

Association between vasomotor rhinitis and irritable bowel syndrome

Maria Lauriello, M.D.,¹ Alberto Eibenstein, M.D.,¹ Anna Maria Angelone, Ph.D.,² Marina Pasqua, M.D.,³ Cinzia Tucci, M.D.,³ Carla Di Giacomo, M.D.,⁴ Arnaldo Salerno, M.D.,⁵ Giuseppe Frieri, M.D.,² and Marco Fusetti, M.D.¹

ABSTRACT

Background: Vasomotor rhinitis (VMR) and irritable bowel syndrome (IBS) are two of the most widespread pathologies in industrialized countries, and they have a substantial impact on health-related quality of life.

Objective: To investigate the relationship between VMR and IBS to provide evidence to classify VMR and IBS as a sole disorder.

Methods: The study included 150 patients from San Salvatore Hospital, L'Aquila: 50 with VMR, 50 with IBS, and 50 healthy volunteers.

Results: With regard to a probable link between VMR and IBS, 62 patients of the whole population, 150 patients (41.3%) were affected by both VMR and IBS, 33 subjects (22%) were not affected by VMR or IBS, 25 patients (16.67%) only had VMR, and 30 patients (20%) only had IBS. When considering the 87 subjects affected by VMR, 62 of them also had IBS (71.26%). In turn, when considering all 92 subjects with IBS, 62 (67.39%) had VMR. We found a significant association among IBS and nasal obstruction, rhinorrhea, and turbinates, and among VMR and a change in stool consistency and abdominal pain. Among the patients affected by nonallergic rhinitis (NAR), we found a prevalence of NAR with eosinophils (31%) compared with the other cytologic types.

Conclusion: This study expanded the knowledge of the link between VMR and IBS, also the correlation between typical VMR symptoms and IBS, and about the correlation between typical IBS symptoms and VMR. For future implications, the diagnosis of NAR indicated the need to check for the presence of IBS, by using the Rome III criteria, and a diagnosis of IBS indicated the need to check for the presence of VMR. More studies are needed to find the pathogenetic mechanisms to explain the clinical correlation between VMR and IBS as seen in the present study.

(Allergy Rhinol 7:e249–e255, 2016; doi: 10.2500/ar.2016.7.0184)

Vasomotor rhinitis (VMR) represents a global health problem that affects between 10 and 25% of the world population. The impact of the disease is often underappreciated with patients with VMR having a significantly impaired health-related quality of life. Furthermore, the disease has a profound socioeconomic impact.¹ Patients with irritable bowel syndrome (IBS) have lower work productivity and higher absenteeism; they take more medications; and require more physician visits, diagnostic tests, and hospitalizations compared with patients without IBS and of the same age.² Due to the fluctuating nature of the symptoms, it is difficult to discriminate truly incidental cases from

cases that represent just a flare up of the disease, especially in studies with only a short follow-up.³ The prevalence of IBS varies considerably, depending on the criteria applied. Prevalence estimates of IBS in North America range from 5 to 10%.⁴

Both conditions are characterized by a common autonomic dysfunction of nociceptive nerve sensors and by a neurogenic inflammation,^{5–33} but, because alterations of an autonomic system may occur in several organs, we wanted to study a relationship between VMR and IBS. Baraniuk indicated that nonallergic rhinitis (NAR) is only one part of a large pattern of autonomic and other mucosal organ dysfunction syndromes, e.g., gastroesophageal reflux, asthma, and IBS.²⁸ The aims of our study were to point out the link between VMR and IBS, and also the correlations between typical VMR symptoms (e.g., rhinorrhea and nasal obstruction) and IBS, and, moreover, the correlations between typical IBS symptoms (e.g., diarrhea and constipation and VMR). A further objective was to make a diagnosis of NAR subtypes by nasal cytology. With the aim of explaining the significant association between VMR and IBS, we hypothesize a multiple mucosal hyperresponsiveness to several stimuli.

From the ¹Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, ²Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy, ³Specialty School of ENT, University of L'Aquila, L'Aquila, Italy, ⁴Specialty School of Gastroenterology, University of L'Aquila, L'Aquila, Italy, and ⁵Specialty School of General Surgery, University of Florence, Florence, Italy

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Marina Pasqua, M.D., Department of Life, Health and Environmental Sciences, Università degli Studi dell'Aquila, Via Oliviero Evangelista, 20, L'Aquila, 67100, Italy

E-mail address: marina.pasqua86@gmail.com

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Table 1 Characteristics of patients

	ENT Group, Mean ± SD	GD, Mean ± SD	Healthy Group, Mean ± SD	<i>p</i>
Age, y	38.2 ± 15.3	39.7 ± 14.7	40.8 ± 14.6	0.6174
BMI, kg/m ²	24 ± 4	23.71 ± 3.4	24.9 ± 3.4	0.1926

ENT = Ear Nose and Throat; GD = Gastroenterology Department; SD = standard deviation; BMI = body mass index.

Table 2 Synthesized descriptive analysis

Clinical Characteristics	ENT, no. (%)	GD, no. (%)	Controls, no. (%)
Periodic obstruction	8 (16)	18 (36)	6 (12)
Alternating obstruction	6 (12)	5 (10)	9 (18)
Persistent obstruction	36 (72)	15 (30)	3 (6)
No obstruction	—	12 (24)	—
Persistent rhinorrhea	35 (70)	7 (14)	1 (2)
Periodic rhinorrhea	15 (30)	22 (44)	10 (20)
No rhinorrhea	—	21 (42)	39 (78)
Normal turbinates	—	7 (14)	33 (66)
Hypertrophic turbinates	50 (100)	14 (28)	7 (14)
Hyperemic turbinates	—	17 (34)	6 (12)
Pale turbinates	—	12 (24)	4 (8)
Change in stool consistency	31 (62)	33 (66)	6 (12)
Abdominal pain for at least 3 days a month in 3 months	33 (66)	50 (100)	9 (18)
Abdominal pain for at least 90 days in 1 year	23 (46)	38 (76)	9 (18)
Mucus in stool	10 (20)	18 (36)	4 (8)
IBS-D	16 (32)	18 (36)	1 (2)
IBS-C	6 (12)	9 (18)	2 (4)
IBS-M	11 (22)	23 (46)	6 (12)

ENT = Ear Nose and Throat Department; GD = Gastroenterology Department; IBS-D = irritable bowel syndrome with diarrhea; IBS-C = irritable bowel syndrome with constipation; IBS-M = irritable bowel syndrome-mixed.

METHODS

A total of 150 subjects were recruited consecutively for this study, from April 2013 to September 2014, after obtaining informed consent: 50 patients with VMR (male-to-female ratio, 1:1) from the Ear Nose and Throat department of San Salvatore Hospital, L'Aquila; 50 patients with IBS (male-to-female ratio, 1:1) from the gastroenterology department of San Salvatore Hospital, L'Aquila; and 50 otherwise healthy volunteers (male-to-female ratio, 1:1) (Table 1). The inclusion criteria were diagnosis of VMR or IBS, and negative responses to skin-prick tests. The exclusion criteria were smoking and any other acute or chronic nasal and/or gastroenteric disease. All the subjects had to answer an examiner-guided questionnaire about their clinical history and nasal symptoms. They then had nasal fibroscopy and nasal cytology. We classified NAR subtypes by nasal cytology. Furthermore, all the subjects had to answer an examiner-guided questionnaire about the IBS, validated by the Roma III criteria.³⁴

Statistical Analysis

Descriptive analyses were conducted for all variables: habit characteristics, IBS symptom duration, the presence of mucus in the stool, nasal obstruction, rhinorrhea, and hyperemic and/or hypertrophic turbinates. The Shapiro-Wilk normality test was used for continuous variables to decide parametric or nonparametric tests in data analysis. For comparison of continuous variables in the three independent groups, the mean comparison test, analysis of variance, was used when the variables had normal Gaussian distribution, and the Kruskal-Wallis test for median comparison was used when the variables did not reach Gaussian distribution. A logistic regression univariate model was performed when VMR disease, IBS, and both were independently associated with symptoms. The variables nasal obstruction, rhinorrhea, and turbinates were dichotomized. The presence of obstruction included the persistence, periodicity, and presence or absence of symptomatology. The variable rhinorrhea in-

Table 3 Estimated associations expressed with OR (95% CI), and a value $p < 0.05$ was considered

	VMR+		IBS+		Both VMR and IBS	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Obstruction	7.07 (2.88–17.34)	0.00	5.57 (2.35–13.2)	0.00	10.6 (3.74–30.36)	0.00
Rhinorrhea	14.2 (5.32–38.03)	0.00	8.48 (3.29–21.85)	0.00	15.4 (5.43–44.03)	0.00
Turbinates	21.6 (–7.59 to 61.41)	0.00	12.75 (4.69–34.64)	0.00	23.4 (7.68–71.27)	0.00
Change in stool consistency	3.80 (1.06–13.65)	0.04	6.14 (1.74–21.63)	0.00	4.76 (1.29–17.48)	0.01
Abdominal pain for 3 days a month in 3 months	12.4 (4.33–35.71)	0.00	23.02 (7.80–67.93)	0.00	23.3 (7.45–73.04)	0.00
Abdominal pain for 90 days in 1 y	6.89 (2.43–19.52)	0.00	8.71 (3.08–24.63)	0.00	9.49 (3.21–28.02)	0.00
Mucus in stool	4.04 (0.88–18.50)	0.07	6.43 (1.43–28.81)	0.01	4.94 (1.05–23.15)	0.04

OR = Odds ratio; CI = confidence interval; VMR = vasomotor rhinitis; + = presence of disease; IBS = irritable bowel syndrome.

cluded periodic or persistent symptoms. Turbinates were considered positive if they were hypertrophic and/or hyperemic (Table 2). Estimated associations were expressed by using odds ratio (OR) with 95% confidence intervals (CI), and a value of $p < 0.05$ was considered. Statistical analysis was performed by using the statistical package Stata/IC 12.1 (StataCorp LP, College Station, TX) (Table 3).

Informed Consent

The participants were given a consent form and were informed about the study and the standard of anonymization. The University of L'Aquila certified that the project study, to the best of its knowledge, qualified as an exempt study limited to the collection of clinical data and that the study had no more than minimal risk.

RESULTS

No significant differences were recorded among the study groups with regard to age and body mass index. With regard to a probable link between VMR and IBS, 62 patients of the whole population, 150 patients (41.3%) had both VMR and IBS, 33 subjects (22%) did not have VMR or IBS, 25 patients (16.67%) had only VMR, and 30 patients (20%) had only IBS. When considering the 87 subjects with VMR, 62 also had IBS (71.26%). When considering all the 92 subjects with IBS, 62 (67.39%) of these patients had VMR. We found a significant association between VMR and IBS (OR 2.73 [95% CI, 1.38–5.37]; $p = 0.004$) (Table 4).

Nasal Obstruction

We confirmed a significant association between VMR and nasal obstruction (OR 7.07 [95% CI, 2.88–17.34]; $p = 0.001$). Furthermore, nasal obstruction was significantly associated with IBS (OR 5.57 [95% CI,

Table 4 Patients with VMR, IBS, and both

	Patients with VMR+	Patients with VMR–	Patients, Total
IBS+	62	30	92
IBS–	25	33	58
Total	87	63	150

VMR = Vasomotor rhinitis; IBS = irritable bowel syndrome; + = with VMR; – = without VMR.

2.35–13.2]; $p = 0.001$) and to both diseases (OR 10.6 [95% CI, 3.74–30.36]; $p = 0.001$) (Fig. 1).

Rhinorrhea

A significant association between VMR and rhinorrhea was confirmed (OR 14.2 [95% CI, 5.32–38.03]; $p = 0.001$). Moreover, a significant association between IBS and rhinorrhea (OR 8.48 [95% CI, 3.29–21.85]; $p = 0.001$) and this symptom and both diseases (OR 15.47 [95% CI, 5.43–44.03]; $p = 0.001$) was demonstrated (Fig. 2).

Turbinates

Hyperemic and/or hypertrophic turbinates were significantly associated with VMR (OR 21.6 [95% CI, 7.59–61.41]; $p = 0.001$), IBS (OR 12.75 [95% CI, 4.69–34.64]; $p = 0.001$), and both diseases (OR 23.4 [95% CI 7.68–71.27]; $p = 0.001$).

Change of Stool Consistency

A change in stool consistency was significantly associated with IBS (OR 6.14 [95% CI, 1.74–21.63]; $p = 0.004$), the present study has demonstrated that this symptom was significantly associated with VMR (OR 3.80 [95% CI, 1.06–13.65]; $p = 0.04$) and both diseases (OR 4.76 [95% CI, 1.29–17.48]; $p = 0.01$).

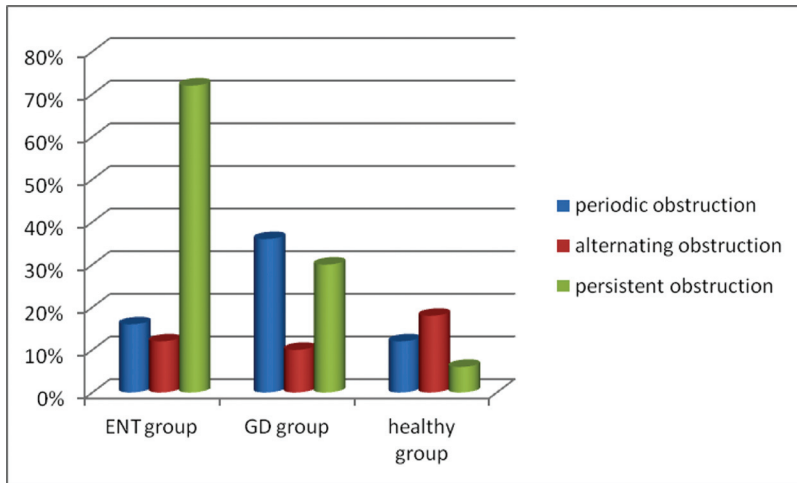


Figure 1. Association of vasomotor rhinitis (VMR) and irritable bowel syndrome (IBS), and of both diseases with nasal obstruction.

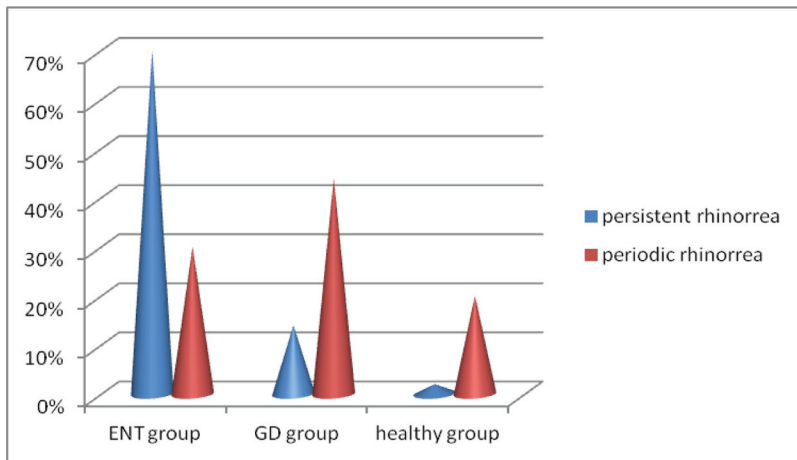


Figure 2. Association of vasomotor rhinitis (VMR) and irritable bowel syndrome (IBS), and of both diseases with rhinorrhea.

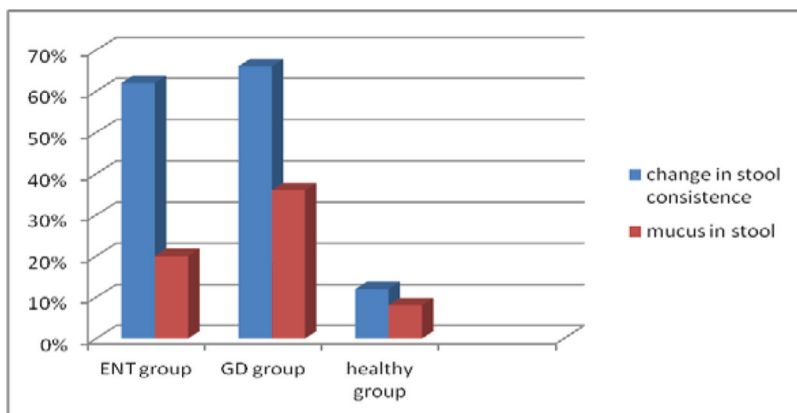


Figure 3. Association of vasomotor rhinitis (VMR) and irritable bowel syndrome (IBS), and of both diseases with change in stool consistency and mucus in stool.

Mucus in the Stool

A significant association was confirmed between IBS and mucus in the stool (OR 6.43 [95% CI, 1.43–28.81]; $p = 0.01$) as well as with IBS and VMR (OR 4.94 [95% CI, 1.05–23.15]; $p = 0.04$) (Fig. 3).

Abdominal Pain for at least 3 Days a Month in 3 Months

Results of the present study confirmed a significant association between abdominal pain at least 3 days a

month in 3 months and IBS (OR 23.02 [95% CI, 7.80–67.93]; $p = 0.001$). Moreover, a significant association was also demonstrated between abdominal pain at least 3 days a month in 3 months and VMR (OR 12.44 [95% CI, 4.33–35.71]; $p = 0.002$) as well as with VMR and IBS (OR 23.33 [95% CI, 7.45–73.04]; $p = 0.004$).

Abdominal Pain for at Least 90 Days in 1 Year

A significant association between IBS and abdominal pain for at least 90 days in 1 year was confirmed (OR

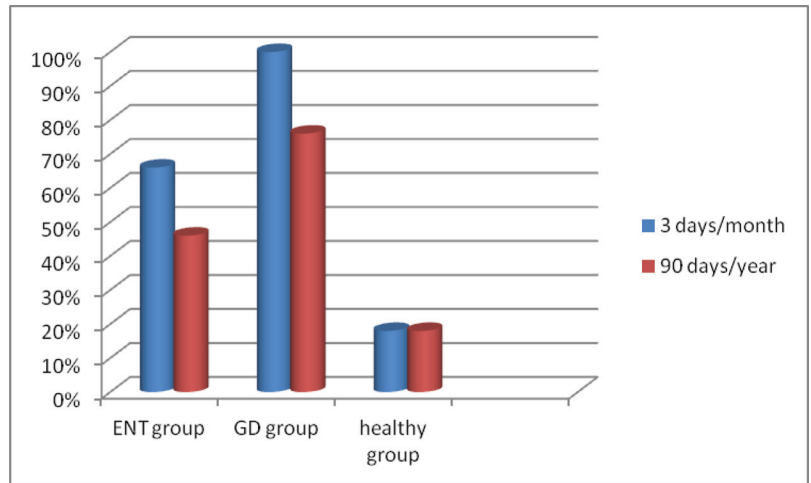


Figure 4. Association of vasomotor rhinitis (VMR) and irritable bowel syndrome (IBS), and of both diseases with abdominal pain.

8.71 [95% CI, 3.08–24.63]; $p = 0.003$). Furthermore, we have demonstrated a significant association between this IBS characteristic with VMR (OR 6.89 [95% CI, 2.43–19.52]; $p = 0.01$) with and with both diseases (OR 9.49 [95% CI 3.21–28.02]; $p = 0.003$) (Fig. 4). When considering all 150 subjects, 87 (58%) had NAR. All patients had a cell-mediated NAR, which was assigned to the type infiltrated by neutrophils (NAR with neutrophils, 27%), by eosinophils (NAR infiltrated by eosinophils [NARES], 31%), by mast cells (NAR with mast cells, 19%), and by both eosinophils and mast cells (NAR with eosinophils and mast cells [NARESMA], 23%) (Table 5).

DISCUSSION

VMR comprises ~71% of NAR. VMR represents a global health problem that affects between 10 and 25% of the world population. The impact of the disease is often underappreciated with patients with VMR and results in significantly impaired health-related quality of life. Furthermore, this disease has a profound socioeconomic impact with direct medical costs and considerable indirect costs that relate both to absence from work and school, and reduced productivity.¹ Also, IBS has a high prevalence that ranges, for example, in North America, from 5 to 10%.⁴ Patients with IBS have lower work productivity and higher absenteeism; they take more medications; and require more physician visits, diagnostic tests, and hospitalizations compared with patients of the same age and without IBS.²

In the present study, a clinical relationship between VMR and IBS was demonstrated. The primary objective of our study was to investigate the link between VMR and IBS. We identified the presence of IBS symptoms in patients with VMR. In our study, the results indicated a significant association between VMR and abdominal pain for at least 3 days a month in 3 months as well as between VMR and abdominal pain for at least 90 days in 1 year. Furthermore, a significant as-

sociation between VMR and a change in stool consistency was observed. Interestingly, we identified the presence of nasal symptoms in patients with IBS: a significant association between IBS and nasal obstruction, between IBS and rhinorrhea, and between IBS and hyperemic and/or hypertrophic turbinates was observed. A significant association with nasal obstruction, rhinorrhea, hyperemic and/or hypertrophic turbinates, a change in stool consistency, pain for at least 3 days a month in 3 months, and pain for at least 90 days in 1 year was detected in patients with both diseases.

The clinical association between VMR and IBS found in the present study, according to Baraniuk,²⁸ were shown by different studies with physiologic and pathologic correlations; there are studies that report neurogenic inflammation and autonomic dysfunction in both VMR⁵ and IBS.^{6,7} Increased nociceptive C-fiber activity may lead to nasal dysfunction in idiopathic rhinitis⁸: neuropeptides (*i.e.*, substance P and neurokinin A, calcitonin gene-related peptide, and gastrin-releasing peptide) are released from C-fibers by antidromic stimulation, which produces a localized increase in vascular permeability and nasal secretion.^{9,10} Central nervous system communication with the gut is mediated through the sympathetic and parasympathetic pathways of the autonomic nervous system by modulation of the enteric nervous system as well as *via* the hypothalamic-pituitary-adrenal axis. Activation of the axis takes place in response to both physical and psychological stressors,¹¹ both of which have been implicated in the genesis of IBS.¹²

The high prevalence of IBS in NAR is important because of correlations of IBS subtypes with specific abnormalities in the enteric serotonin (5-HT) and dopamine systems as well as central pain, sympathetic autonomic, and parasympathetic autonomic nervous system.³⁰ The molecular defects of these syndromes may provide insight into potential subsets of NAR.^{31,32}

Table 5 NAR subtypes for each group

	ENT, no. (%)	GD, no. (%)	Controls, no. (%)
NARES	15 (30)	9 (31)	3 (37.5)
NARNE	12 (24)	9 (31)	2 (25)
NARESMA	12 (24)	6 (21)	2 (25)
NARMA	11 (22)	5 (17)	1 (12.5)

NAR = Nonallergic rhinitis; ENT = Ear Nose and Throat Department; GD = gastroenterology department; NARES = NAR infiltrated by eosinophils; NARNE = NAR with neutrophils; NARESMA = NAR with eosinophils and mast cells; NARMA = NAR with mast cells.

Potential of 5-HT release and activation of 5-HT_{1P} or 5-HT₃ receptors have been linked to diarrhea-predominant IBS. Conversely, reduced release of 5-HT, desensitization of 5-HT₄ prokinetic receptors, and reduced dopaminergic function have been implicated in constipation-predominant IBS.

The expression of transient receptor potential vanilloid 1 (TRPV1) has been found enhanced in upper airway hyperresponsiveness.¹⁵⁻¹⁸ Van Rijswijk *et al.*¹⁹ note that repeated nasal provocation with capsaicin could significantly reduce nasal symptoms in patients with idiopathic rhinitis, which indicates either C-fiber desensitization, degeneration, or TRPV1 inactivation. Increased expression of the TRPV1 protein was demonstrated in mucosal nerve fibers of patients with IBS, which correlate with their pain symptom severity.²⁰ Keszthelyi *et al.*²¹ postulated that postinflammatory upregulation of the TRPV1 receptor through increased biosynthesis in the nerve terminals of mucosal afferents, which resulted in increased nociceptive sensitivity, represented a mechanism potentially responsible for such sustained effect.

When studying chronic pain, Dray *et al.*²² noticed that cytokines, including interleukin (IL) 1, IL-6, IL-8, IL-11, and tumor necrosis factor α , may induce hyperalgesia by acting *via* a common final pathway mediated by the induction of nerve growth factor from fibroblasts, keratinocytes, and neural Schwann cells, which may increase neural sensitivity to inhaled irritant factors. Administration of substance P to human nasal mucosa *in vitro* can increase cytokine expression.²³ Significantly increased levels of some proinflammatory cytokines, such as tumor necrosis factor α , IL-1 β , and IL-6, were reported in patients with IBS.²⁴ Dinan *et al.*²⁵ reported that the serum concentrations of the proinflammatory cytokines IL-6 and IL-8 were elevated in all IBS subgroups (diarrhea predominant, constipated, and alternated periods with diarrhea and constipation).

The discrimination between saprophytes- and foreign pathogens is mainly mediated by a family of

receptors, termed pattern recognition receptors, which interact with specific ligands of the invading hosts (pathogen-associated molecular proteins).²⁶ Pattern recognition receptors are mainly expressed by epithelial cells, antigen-presenting cells, regulatory T cells, and other cells involved in the interaction between the immune system and the environment.²⁷⁻²⁹ Toll-like receptors (TLR) represent the major family of pattern recognition receptors. TLR activation triggers a cascade of reactions, which lead to increased expression of proinflammatory genes.³⁰ Lauriello *et al.*²⁵ pointed out that, in VMR, both TLR4 and TLR9 seemed to be significantly downregulated.⁸⁻³¹ Results of biopsy study²⁶ indicate that the expression of the TLR family is altered in IBS. TLR4 was increased in colonic mucosal biopsy specimens from patients with IBS compared with healthy controls.^{32,33}

Also, we studied nasal cytology to make a diagnosis of NAR subtypes. All 87 patients with VMR were subdivided into NAR with neutrophils (27%), NARES (31%), NAR with mast cells (19%), and NARESMA (23%), and we found a predominance of NARES compared with the other cytologic types. The increased incidence of NAR with neutrophils was linked to physical and chemical aggression of the mucosa because the individuals most affected are factory workers, inhabitants of industrialized centers, and heavy smokers. The persistence of neutrophils and the release of chemical mediators (neutrophil elastase) are the main cause of formation of free radicals and consequent suffering mucosal epithelium. Patients with NARESMA and NARES had the worst quality of life.³⁵ Patients with NARESMA had a more-intense impairment of dry nose, snoring, and sore throat, whereas patients with NARES showed more-severe postnasal drip.

CONCLUSION

This study demonstrated the link between VMR and IBS. In particular, it showed a significant presence of typical VMR symptoms (*e.g.*, rhinorrhea and nasal obstruction) in patients with IBS as well as typical IBS symptoms (*e.g.*, diarrhea and constipation) in patients with VMR. This strong association can be explained when considering a common pathophysiologic pathway such as a chronic neurogenic inflammation. As future implications, the diagnosis of NAR suggests a need to check for the presence of IBS (by using the Rome III criteria²), and the diagnosis of IBS indicates the need for evaluation of nasal symptoms and to perform nasal cytology with the aim of classifying the type of NAR. More studies are mandatory to find out the pathogenetic mechanisms to explain the strong clinical correlation between VMR and IBS as indicated in the present study.

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