treatment.[29] These allergic inflammatory mechanisms in the intestines may explain the link between allergic diseases and IBS.

Although the relationship of IBS with allergic diseases is not known in all aspects, many epidemiological data show that the frequency of IBS increases in allergic diseases such as AR, AA, and CU. In this study, we aimed to show a possible relationship between IBS and allergic diseases. Tobin et al[5] coined the term "atopic IBS" in their prospective study, as they demonstrated that the prevalence of IBS increased with the presence of atopic diseases but not with non-atopic diseases. They demonstrated that patients with atopic diseases (seasonal allergic rhinitis, allergic eczema, and AA) were 3.2 times more likely to meet IBS diagnostic criteria and defined this subgroup of patients as "atopic IBS." Tsiakiris et al[30] investigated functional somatic syndromes' comorbidity, including fibromyalgia, IBS, and migraine, in AR and AA patients. In this study of 164 patients with AA, 298 with AR, and 2.876 controls, the frequency of IBS was 2.3 times higher in patients with AA and 2.8 times higher in AR.[30] Another study reported that the risk of IBS was 2 times higher in patients with AA compared to other pulmonary diseases and healthy controls.[31] A meta-analysis published in 2019 reported a 2-fold increase in IBS in asthmatics and asthma risk increased 2.2-fold in patients with IBS.[32] Similar to AR and AA, the risk of IBS also increased in patients with CU. Fang et al[26] compared 108 atopic patients (49 with AR, 59 with CU) and 74 controls and reported an increase in the frequency of IBS in CU patients compared to controls[26]; and in a database study evaluating 11 271 CU patients, it was shown that the frequency of IBS was 1.86 times higher.[33]

Per our results and the current literature, it can be said that there is meaningful and supportive evidence for the link between IBS and allergic diseases. However, in our study, we failed to show an association between IgE levels with IBS. Moreover, most of the patients in the study were IBS-C rather than IBS-D. These results warrant further study regarding the exact mechanisms underlying atopic IBS.

Anxiety as the Common Link Between Allergic Diseases and Irritable Bowel Syndrome

Anxiety may be another factor explaining the link between IBS and allergic diseases. Numerous reports in the literature show that anxiety, depression, and the inability to cope with stress are more common in allergic diseases and are associated with disease severity in these diseases.[8] Furthermore, a study examining the relationship between IBS, functional dyspepsia, and functional constipation with allergic diseases, anxiety and depression in a cohort of 30 000 primary care records over a 5-year period reported that mood disorders partially explain the association of functional bowel diseases with allergic diseases.[7] In another population-based study of 3542 people, Koloski et al[34] demonstrated asthma and food allergy were associated with IBS, but not independently, after controlling for age, gender, and psychological distress.[34] Therefore, it has been stated that these 3 diseases have 2 overlapping clusters with each other.[7]

In contrast with current literature, we have demonstrated a higher prevalence of IBS in patients with allergic diseases than previously reported. Several factors can explain these results. Prevalence of IBS according to Rome criteria varies based on which Rome criteria is used (III vs IV), the population of the study, country of origin, and method of the questionnaire,[3] with the most recent report in Turkey being 9.8% according to Rome III and 3.9% according to Rome IV criteria, using an internet-based survey.[2] Additionally, Rome IV diagnoses fewer patients than Rome III, but it diagnoses patients with more severe symptoms and higher psychological comorbidity burden.[3,4] These results were further confirmed in another study, with 61.6-87.4% of the study population fulfilling the diagnostic criteria for Rome III also fulfilling the diagnostic criteria of Rome IV. Patients that fulfill the Rome IV criteria also had more severe symptoms, a higher psychological comorbidity burden, and lower quality of life.[35] In addition to these, Rome IV criteria may be diagnosing more allergic patients with IBS, but since this is the first study to use Rome IV criteria to analyze the prevalence of IBS in allergic patients, further studies are needed to confirm if this is the case. Additionally, in our study, IBS prevalence in the control group was 9.3%, which is higher than previously reported. This result can be due to the control group being hospital-dwelling individuals seeking healthcare rather than the average population.

In concordance with these data, we have demonstrated that anxiety increased the risk of IBS approximately 14 times, and independently, the presence of allergic disease increased the risk 10 times. Moreover, in the allergic patient subgroup, anxiety increased the risk of IBS approximately 18 times. Therefore, we propose that the "atopic IBS" disease should be considered as "psycho-atopic IBS."

Due to the study's cross-sectional nature and the patients' use of different treatment regimens for different diseases, we did not have the chance to examine the effects of the drugs used on anxiety, depression, and IBS in detail. Although it is not the primary purpose of our study, a comprehensive study comparing the frequency of allergic diseases in IBS patients admitted to the gastroenterology clinic should focus on further studies.

CONCLUSION

There is a significant relationship between IBS, allergic diseases, and anxiety and depression. As far as we know, in this first study using Rome IV criteria, we observed that the frequency of IBS was higher in allergic patients, especially in patients with anxiety. Allergic inflammation in the intestines due to increased Th2-mediated immune response in allergic diseases may explain the increased frequency of IBS in atopic patients. Anxiety may be another factor explaining the link between IBS and allergic diseases. Awareness of a disease cluster where these 3 groups intersect will guide clinicians from different disciplines involved in patient treatment and follow-up.

Ethics Committee Approval: This study was conducted per the Declaration of Helsinki. Approval for this study was obtained from the Hatay Mustafa Kemal University Medical School Non-Interventional Studies Ethics Committee (Date: January 16, 2020, Approval number: 01/19). Additional approval to carry out the study was gained from the Hatay Provincial Health Directorate Scientific Studies Review Commission.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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