Secretor Status and Anxiety Are Risk Factors for Getting Irritable Bowel Syndrome

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حالة الإفراز والقلق
من عوامل الخطر للاصابة بمتلازمة القولون العصبي

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Abstract

Irritable Bowel Syndrome (IBS) is a functional disease of gastrointestinal tract (GIT) that affects 10-20% of the population worldwide and is distinguished by abdominal pain/discomfort and changes in bowel habits that is accompanied by diarrhea, constipation, or both. Control-based study was conducted on 50 Iraqi patients with IBS who were presented at private clinics for gastrointestinal diseases (GIDs), along with 20 healthy individuals matched in their age and gender to act as control group. The study lasted from November 2021 to May 2022 and aimed to determine the frequency of IBS subtypes among Iraqi patients, as well as the influence of several factors on disease's initiation, type and severity such as age and gender, anxiety, obesity, hematological indices, and secretor status. In comparison with control group, patients showed significant higher frequency of severe anxiety and non-secretor cases particularly in those with IBS-c type. However, BMI, blood groups, and all complete blood count parameters revealed non-significant difference between patients and control groups. Among patients of different types of IBS, results showed that blood group A is highly correlated with IBS-d, and IBS-m patients, while blood type O is highly correlated with IBS-c. Also, platelet-lymphocyte ratio (PLR) is significantly associated with IBS types, which is elevated in patients with IBS-c in comparison with other types of disease. It can be concluded that people who are non-secretors and having experience of severe anxiety may be at higher risk for getting IBS.

Keywords: Anxiety, BMI, IBS, Non-secretor, PLR

المستخلص

متلازمة القولون العصبي (IBS) هو مرض وظيفي في الجهاز الهضمي (GIT) يصيب 20-10٪ من السكان في جميع أنحاء العالم ويتميز بألم / انزعاج في البطن وتغيرات في عادات الأمعاء المصحوبة بالإسهال أو الإمساك أو عليهما. أجريت دراسة قائمة على التحكم على 50 مريضًا عراقيًا مصابًا بمتلازمة القولون العصبي والذين تم تقديمهم إلى عيادات خاصة لأمراض الجهاز الهضمي (GIDS) ، إلى جانب 20 فردًا سليمًا مطابقين في العمر والجنس ليكونوا مجموعة تحكم. استمرت الدراسة من نوفمبر 2021 إلى مايو 2022 وهدفت إلى تحديد تواتر الأنواع الفرعية لمتلازمة القولون العصبي بين المرضى العراقيين ، بالإضافة إلى تأثير العديد من العوامل على بدء المرض ونوعه وشدته مثل العمر والجنس والقلق والسمنة ومؤشرات الدم وحالة الإفراز. بالمقارنة مع مجموعة التحكم ، أظهر المرضى تواترًا أعلى بكثير من القلق الشديد وحالات عدم الإفراز خاصة في أولئك الذين يعانون من النوع C من متلازمة القولون العصبي. ومع ذلك، كشف مؤشر كتلة الجسم وفصائل الدم وجميع معايير تعداد الدم الكامل عن وجود فروق غير مهمة بين المرضى ومجموعات المراقبة. بين مرضى أنواع مختلفة من القولون العصبي، أظهرت النتائج أن فصيلة الدم A ترتبط ارتباطًا وثيقًا بمرضى القولون العصبي من النوع d و BS-m]، في حين أن فصيلة الدم 0 ترتبط ارتباطًا وثيقًا بمرضى القولون العصبي من النوع C. أيضًا، ترتبط نسبة الصفائح الدموية إلى الخلايا الليمفاوية بشكل كبير بأنواع القولون العصبي، والتي ترتفع لدى مرضى القولون العصبي من النوع ع مقارنة بأنا)) أخرى من الأمراض. يمكن أن نستنتج أن الأشخاص الذين لا يفرزون الصفائح الدموية ولديهم خبرة في القلق الشديد قد يكونون أكثر عرضة للإصابة بالقولون العصبي.

الكلمات المفتاحية: حالات الافراز، القلق، الاصابة بالقولون العصبي

Introduction

The irritable bowel syndrome (IBS) is a functional gastrointestinal tract (GIT) disorder that affects 10% to 20% of the population and is characterized by abdominal pain/discomfort, as well as changes in bowel habits. The natural history of the condition is relapse and recovery (Giuseppe *et al.,* 2020). Anxiety in general people is widespread with IBS, and it is linked to a worsening of GIT symptoms. Adults with IBS have significant rates of anxiety and depression, which may be linked to visceral hyperalgesia and autonomic nervous system dysfunction (Black *et al.,* 2020). Furthermore, fresh evidence reveals that in around two-thirds of IBS cases, psychological distress develops after the beginning of GIT symptoms (Pimentel and Lembo, 2020). On the other hand, people can all be classed as "secretors" or "non-secretors" depending on their capacity to secrete ABO blood group antigens in body fluids (Kim *et al.,* 2002). According to the presence or lack of A, B, and H antigens on the surface of RBCs, the ABO system separates blood types into A, B, AB, and O (Yazer, 2005). In the fluids, the "O" blood type secretes just H element, both A and H substances are secreted by blood group "A", and both B and H substances are secreted the blood group "B" (Kim *et al.,* 2002; Yazer, 2005). Approximately 80% of the population is secretors, meaning they secrete H-substance regardless of their ABO blood group (Ndeh *et al.,* 2022). ABH secretions are regulated by the fucosyltransferase-2 secretor gene, which is found on the short arm of chromosome 19 and has two alleles: dominant "Se" and recessive "se." (Se Se) and (Se se) have a dominant secretor phenotype in their inheritance pattern, whereas (se se) has a recessive non-secretor phenotype. As a result, secretes blood group "O" only material H in the fluids, while secretes blood group "A" both substances A

and H, and secretes blood group "B" both substances B and H (Smart and Armstrong, 2008; Kazmi, 2019). Accordingly, the present study is aimed to investigate whether the hematological indices, anxiety, and secretor status in Iraqi people can act as risk factors for getting IBS.

Materials and Methods

Case-control study was carried out on 50 Iraqi patients with IBS and 20 normal individuals who were matched in age and gender to the patients to act as the control group during the seven months from November 2021 to May 2022. All patients (males and females) with IBS were collected from private clinics specialized in GIDs in Baghdad / Iraq, while those in control group were collected from educational institutions and from outside the framework of private clinics. The height and weight of all subjects are measured to calculate body mass index (BMI). Blood samples are obtained from all subjects to determine many parameters including blood groups, complete blood count (CBC). Saliva samples also are obtained from all subjects to determine their secretor status (Bercher, 2005). All subjects (patients and control) determined their degree of anxiety by using the Generalized Anxiety Disorder Assessment (GAD-7). Body mass index (BMI) was calculated from dividing the body weight (in kg) by the square height (in meter), so its unit is kg/m2. The hemagglutination slide method was used to determine blood groups based on the ABO and Rh systems (Rowley *et al.,* 2012). WBCs, RBCs, Hb, PLT, Granulocyte, Monocyte, and Lymphocyte are measured immediately and in different percentages by the Samsung analyzer (Koepke, 1991), while platelets-lymphocyte ratio (PLR) was calculated from dividing platelet count by absolute count of lymphocyte.

Results

Several parameters were investigated in two groups of subject; the first group includes 50 patients with different types of IBS, while the second group includes 20 normal subjects to act as control group. Table-1 shows that gender and age of subjects in both groups are matched and without significant difference.

Table-1: Matched age and gender in patients and control groups

Character		Patients (n=50)	Control (n=20)	P value
Age (year)	Range	20 - 70	20 – 60	1.0
	M ± SD	33.1 ± 13	33 ± 10.3	
Gender (n, %)	Female	33 (66%)	12 (60%)	0.636
	Male	17 (34%)	8 (40%)	

Among all factors of questioners list, only anxiety score reveals significant difference ($P < 0.0001$) between patients and control groups. Figure-1 shows that the majority of patients (64%) suffer from severe anxiety, while the most subjects in control group (75%) have mild anxiety. This result indicates that anxiety score may act as risk factor for getting IBS.

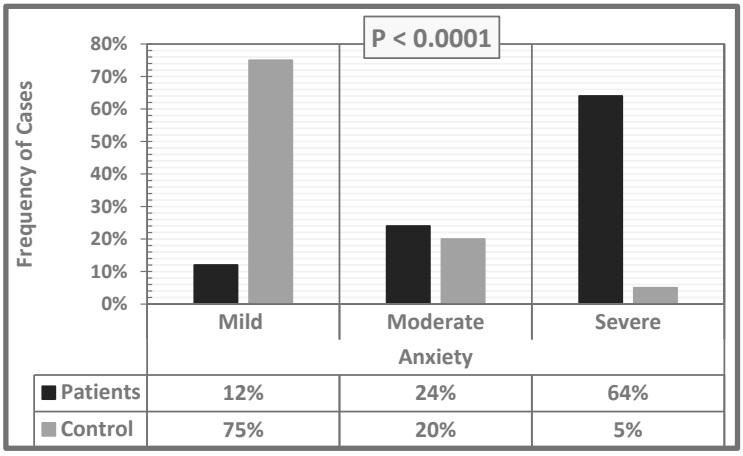

Figure-1: Anxiety categories in patients and control groups.

Table-2 shows non-significant difference in the BMI between patients (27.7 ± 5.6 Kg/m2) and control group (26.2 ± 3.9 Kg/m2). By calculating the frequency of cases with different categories of BMI, Figure-2 also shows non-significant difference between two groups, in which only 24% and 20% of cases are obese in patients and control groups respectively.

Table-2: Body mass index (BMI) in patients and control groups

Parameter	Patients	Control	P value
Weight (Kg)	76.2 ± 15.3	73.2 ± 14.4	0.452
Height (m)	1.65 ± 0.09	167 ± 0.1	0.664
BMI (Kg/m2)	27.7 ± 5.6	26.2 ± 3.9	0.275

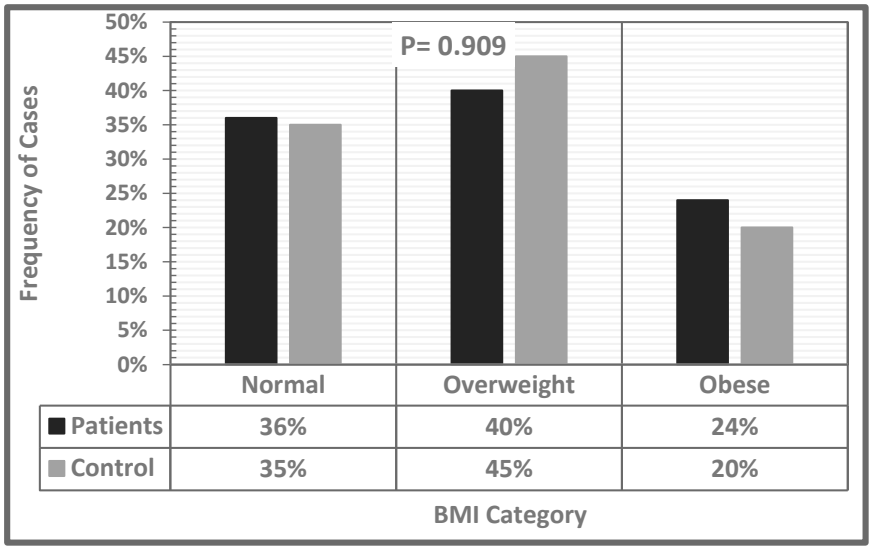

Figure-2: Frequency of cases with different categories of BMI in patients and control groups.

According to the ABO system, Figure-3 shows a non-significant difference in the distribution of A, B, AB, and O blood groups between

patients and control groups. This figure also shows the non-significant difference in the distribution of positive and negative groups based on the Rh system, and Rh +ve group is the most common in both groups (90%, and 85% respectively).

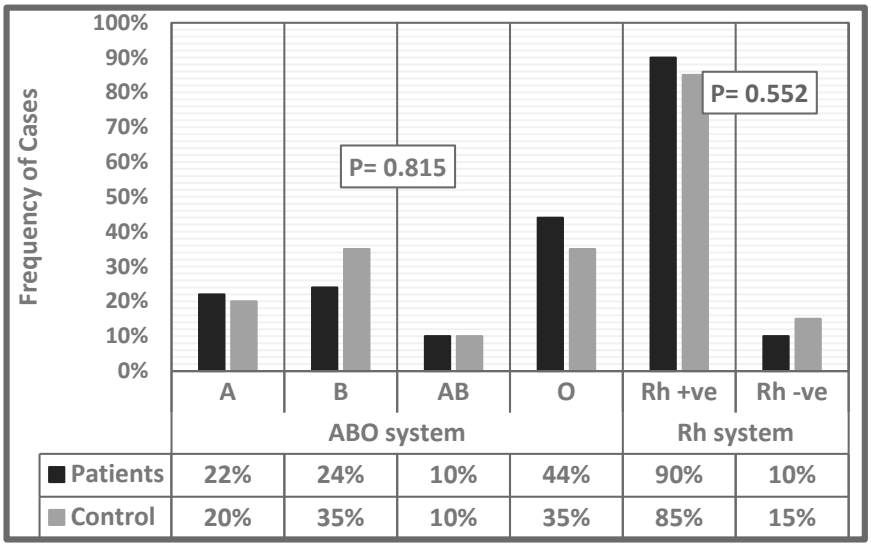

Figure-3: Distribution of blood groups in patients and control groups based on ABO and Rh systems

The values of RBCs count, hemoglobin content (Hb), hematocrit (Hct), as well as all RBCs indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and RBC distribution width (RDW) in both groups are within their normal range and without significant difference between patients and control groups (Table-3).

Table-3: The values of RBCs indices in patients and control groups

RBCs indices		Normal range	Patients (n=50)	Control (n=20)	P value
Count (x106/µl)	M	4.2 - 5.9	5 ± 0.6	4.9 ± 0.5	0.843
	F	3.5 - 5.5	4.3 ± 0.5	4.2 ± 0.7	0.641
Hb (g/dl)	M	13.2 - 16.5	14.3 ± 1.4	13.8 ± 1.5	0.439
	F	11.5 - 15.5	11.9 ± 1.3	12.1 ± 1.5	0.778
Hct (%)	M	40 - 50	43.8 ± 4.1	42.1 ± 4	0.332
	F	36 - 48	36.4 ± 4	36 ± 6	0.710
MCV (fl)		80 - 97	86.2 ± 6.6	84.7 ± 5.1	0.377
MCH (pg)		27 - 31	28.2 ± 2.4	27.5 ± 2.3	0.245
MCHC (g/dl)		32 - 36	32.7 ± 1.1	32.5 ± 1.2	0.395
RDW (%)		11.5 - 14.5	13.8 ± 1.9	14.3 ± 1.3	0.283
M= male; F= female					

The total and differential counts of WBCs in both groups are within their normal range and without significant difference between patients and control groups as shown in Table-4.

Table-4: Total and differential count of WBCs in patients and control groups

WBCs count (x103/µl)	Normal range	Patients (n= 50)	Control (n=20)	P value
Total	4 - 11	6.9 ± 1.7	6.6 ± 2.5	0.437
Granulocyte	2 – 7.8	4.2 ± 1.3	4 ± 1.9	0.561
Lymphocyte	1 – 4.1	2.2 ± 0.7	2 ± 0.6	0.169
Monocyte	0.2 – 0.8	0.49 ± 0.21	0.57 ± 0.22	0.171

The values of platelets count and their indices such as mean platelet volume (MPV), platelet distribution width (PDW), platelet crit (Pct), and platelet-lymphocyte ratio (PLR), all of them in both groups are within their normal range and without significant difference between patients and control groups as shown in Table-5.

Table-5: Platelet indices in patients and control groups

Platelet's indices	Normal range	Patients (n= 50)	Control (n= 20)	P value
Count (x 103/µl)	150 - 450	247 ± 58	242 ± 49	0.690
MPV (fl)	7.2 – 11.7	9.3 ± 1.1	8.8 ± 0.9	0.058
PDW (%)	9 – 17	13.8 ± 2.4	13.2 ± 2.6	0.399
Pct (%)	0.20 – 0.24	0.22 ± 0.06	0.21 ± 0.04	0.359
PLR	NA	114 ± 40	129 ± 38	0.161

Based on a 95% confidence interval (95% CI), the normal range of non-secretors' proportion in the general population is 0.13 up to 0.29. Figure-4 shows that 16/50 are non-secretors in the patient's group with a proportion of 0.32, which is significantly higher than the upper limit of normal range, while only 5/20 are non-secretors in the control group with a proportion of 0.25, which is within the normal range.

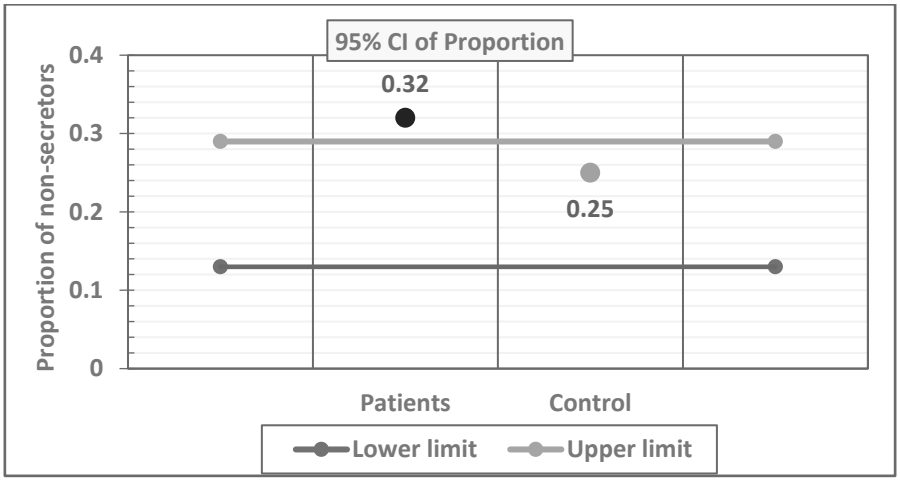

Figure-4: Proportion of non-secretors in patients and control group based on 95% confidence interval.

Discussion

It is well known that IBS patients have experience of severe anxiety when coincided with GAD-7. Lee *et al.* (2009) revealed a probable link between IBS and some psychiatric diseases and that IBS and GAD are linked to both symptoms and disease. Also, several studies reported a high presence of anxiety in IBS patients compared to healthy people who was also significantly associated with poor quality of life (QOL) (Lee *et al.,* 2017; Üçüncü *et al.,* 2020; Rijnaarts *et al.,* 2021). It is suggested that stress stimulates mucosal neuroendocrine secretion, autonomic efferent neurons, and afferent neuron sensitization, resulting in GIT motility problems and visceral hypersensitivity leading to worsening the brain-gut connection (Kosako *et al.,* 2018). As a result, serotonin indirectly impacts the occurrence of systemic illnesses in IBS patients via brain-gut interactions because the central nervous system has a considerable effect on blood flow, secretion, and motility of GIT, so emotions (fear, anger, and anxiety), unpleasant stimuli, and physical stress can all cause stomach emptying and intestinal transit to be delayed (Mayer, 2000). Recent studies suggested that the displacement of bacteria as a result of changing the secretion of the mucous membrane and the function of the barrier causes discomfort in the GIT and thus causes anxiety and depression (Kosako *et al.,* 2018; Niewinna *et al.,* 2020).

Comparing these findings with those attained by other researchers, the majority of previous studies found no link between BMI and the risk of IBS (Guo *et al.,* 2014; Arasteh *et al.,* 2018; Akhondi *et al.,* 2019). In disagreement with these findings, IBS was shown to be substantially linked to obesity (Foster *et al.,* 2003). Other researchers have shown that there is a link between BMI and digestive illnesses particularly IBS and that weight

growth influences the disease's symptoms (Sadik *et al.,* 2010). It was hypothesized that obesity plays a significant part in its pathogenesis since the condition is more prevalent in obese persons than in non-obese ones (Pickett-Blakely, 2014).

Since there is no previous study focused on the link between the blood groups and IBS, the above results can be interpreted that this significant correlation is due to indirect influence of blood group on initiation of IBS via their specific effect on blood pressure disorders and atherosclerosis, both of which can indirectly induce a state of stress and anxiety that leads to IBS disease. To confirm this interpretation, previous studies found that ABO antigens indirectly influencing arterial pressure and cardiovascular diseases by influencing renin levels and affecting plasma angiotensin and aldosterone secretion (Nemesure *et al.,* 2006; Nishi *et al.,* 2012).

Few studies have examined the relationship between RBC count and IBS in the current results compared to the results of others. According to Cakal *et al.* (2009), and Song *et al.* (2012) refer that RDW was associated with disease severity in patients with IBD, not IBS. As indicated by Aktas *et al.* (2014) MPV has not been examined in functional gastroenterology but has been an inflammatory marker in IBD patients not in IBS. Also, according to Ratnakumaran *et al.* (2018) refers to hemoglobin having no association with IBS. Furthermore, in a study in Iran by Vaghari-Tabari *et al.* (2020), IBS patients and RBC count also found no relationship between them.

The white blood cell count (WBC) is a nonspecific measure of inflammation that commonly rises after acute or chronic infections and some research show that WBC spikes within the clinically normal range may be indicative of chronic nonspecific inflammation (Erlinger *et al.,* 2004). Result

of this study found no significant changes in WBCs between patients and healthy persons or between forms of IBS, implying that there are no physiological abnormalities and all of which are within the normal range.

The significance of these findings opens the door to investigate whether this trait was considered as a genetic risk factor for GITs disease including IBS, because previous studies found that secretor status can introduces a proof of exposure to numerous dangerous agents, and as health and disease biomarkers to diagnose systemic disorders (Schipper *et al.,* 2007; Motamayel *et al.,* 2018). It has been reported that the absence of ABH soluble substances in intestinal secretions (non-secretors) decrease hydrolase enzyme activity, which has a significant influence on bacterial and lectin adherence to the intestine microvilli. As a result, non-secretors have higher risk of infection because the absence of ABH compounds in intestinal secretions stimulates microbe adherence, increasing the risk of duodenal ulcers, colitis ulcerative, sclerosing cholangitis and pancreatitis (Azevedo *et al.,* 2008; Folseraas *et al.,* 2012; Weiss *et al.,* 2016).

According to these findings, it can be concluded that people who are non-secretors and having experience of severe anxiety may be at higher risk for getting IBS.

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