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Is there any association between irritable bowel syndrome subgroups and autonomous dysfunction

A.E. YILDIRIM[1], M. KORKMAZ[1], R. ALTUN[1], S.C. SANDIKÇI[2], S. OCAL[1], H. SELÇUK[1]

[1]Department of Gastroenterology, [2]Department of Internal Medicine, Başkent University, Faculty of Medicine, Ankara, Turkey

Abstract. – OBJECTIVE: Irritable bowel syndrome (IBS) is a common functional intestinal disorder. Although there are marked improvements in the conceptualization of IBS pathophysiology in brain-intestinal interaction disorder, there is no definite consensus in the role of autonomic dysfunction (AD) in disease development and symptom progression. The aim of this study was to evaluate autonomous dysfunction in IBS subgroups.

PATIENTS AND METHODS: A total of 50 patients and 49 healthy controls were included. IBS subgroup types and demographic characteristics of patients were recorded. AD investigations were made up of parasympathetic and sympathetic tests.

RESULTS: There was no statistically significant difference was determined between the groups in accordance to demographic characteristics such as age, gender, BMI and resting heart rate ($p > 0.05$). Three parasympathetic and one sympathetic autonomic neuropathy tests were found significantly different (respectively $p < 0.001$, $p = 0.001$, $p = 0.016$, $p < 0.001$, $p = 0.375$). There were significant decreases in parasympathetic tests in IBS-C patients; however, in the control group, there were significant decreases in sympathetic tests when compared with IBS-D patients ($p < 0.001$). The severity of AD in IBS-C subgroup was more pronounced than the IBS-D subgroup. No correlation was determined between dysautonomia and disease duration ($p > 0.05$).

CONCLUSIONS: AD may have a role in IBS pathophysiology. Deterioration of the autonomous system not only affects the gastrointestinal system but also other systems including the cardiovascular system. Patients may also be susceptible to more diverse problems.

Key Words:
IBS, Autonomous neuropathy, Dysautonomia, Sympathovagal balance.

Introduction

Irritable bowel syndrome (IBS) is characterized by chronic abdominal pain, abdominal discomfort and altered bowel habits in the absence of any organic cause. It is a prevalent important functional disorder primarily in females, physically, psychologically, socially and economically without any fatal outcome[1]. It is the most common diagnosis in gastroenterology outpatients clinic and the fourth most common diagnosis of first line healthcare. It is the second most common disease causing work absenteeism other than the common cold[2]. Direct and indirect cost analyses performed in United States of America have shown approximately 1.35 billion dollars and 200 million dollars of annual health care expenses, respectively[3].

Although its prevalence in Western countries differs 3-25% according to diagnostic criteria, it is approximately10% in the majority of studies[4-5]. The prevalence is lower in Asian countries than in European, and it is reported as 0.8-14%[6]. In Turkey prevalence is reported as 6.2-19.1%[7-9]. Great differences in prevalence ratios may be due to differences in race, socioeconomic state, methods used to define IBS.

Previous studies have blamed gastrointestinal motility and visceral hypersensitivity. In recent publications, new findings indicating various factors such as inflammation, changes in fecal flora, bacterial overgrowth, food allergy, psychosocial dysfunction, genetic factors, and deterioration of central nervous system-intestinal interaction have gained importance. Pathophysiological mechanisms of IBS have yet to be defined.

Visceral hypersensitivity is modulated by the autonomous nervous system (ANS), and central nervous system (CNS) modulate and coordinate

Corresponding Author: Abdullah Emre Yildirim, MD; e-mail: yildirimemrea@yahoo.com

gastrointestinal system motility, secretion activity and immune functions via autonomic pathways by affecting enteric nervous system (ENS)[10-14]. ANS dysfunction could play a role in the pathogenesis of IBS because of the data regarding changes in somatic and visceral perceptions in IBS patients[15]. There are conflicting results in the literature about the presence of correlation between sympathetic and parasympathetic system dysfunction and autonomic balance (including parasympathetic and sympathetic activity association) in IBS patients[16-21]. The lack of an exact pathophysiologic mechanism of IBS also challenges targeted specific treatment modalities.

IBS patients can further be classified according to their dominant symptom such as constipation dominant (IBS-C), diarrhea-dominant (IBS-D) or mixed (IBS-M) patients. The aim of the present study was to investigate if there are any correlations between IBS subgroups and autonomous dysfunction.

Patients and Methods

A total of 50 patients aged between 20-60 years, who applied to Gastroenterology outpatient clinic of Baskent University Ankara Hospital between May 2011 and July 2011 with complaints (abdominal pain or irritability, defecation or changed bowel habits with flatulence); and diagnosed as IBS according to Roma III criteria by a gastroenterologist with expertise in IBS. Patients' clinical, laboratory, and imaging methods were included in the study[22]. Patients who had cardiovascular, neurological, renal, chronic endocrine diseases, and were using vasoactive medications (calcium channel blockers, angiotensin converting enzyme inhibitor and receptor blocker, beta and alpha blockers, centrally active antihypertensives, diuretics), centrally-acting drugs or those that could affect ANS function (anxiolytics, narcotics, antidepressants), spasmolytic, and prokinetic were excluded from the study. The control group was composed of 49 healthy individuals who were younger than 60 years, had no history of IBS, and did not satisfy exclusion criteria. Patients and healthy individuals were informed about study details, and their informed consents were provided before the study.

The present study was approved by Baskent University Medical School and Health Institute Research Committee, and was supported by Baskent University Research Fund.

IBS subtypes according to the Roma III criteria, demographic characteristics, and anthropometric measurements of patients were recorded.

Autonomous neuropathy tests were applied to patients on the same day in an adequately warm and quiet room. During these tests, standard ECG device (Hewlett Packard Page Writer 2004 electrocardiogram Sanborn series, Waltham, MA, USA), blood pressure measuring device (ERKA perfect aneroid, ERKA, Bad Tölz, Germany) and monitor pulse oxymeter (Elance Spacelabs Healthcare Medical, Issaquah, WA, USA) were used.

Diagnosis and severity determination of autonomous dysfunction were performed by using Ewing and Clarke's criteria[23]. Autonomous neuropathy tests were composed of 3 parasympathetic and 2 sympathetic tests (Table I).

Statistical Analysis

"IBM SPSS v.11.0 for Windows (SPSS Inc., Chicago, IL, USA) statistics program was used during statistical evaluation. Continuous variables were showed by mean ± standard deviation or median value (minimum-maximum), whereas categorical variables were shown by percentage. Chi-square test was used for comparing categorical variables, Student's *t*-test or MannWhitney U test was used in the evaluation of differences between parametric variables between the groups. Kruskal-Wallis test was used to compare differences between more than two groups. MannWhitney U test was used in multiple comparisons of variables with statistically significant differences. Spearman correlation test was used to evaluate correlations between variables. Including autonomous neuropathy tests, Multivariant ANOVA test was used in evaluating parameters affecting scores. The level of significance was accepted at $p < 0.05$ in all analyses.

Results

In the present study, 50 IBS and 49 control patients were included. Of the study cohort, 65.7% (n=65) were female, and 34.3% (n=34) were male. The mean age was 37.2 ± 10.8 years.The relative frequencies of the IBS subtypes were IBS-C: 40% (n=20), IBS-D: 26% (n=13), and IBS-M: 32% (n=16). Of IBS patients, 74% (n=37) were female, and 26% (n=13) were male with the mean age of 41.1±11.2 years, while in the control group 57.1% (n=28) were female and 42.9% (n=21) were male with the mean age of

Table I. Tests of autonomic function, and classification of severity[23].

	Method	Comment
Active standing (parasympathetic)	Wearing an ECG monitor the subject rests supine to achieve stable baseline HR levels. The subject then stands and the ratio is calculated of the longest RRI (around the 30th beat) to the shortest RRI (around the fifteenth beat)	≥ 1.04 normal 1.01-1.03 borderline < 1.0 abnormal
Deep breathing (parasympathetic)	With ECG monitoring in a sitting position the patient breathes deeply and evenly at 6 breaths per minute. The maximum and minimum HR during each cycle is noted for 3 consecutive cycles. The mean difference between maximum and minimum HR is calculated	> 9 beats/min. normal (age > 60) ≥ 15 beats/min. normal (age < 60) 11-14 at the borderline ≤ 10 abnormal
Valsalva (parasympathetic)	After resting, the patient expires for 15 seconds against a closed glottis (pressure of 40 mmHg). The ratio of the longest RRI just after the Valsalva, and the short RRI during the strain is calculated	≥ 1.11 normal (age > 60) 1.11-1.2 borderline ≥ 1.21 normal (age < 60)
Valsalva (sympathetic)	The same method as for Valsalva (parasympathetic) but BP is recorded	In normal patients there will be a BP overshoot shortly after releasing the strain
Isometric exercise (sympathetic)	Using a dynamometer, hand grip is maintained at 30% of maximum grip for 5 minutes. Diastolic pressure is measured before exercise and just before release, the difference is calculated	≥ 16 mmHg normal 11-15 mmHg borderline ≤ 10 mmHg abnormal
Cold pressor (sympathetic)	One hand is held in iced water for 1 minute. Diastolic BP is measured, before and after, the increase is calculated	≥ 15 mmHg normal 11-14 mmHg borderline ≤ 10 mmHg abnormal
Dysautonomia may be classified as: None: all tests normal or borderline Early: one abnormal HR test or two borderline Definite: two or more abnormal HR tests Severe: two or more HR rate tests abnormal, plus one borderline or abnormal BP test Atypical: any other combination of abnormal tests		

Abbreviations: HR, heart rate; BP, blood pressure; RRI, R-R int erval; ECG, electrocardiogram; bpm, beats per minute.

38.2±8.8 years. The mean body mass index (BMI) in our patient population was 24.8 ± 4.12; however, in the control group, the mean BMI was 24.7 ± 4.28. The mean heart rate was found 68 ± 3 and 67 ± 2, respectively in patients and control group. No statistically significant difference was determined between the groups in accordance to demographic characteristics such as age, gender, BMI and resting heart rate ($p = 0.22$, $p = 0.07$, $p = 0.934$, and $p = 0.710$, respectively).

When autonomous neuropathy test results were evaluated between the groups, significant differences were determined in response to standing up, response to deep breathing, response to Valsalva, and response to isometric exercise ($p < 0.001$, $p = 0.001$, $p = 0.016$, $p < 0.001$, respec-

Table II. Autonomous neuropathy test results in patient and control groups.

	Patient	Control	p
Response to standing up (sec)	1.0046 ± 0.1713	1.104 ± 0.0675	< 0.001
Response to deep breathing (beat/min)	12.52 ± 6.04	15.80 ± 2.66	0.001
Response to Valsalva (sec)	1.2886 ± 0.1289	1.239 ± 0.0599	0.016
Response to isometric exercise (mmHg)	11.68 ± 4.50	15.02 ± 2.78	< 0.001
Response to cold pressor (mmHg)	14.30 ± 10.10	15.63 ± 2.95	0.375

Table III. Autonomous neuropathy tests result of IBS subgroups and control group.

	IBS-C (N = 20)	IBS-D (N = 13)	IBS-M (N = 16)	Control (N = 50)	p
Response to standing up (sec)	0.91 ± 0.13	1.07 ± 0.132	1.06 ± 0.19	1.10 ± 0.07	< 0.001
Response to deep breathing (beat/min)	10.98 ± 5.78	14.54 ± 3.79	12.58 ± 7.60	15.80 ± 2.64	0.002
Response to Valsalva (sec)	1.29 ± 0.13	1.29 ± 0.14	1.27 ± 0.11	1.24 ± 0.06	0.346
Response to isometric exercise (mmHg)	14.40 ± 4.52	9 ± 2.27	10.94 ± 3.94	14.80 ± 3.16	< 0.001
Response to cold pressor (mmHg)	18.0 ± 13.91	10.62 ± 5.07	12.83 ± 5.86	15.52 ± 2.94	0.003

tively); there was no significant difference in response to cold pressor ($p = 0.375$) (Table II).

When we compared autonomous neuropathy test results between IBS subgroups and control group we have found significant differences in response to standing up, response to deep breathing, response to isometric exercise, and response to cold pressor ($p < 0.001$, $p = 0.002$, $p < 0.001$, $p = 0.003$, respectively), but not in response to Valsalva ($p = 0.346$) (Table III).

Autonomous neuropathy tests were interpreted separately in all IBS groups and controls as normal, borderline normal, and abnormal. Results are shown in detail in Table IV. The severity of dysautonomia levels was determined after evaluation of all autonomous neuropathy tests and the results are shown in detail (Table V).

The results of autonomous neuropathy tests and severity of dysautonomia levels were interpreted separately in IBS subgroups (Tables VI and VII).

We did not find any correlation between disease duration and autonomous neuropathy test in IBS group.

Table IV. Interpretation results of autonomous neuropathy tests of IBS and control groups.

		IBS (n = 50)	Control (n = 49)	p
Response to standing up (%)	Normal	40	95.9	< 0.001
	Borderline normal	10	0	
	Abnormal	50	4.1	
Response to deep breathing (%)	Normal	38	67.3	< 0.001
	Borderline normal	22	30	
	Abnormal	40	2	
Response to Valsalva (%)	Normal	80	91.8	0.226
	Borderline normal	14	6.1	
	Abnormal	6	2	
Response to isometric exercise (%)	Normal	30	51	< 0.001
	Borderline normal	28	40.8	
	Abnormal	42	8.2	
Response to cold pressor (%)	Normal	50	69.4	0.054
	Borderline normal	22	20.4	
	Abnormal	28	10.2	

Table V. Dysautonomia types in IBS and control groups.

		IBS (n = 50)	Control (n = 49)	p
Outcome (%)	Normal	18	87.8	< 0.001
	Atypical	16	4.1	
	Early dysautonomia	36	6.1	
	Definite dysautonomia	14	2	
	Severe dysautonomia	16	0	

Table VI. Interpretation results of autonomous neuropathy tests in IBS subgroups.

		IBS-K (n = 20)	IBS-D (n = 13)	IBS-M (n = 16)	p
Response to standing up (%)	Normal	15	69.2	50	0.009
	Borderline normal	5	15.4	12.5	
	Abnormal	80	15.4	37.5	
Response to deep breathing (%)	Normal	25	46.2	43.8	0.017
	Borderline normal	10	46.2	18.8	
	Abnormal	65	7.7	35.7	
Response to Valsalva (%)	Normal	80	84.6	75	0.971
	Borderline normal	15	7.7	18.8	
	Abnormal	5	7.7	6.3	
Response to isometric exercise (%)	Normal	55	0	25	0.003
	Borderline normal	25	23.1	37.5	
	Abnormal	20	76.9	37.5	
Response to cold pressor (%)	Normal	65	30.8	50	0.094
	Borderline normal	25	23.1	12.5	
	Abnormal	10	46.2	37.5	

Discussion

Although IBS constitutes 25-50% of patients who are examined at Gastroenterology Outpatient Clinics and studies have been performed since 1950s, its etiopathogenesis is not clearly defined yet. While previous studies have been concentrated on gastrointestinal motility, and visceral hypersensitivity, new findings indicating various factors such as inflammation, changes in fecal flora, bacterial overgrowth, food allergy, psychosocial dysfunction, genetic factors, and deterioration of central nervous system-intestinal interaction have gained importance in recent publications.

It is accepted that there is an axis regulating sensory and motor functions between the brain and intestines, and CNS has a regulatory role in motility on ESS via sympathetic and parasympathetic pathways of autonomous nervous system. It is believed that visceral hypersensitivity and abnormal colonic motility are evolved because of the regulation defect between CNS and ESS[24].

In some recent studies[20,21,25-28], autonomic dysfunction was determined in IBS patients. Although results in those studies have been conflicting, it was reported as the common finding that sympathetic activity was increased, and parasympathetic activity was decreased in IBS patients when compared with healthy individuals. It was also reported that anxiety and depression caused autonomic dysfunction in IBS patients, and there were differences in gender and IBS patients in other studies.

There have been many reports regarding ANS function in patients with IBS. Available data remains controversial, likely due to differences in methodologies used to assess ANS function. They used methods for measuring several cardiac autonomic nerve functions, such as response to standing up, response to deep breathing, Valsalva, isometric exercise and cold pressor. We could not find any article about this topic that used all cardiac autonomous neuropathy tests all together. We preferred using all of indirect, noninvasive and simple cardiac autonomous neu-

Table VII. Dysautonomia types in IBS subgroups.

		IBS-K (n = 20)	IBS-D (n = 13)	IBS-M (n = 16)	p
Outcome (%)	Normal	10	15.4	31.3	< 0.001
	Atypical	0	53.8	6.3	
	Early dysautonomia	30	30.8	43.7	
	Definite dysautonomia	35	0	0	
	Severe dysautonomia	25	0	18.8	

ropathy tests in order to determine autonomous dysfunction because; it can be performed in outpatient clinic conditions; do not require a specific device or equipment; do not require preparation before application; easily applicable, and might allow separate evaluations of sympathetic and parasympathetic responses. Buysschaert et al[29] and Emmanuel et al[30] previously reported a close association between cardiac autonomic measures and gastrointestinal autonomic function. So we thought that it is easy and convenient to use cardiac autonomic tests in order to investigate autonomic dysfunction inIBS patients.

There was no significant difference in demographic characteristics between IBS patients and controls. Basal demographic characteristics of both groups, such as age, gender, and BMI, were well-matched. Our study group consisted of more female patients aged more commonly between 2-4 decade which were also consistent with previous epidemiological studies. Similar to turkish IBS prevalence study results performed by Celebi et al[7], the majority of IBS patients belonged to IBS-C subgroup in the present study.

Our results indicated that there were deteriorated parasympathetic and sympathetic autonomous nervous system responses in IBS patients. These findings were similar to results of a previous study performed by Waring et al[27]. However, it was shown in this study that equilibrium was provided by shifting towards the sympathetic system, as parasympathetic responses deteriorated, and there were increases in sympathetic autonomous neuropathy tests. In the present study, although there was statistically an insignificant decrease in one of the tests reflecting sympathetic activity, there were decreases in both sympathetic autonomous nervous system tests in IBS patients when compared with controls. Therefore, there was no increase in sympathetic activity due to parasympathetic disorder. This might be caused by unequal distribution of patient numbers in IBS-C and IBS-D subgroups.

The decrease in results of parasympathetic tests (response to standing up and response to deep respiration) was significantly different in IBS-C patients. However, the decrease in sympathetic tests (response to isometric exercise and response to cold application) was significantly more prominent in IBS-D patients. In IBS-M patients, all tests were significantly more decreased than the controls. According to these results, it may be claimed that there are disorders in the parasympathetic nervous system in IBS-C patients, whereas in the sympathetic nervous system in IBS-D patients. While decreases in parasympathetic response and increases in sympathetic response were statistically significant in IBS-C group, the opposite was true for IBS-D patients. It was reported in previous studies that sympathetic activity was increased and parasympathetic activity was decreased in IBS patients when compared with the control group[26,27]. As clinical characteristics of IBS subgroups were different, similar studies were performed with the idea that different autonomous dysfunctions might be responsible for its pathophysiology. Lee et al[31] showed that parasympathetic activity was decreased in IBS-C patients. However, only two tests showing sympathetic and parasympathetic activities were used in that study. Similarly, 24-hour heart rate variability was used to evaluate the equilibrium between sympathetic and parasympathetic systems in a study performed to investigate ANS functions in female patients with IBS, and it was shown that parasympathetic response was decreased in IBS-C group[26]. A recent study[32] revealed that parasympathetic dysfunction seemed to be more obvious in the IBS-C subgroup. In the present study, we used 5 tests, and we determined a similar difference in IBS-C group, whereas increased sympathetic activity was determined in IBS-D group with decreasing parasympathetic response.

Under the light of these results, when use of tricyclic antidepressants (TCAs) and selective serotonin releasing inhibitors (SSRIs) in IBS treatment are reviewed, and if parasympathetic activity is deteriorated and depression score is increased in IBS-C group; then, it is more appropriate to use SSRIs than TCAs, because parasympathetic (anticholinergic) effects of TCAs are more prominent. It has been reported that selection of SSRIs are more appropriate in IBS patients with constipation and TCAs in IBS with diarrhea, because anticholinergic effects of TCAs may increase constipation in IBS cases with constipation[33].

When the severity of dysautonomia was calculated in IBS group by using Ewing and Clarke's criteria, dysautonomia presence and its severity were determined statistically significant. These outcomes indicated that ANS involvement of IBS group was more common and severe than in the control group. In the literature review, there is no other study which has compared and showed correlation between IBS and severity of autonomous dysfunction.

When dysautonomia severity levels of IBS subgroups were investigated our findings indicated that parasympathetic responses were abnormal in IBS-C group, whereas sympathetic responses were abnormal in IBS-D group. Definite and severe autonomous dysfunctions were encountered in IBS-C and IBS-M groups; there was no definite or severe autonomous dysfunction in IBS-D subgroup, but early dysautonomia was determined around 31%. These findings indicated that autonomous dysfunction in the IBS-C patients was more severe than in the IBS-D patients. The cause of more severe dysautonomia is unknown in IBS-C patients, and we could not find any study to elucidate this issue in the literature.

There was no statistically significant correlation between disease duration and autonomous dysfunction in IBS group. Therefore, it might be extracted that there was no correlation between disease duration and presence of autonomous dysfunction, and its severity.

In summary, it is shown that autonomic cardiovascular regulation is deteriorated in IBS. The deterioration was variable according to IBS subgroups, and it was in the form of parasympathetic deterioration in IBS-C, whereas in sympathetic one in IBS-D. The severity of autonomous dysfunction was more prominent in IBS-C subgroup than IBS-D subgroup. No correlation was encountered between disease duration of dysautonomia and gender. As the ANS activity involves multiple organs, dysfunctions of the ANS usually encompass various and multiple disorders and may impair the quality of life. In addition to the potential role of autonomous dysfunction in IBS pathophysiology, deteriorations of autonomous cardiovascular responses have another importance in morbidity and mortality in these patients. In a multicenter study conducted on 1248 patients, it was shown[34] that autonomic cardiovascular response, determined in post-myocardial infarction period by heart rate variability, had prognostic importance in the development of post-MI ejection fraction and arrhythmia. If it is considered that morbidity and mortality may be affected by cardiovascular events, which may be encountered as the result of myocardial infarction, and deterioration of cardiovascular responses related to dysautonomia in IBS patients; we believe that these patients should be evaluated in more detail for potential cardiovascular diseases, and primary precautions should be carefully taken. Moreover, centrally active drugs which may be given in the treatment of IBS patients should be carefully selected, because autonomous response findings are variable between the subgroups. Further comprehensive studies with larger scales are required to explain potential underlying mechanisms.

The present study has some limitations. ANS activity was not measured with an invasive, direct, accurate test such as microneurography. It directly records the sympathetic nerve traffic, but it is an invasive and troublesome procedure[35]. IBS-D subgroup can be evaluated with this invasive test. Although our patient population was a homogenous group of IBS patients compared to the control group, our data revealing the IBS subtypes could not reflect the standard population results because of the limited patient size.

Conclusions

We observed a significant relationship between the AD and IBS subgroups. In the clinical management of IBS similar to the literature, we propose that the addition of an autonomic evaluation proves a useful means to evaluate more subjective or functional aspects of the disease.

Conflicts of Interest and Source of Funding

The authors have no conflicts of interest or financial ties to disclose.

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