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Original Article

Evaluation of the Prevalence of Irritable Bowel Syndrome in Patients with Rheumatoid Arthritis

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Abstract

Background: Changes in auditory function have been noted in post-menopausal women attributed in part to the lower levels of ovarian hormones. Decreased levels of ovarian hormones may alter auditory neurotransmission time, as evaluated by Auditory Brainstem Responses (ABR). Thus, the objective of this study was to compare the mean inter-peak ABR latencies and post-menopausal women compared to non-menopausal women.

Methods: In this cross-sectional study, research sample consisted of 60 women as case group in the age range of 45-55 years, who were post-menopausal and had normal hearing. The control group with similar characteristics were non-menopausal. Two groups were estimated by ABR and then the means of the variables that had a normal distribution were compared with each other by independent t-test.

Results: All differences between two groups were not significant, as follows; Mean I-III inter-peak ABR latencies (p-value=0.714), mean III-V inter-peak ABR latencies (p-value=0.691) and mean I-V inter-peak ABR latencies (p-value=0.483).

Conclusion: Menopause does not cause abnormal results in auditory brainstem responses.

Keywords: Auditory brainstem responses, Estrogen, Menopause, Progesterone

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Introduction

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology characterized by symmetrical peripheral polyarthritis. It is the most common inflammatory arthritis and has a prevalence of about 0.5 to 1% worldwide, leading joint damage and disability. The incidence of the disease increases between 25 to 55 years, then reaches plateau until the age of 75 and then decreases. The disease usually presents with inflammatory symptoms of the joints, tendons and bursae with morning stiffness of more than an hour. The small joints of the hands and feet are usually the first to be involved (1).

In chronic diseases, the quality of life is an important issue that needs to be considered. Although with help of the new generation of anti-rheumatic drugs called DMARDs (Disease-Modifying Antirheumatic Drugs), the quality of life has been improved, it is still far away from the ideal (2). Consequently, any factors with adverse impact should be addressed and corrected as much as possible. In this study, we investigated the prevalence of Irritable Bowel Syndrome (IBS) in patients with rheumatoid arthritis. IBS is one of the most common types of functional gastrointestinal disorders, characterized with chronic and recurrent abdominal pain and changes in bowel movements. The prevalence of IBS varies according to the country as well as the diagnostic criteria used, ranging from 1% to more than 45% (3). For example, in a study examining the prevalence of IBS in Japan, it estimated its prevalence based on the Rome II criterion at 9.8% and according to the Rome III criterion (4), or in Korea its prevalence based on the Rome II and Rome III criteria at 8% and 9% (5), but in general, the global average prevalence is estimated at 11% (3). According to the studies conducted in our country, the prevalence of IBS is lower than the statistics obtained from Western countries and according to the Rome III criterion, its prevalence is estimated at 1.1% (6).

The prevalence of IBS was estimated to be higher by 3.5% based on previous criteria (although the prevalence was expected to be higher according to this criterion due to the shorter time required to diagnose IBS based on Rome III). In any case, Iran is one of the countries with a low prevalence of IBS (7). The prevalence of IBS is generally higher in women (3,6,8-10) but depending on the study, its prevalence has been reported to be equal in both sexes (11) and even higher in men (12,13). Of course, the criterion used was also involved in this matter, so that in a study conducted in Korea, only with the Rome III criterion, the prevalence of IBS was higher in women (5).

In addition to the gastrointestinal symptoms, IBS can be associated with extra-gastrointestinal symptoms such as other functional diseases, fibromyalgia, migraine headaches, back pain, persistent tiredness, urogenital symptoms (such as frequency, urogenesis, and dysparion), psychiatric symptoms, and even asthma and asthma (14-18). The pathogenesis of IBS is not fully understood, but changes in gastrointestinal motility, visceral hypersensitivity, gas handling disorders, psychosocial factors, infections, and finally immune dysregulation are among the issues raised (19,20). Immune system disorders have been the subject of numerous studies and in this case, evidence such as changes in the function of the mucosal immune system (increased T cell and mast cells of the intestine) and systemic immune system and the presence of autoantibodies like anti-enteric autoimmune antibodies and antibodies. Researchers have considered the enteric nervous system and anti-GnRH antibodies (21-25), although not all studies have confirmed this link between IBS and autoimmune diseases (18,26).

Therefore, in this disorder, without any organic cause, it is associated with other functional disorders and psychological disorders, all of which can lead to impaired quality of life. Symptoms and seizures of IBS are mainly due to psychological stress or due to physical stressors (such as gastroenteritis) (9,27). Although the nature of this disease is functional, it is equivalent to structural and gastrointestinal diseases that disrupt the quality of life of individuals (3) and imposes a heavy burden on the health system (28).

Materials and Methods

In this cross-sectional study, we considered 111 patients with rheumatoid arthritis (diagnosed by the rheumatologist of the center) who referred to the rheumatology clinic of Imam Khomeini Hospital (RA) for routine examinations and follow-up and were randomly selected. In order

to ask about their gastrointestinal symptoms a questionnaire that contains demographic information including age, sex, occupation, marital status (single, widow, divorced, married), level of education (illiterate, elementary and undergraduate, diploma, university), height, weight and Body Mass Index (BMI), smoking, alcohol or drug use, history of abdominal surgery (including appendectomy) and history of other comorbidities, duration of rheumatoid arthritis, medications taken, gastrointestinal symptoms including gluten sensitivity, pain/discomfort, abdominal (and if present), constipation, diarrhea, bloating, heartburn / acid regurgitation, anal pain, nausea/vomiting, fecal incontinence, difficulty defecating, feeling of not emptying after defecation, phlegm, stool, blood/melena, anorexia/weight loss and dysphagia, and family history of digestive problems (including IBS, celiac disease, history of colon cancer) was made. Inclusion criteria were patients with rheumatoid arthritis who were satisfied with the inclusion plan and exclusion criteria included dissatisfaction with the inclusion plan or a history of organic abdominal problems and abdominal surgery, and red flag symptoms (gastrointestinal bleeding, anemia, weight loss, fever, a family history of colon cancer, the onset of symptoms after the age of 50, and a fundamental change in the type of gastrointestinal symptoms.

The patients were then routinely tested for each visit (including CBC, ESR, CRP, and in some cases RF and Anti-CCP). {These tests are not requested by this party but are part of the routine tests. They have been requested by the treating physician in the previous appointment and are presented in each appointment routine}.

To evaluate the severity of rheumatoid arthritis, we used the DAS-28 criterion, an example of which is shown in figure 1.

To prevent sample loss, 10% of the additional sample volume was selected. Finally, we estimated the prevalence of IBS in the patients.

Based on the available guidelines, IBS is diagnosed primarily on the basis of a detailed history, examination, and routine examination (which of course does not include colonoscopy) in a person who meets the clinical criteria and does not have any red flags. These risk symptoms consist of gastrointestinal bleeding, anemia, weight loss, fever, family history of colon cancer, the onset of symptoms after age 50, and a fundamental

FORM A		LEFT		RIGHT	
		SWOLLEN	TENDER	SWOLLEN	TENDER
Shoulder					
Elbow					
Wrist					
Metacarpophalangeal (MCP)	1				
	2				
	3				
	4				
	5				
Proximal Interphalangeal (PIP)	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
TOTAL		SWOLLEN		TENDER	

FORM B	
Swollen (0–28)	
Tender (0–28)	
ESR	
VAS disease activity (0–100mm)	

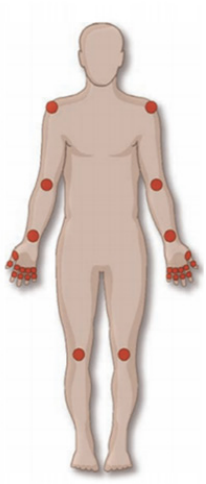

Figure 1. DAS-28 criteria for calculating the severity of rheumatoid arthritis activity.

change in the type of gastrointestinal symptoms (9). Therefore, since the diagnosis of IBS is based on an individual's symptoms, its accuracy has its own limitations. For this purpose, criteria such as the Manning criterion, Kruis scoring system, and Rome criteria have been proposed, which are mostly used to identify people with IBS for research purposes. And the latter is the most widely used criterion. So far, 4 copies of the Rome criterion have been presented, the last of which is related to 2006, and compared in table8) 1), but before the implementation of this project, the Rome IV criterion was also published. This criterion was utilized. According to the Rome IV standard, IBS is defined as recurrent abdominal pain, at least once a week, over the past three months (and at least 6 months after its onset) with at least two adverse events; regarding defecation, it begins with a change in the stool frequency and the shape/form of the stool (13).

Table 1. Criteria for IBS Diagnosis - Based on the collection of Ford AC *et al* (8)

Duration of symptoms	Symptoms, signs and tests	Criterion type
None	Abdominal pain relieved by defecation More frequent stools with onset of pain Looser stools with onset of pain Passage of mucus per rectum Feeling of incomplete emptying Patient-reported visible abdominal distension	Manning *et al* (1978)
>2y	Symptoms (reported by the patient using a form): Abdominal pain, flatulence, or bowel irregularity Description of abdominal pain as "burning, cutting, very strong, terrible, feeling of pressure, dull, boring, or 'not so bad'" Alternating constipation and diarrhea Signs (each determined by the physician): Abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS Erythrocyte sedimentation rate 20 *mm*/2*h* Leukocytosis 10 000 *cells/μL* Anemia (hemoglobin 12 *g/dL* for females or 14 *g/dL* for males) Impression by the physician that the patient's history suggests blood in the stools	Kruis *et al* (1984)
≥3M	Abdominal pain or discomfort relieved with defecation or associated with a change in stool frequency or consistency, plus 2 of the following on at least 25% of occasions or days: Altered stool frequency Altered stool form Altered stool passage Passage of mucus per rectum Bloating or distension	Rome I (1990)
≥12 wk (need not be consecutive) in last 1 y)	Abdominal discomfort or pain that has 2 of 3 features: Relieved with defecation Onset associated with a change in frequency of stool Onset associated with a change in form of stool	Rome II (1999)
Symptom onset 6 mo prior to diagnosis	Recurrent abdominal pain or discomfort 3 d per mo in the last 3 mo associated with 2 or more of the following: Improvement with defecation Onset associated with a change in frequency of stool Onset associated with a change in form of stool	Rome III (2006)

Table 2. Demographic information

RA Duration	<=1 y	31 (27.9%)
	1-5 y	51 (45.9%)
	6-10 y	12 (10.8%)
	11-15 y	7 (6.3%)
	>=16 y	10 (9.0%)
Drugs	Prednisolone	86 (77.5%)
	Methotrexate (MTX)	84 (75.7%) (73% tablet, 2.7% parenteral form)
	Hydroxychloroquine (HCQ)	50 (45%) – 6 (5.4%) stop drug due to retinopathy
	Sulfasalazine	21 (18.9%)
	adalimumab	12 (10.8%)
	leflunomide	3 (2.7)
	Azathioprine	1 (0.9%)
History of admission due to RA		Yes 11 (9.9%) No 100 (90.1%)

Table 3. Basic information of rheumatoid arthritis patients

Total number of the patients		111
Gender		Male 24 (21.6%) Female 87 (78.4%)
Age	<35 y	15 (13.5%)
	35-45 y	26 (23.4%)
	46-55 y	33 (29.7%)
	56-65 y	29 (26.1%)
	>66 y	8 (7.2%)
Marital status		Single 10 (9%) Married 100 (90.1%) Widow 1 (0.9%)
Occupation	house-keeper	75 (67.6%)
	employer-hard work	16 (14.4%)
	employer-non hard work	6 (5.4%)
	retired	14 (12.6%)
Smoking		Yes 9 (8.1%) No 102 (91.9%)
Passive smoker		Yes 10 (9%) No 101 (91%)
Comorbidities	Diabetes mellitus	15 (13.5%)
	Hypertension	15 (13.5%)
	Hypothyroidism	8 (7.2%)
	Hyperlipidemia	7 (6.3%)
	Cardiovascular OR cerebrovascular disease	5 (4.5%)
GI symptoms	Constipation	24 (21.6%)
	Bloating	23 (20.7%)
	Reflux	22 (19.8%)
	Abdominal pain	18 (16.2%)
	Diarrhea	8 (7.2%)
	Nausea	5 (4.5%)- in 4 patients (3.6%) was related to MTX

Table 4. Distribution of disease severity based on DAS-28 in rheumatoid arthritis patients

Remission <2.6	24 (21.6 %)
Low disease activity >=2.6- 3.2=<	23 (20.7%)
Mod. disease activity >3.2-5.1=<	20 (18.0%)
High disease activity >5.1	11 (9.9%)
Total number of patients	78

Table 5. Distribution of the severity of rheumatoid arthritis according to DAS-28 criteria in IBS patients compared to non-IBS patients

	Rheumatoid arthritis disease activity score (DAS-28 score)			
	Remission <2.6	Low disease activity >=2.6-3.2=<	Moderate disease activity >3.2-5.1=<	High disease activity >5.1
IBS	2 (25%)	1 (12.5%)	3 (37.5%)	2 (25%)
Non-IBS	22 (31.4%)	22 (31.4%)	17 (24.3%)	9 (12.9%)

According to the Bristol Stool Form Scale, IBS is divided into four main subgroups, which include:

1. Irritable Bowel Syndrome with Constipation (IBS-C) is more than a quarter of bowel movements in hard stools and less than a quarter of bowel movements in loose/watery stools.
2. Irritable Bowel Syndrome with Diarrhea (IBS-D) accounts for more than a quarter of bowel movements in loose/watery stools and less than a quarter of bowel movements in hard stools.
3. Mixed Irritable Bowel Syndrome (IBS-M or Mixed-IBS): More than a quarter of bowel movements are loose/watery stools and more than a quarter of bowel movements are hard stools.
4. Items that do not fall into the above categories are called Unsub typed IBS or IBS-U (5).

After collecting information in the form of a questionnaire, the data were entered into the statistical software SPSS-version 23 and analyzed. In a descriptive analysis of the quantitative data, central indicators were used as Median / Mean ± SD (Range) for quantitative variables and qualitative data as a percent (frequency) for qualitative variables. In the analytical analysis of the data, the Chi-square test (Chi2) was utilized for qualitative variables and their comparison in different groups. ANOVA test was used to compare the means in different groups. In all the statistical analyzes, a significance level of 95% was considered and a confidence interval of 95% was reported for them. First, the information was entered into SPSS software and the average deviation +/- standard deviation was used to display the quantitative information, and frequency and percentage were used for the qualitative information. The significance level was considered less than 0.05. Parametric bread tests were used to distribute abnormal data and parametric tests were utilized to distribute normal data.

Results

In this cross-sectional study, a total of 111 patients with Rheumatoid Arthritis (RA) including 87 women and 24 men in the age range of 18 to 74 years (49 ±12 years) with a duration of less than one year to 30 years (6.3 ±5.3 year) were included in the study. Of these, only one patient had rheumatoid nodules.

The demographic information of the patients is shown in table 2 and the information about rheumatoid arthritis is shown in table 3.

14 patients (12.6%) with rheumatoid arthritis had IBS (9 patients IBS-C, 1 IBS-D, and 4 IBS-M). All of these patients were female.

The disease severity distribution based on DAS-28 is shown in table 4 (due to the lack of access to ESR testing, only 78 patients were able to calculate DAS-28).

Of the 14 patients with IBS, 14 (100%) were female and none were male. Of the 97 non-IBS patients, 73 were female and 24 were male. There was a significant difference between the frequency distribution of men and women in the two groups with and without IBS in terms of gender (p-value: 0.037).

Of the 14 patients with IBS, all were between 35 and 65 years old. There was no significant difference in age rhetoric between the frequency distribution of age groups between the two groups with and without

IBS (p-value: 0.36).

Out of 14 patients with IBS, 13 were married and one was single, and out of 97 non-IBS patients, 87 were married, 9 were single and one was a widow, which was between the frequency distribution of married and single in the affected and non-infected groups. With IBS, there was no significant difference in marital status (p-value: 1.0).

Out of 14 patients with IBS, 13 were housewives and one was employed, and in non-IBS patients, 62 were housewives, 21 were employed and 14 were retired, which was between the distribution of frequency of patients in both groups with and without IBS. There was no significant difference based on occupation (p-value: 0.26).

Of the 14 patients with IBS, 13 were non-smokers and one was a smoker. Of 97 non-IBS patients, 89 were non-smokers and 8 were smokers, but there was no significant difference between the frequency distribution of smokers and non-smokers in the two groups with and without IBS (p-value: 0.9). Relatively similar results were obtained for passive smokers (p-value: 1.0).

Out of 14 patients with IBS, 5 patients, and among non-IBS patients, 36 patients had a history of abdominal surgery. There was no significant difference between the frequency distribution of patients with a history of abdominal surgery in the two groups with and without IBS (p-value: 1.0).

Considering comorbid comorbidities in patients with rheumatoid arthritis, there was no significant difference between the frequency distribution of people in the two groups with and without IBS in terms of the prevalence of diabetes (p-value: 0.68), hypertension (p-value: 0.95), Hypothyroidism (p-value: 1.0), cardiovascular and cerebrovascular diseases (p-value: 1.0).

Also, considering the drugs used to treat rheumatoid arthritis, there is no significant difference between the frequency distribution of people in the two groups with and without IBS in terms of prednisolone (p-value: 0.51) and methotrexate (p-value: 0.34 for tablets). And p-value: 1.0 for parenteral form), hydroxychloroquine (p-value: 0.39), azathioprine (p-value: 1.0), sulfasalazine (p-value: 0.46), biological drugs (p-value: 1.0) and use of Bisphosphates (p-value: 1.0) was not found.

There was no significant difference between the duration of rheumatoid arthritis and the rate of IBS. Out of a total of 14 patients with IBS, in 8 patients it was possible to calculate DAS-28 (6 with missing data) whose data is shown in table 5. No significant difference was observed between the severity of rheumatoid arthritis (according to DAS-28 criteria) between patients with and without IBS (p-value-0.46).

Discussion

The present study is the first study to examine the prevalence of IBS in patients with rheumatoid arthritis. In this study, 111 randomly selected patients with rheumatoid arthritis were evaluated for the presence of IBS symptoms. For this purpose, the latest IBS diagnostic criterion (Rome-IV) was used. In terms of the number of patients selected in this study, similar articles in the field of patients with fibromyalgia and lupus were selected in about 100 patients who are consistent with this study (17,29).

Compared to the prevalence of 1.1% of IBS in the general population of our country, according to this study, 12.6% of the rheumatoid arthritis patients had IBS, all of whom were female, and this prevalence is about 10 times more than the general population of Iran. However, it should be noted that this figure of 1.1% of IBS in the general population of our country is different from what is experimentally seen by internal medicine and gastroenterologists in clinics and private offices.

Conclusion

However, it seems that paying attention to the symptoms of IBS in patients with rheumatoid arthritis and its early detection can play a significant role in improving the quality of life of these patients, which requires the attention of the treating physicians in this regard.

One of the limitations that could be mentioned in this study was the impossibility of calculating DAS-28 as a measure of disease severity (due to the lack of access to ESR in several patients). From patients (70%) this criterion was calculated, it does not seem to have any effects on the final result.

And the other is the type of target community with RA; due to the referral of centers affiliated to University of Tehran and the referral of patients with relatively severe forms of RA to these centers (patients with mild

forms of the disease are mainly treated in their city by rheumatologists and do not return to Tehran), Causes a community with a more severe form of rheumatoid arthritis to be available for study and cannot represent an ideal example.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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