



Association between Rotavirus Infection and Irritable Bowel Syndrome: A Case-Control Study in Kerman, Iran

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Abstract

Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disease of unknown etiology. Researchers have recently drawn attention to the possible role of viruses in the development of IBS and provided evidence in this regard. In this study, it was decided to investigate the possible role of rotavirus infection in the onset of IBS.

Methods: Stool and serum samples were collected from 40 patients with IBS and 40 healthy individuals. To evaluate the previous exposure to rotavirus we checked the presence and concentration of anti-rotavirus IgG by ELISA. ELISA test was performed on the serum samples. A real-time polymerase chain reaction (PCR) test was also used to measure the viral load in the stool. Finally, the data were analyzed by SPSS version 22 software.

Results: No significant relationship was found between anti-rotavirus IgG presence and its level in the serum of case and healthy individuals (P value > 0.05). Moreover, there was no significant difference between the viral genome load in the stool samples of the two groups (P value > 0.05).

Conclusion: According to the results, it seems unlikely that a link exists between rotavirus infection and the onset of IBS, but the possible role of other gastrointestinal viruses, including coronavirus, remains.

Keywords: Irritable bowel syndrome, Rotavirus, Pattern recognition receptors, Coronavirus

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Introduction

Irritable bowel syndrome (IBS) is a complex, common gastrointestinal disease manifested with abdominal pain/discomfort associated with defecation changes. This disease is in the category of functional disorders of the gastrointestinal tract, and structural and biochemical changes are not observed in patients with this disease (1,2). The prevalence of IBS in different parts of the world has been reported to be up to 21%, and in different regions of Iran, from 1.1% to more than 20% (3,4). In a study in 2011, the prevalence of IBS in Kerman province was reported to be 6.2% (5), and the women-to-men ratio in different societies was reported to be 2:1, 3:1, and even 4:1 (6). The symptoms of this disease are chronic and negatively affect daily life, social activities, sleep, sexual activity, and efficiency of the affected person in the workplace and at school (7). Although IBS is not a life-threatening disease, it significantly reduces the patient's quality of life and, in this respect, it ranks first among

other chronic gastrointestinal and non-digestive diseases (6). In addition, IBS imposes exorbitant costs directly and indirectly on the patients, employers, and the health system (8). The exact etiology of this disease is not known (9), but several options, including genetic predisposition (10), anxiety and stress (11), neurological disorders (12), food allergies (13), and changes in intestinal microbiota (14) are found concerning the emergence of this disease. Changes in the intestinal microbiota of patients compared to healthy individuals have drawn researchers' attention to the possible role of infectious diseases in the development of IBS. The association of viruses with diseases of unknown etiology in various diseases including rheumatoid arthritis, multiple sclerosis (MS), lupus, inflammatory bowel disease (IBD), Guillain-Barré syndrome, and Scleroderma has been evaluated and reported as one of the possible etiologies (15-20). Researchers in one study reported an increase in the level of receptors identifying the viral pattern in the patients with IBS compared to the



control group and pointed to the possible role of viruses as one of the possible etiologies of IBS (21). Given this hypothesis, it makes sense that viruses with the power of tropism to the GI, including rotavirus, should be blamed. Rotavirus is a member of the Reoviridae family and, structurally, is a non-enveloped virus with a three-layered protein capsid containing a double-stranded RNA genome (22). The virus is responsible for approximately 40% of pediatric acute gastroenteritis in Iran, and it has been shown that by the age of 2, approximately 96% of individuals have been infected with rotavirus at least once (23). The incubation period of the disease is about one to three days. Complaints and symptoms include fever, abdominal pain, vomiting, and diarrhea that cause dehydration; of course, the disease is often self-limiting (24-27). Considering the increased expression of viral RNA sensing receptors previously reported, it can be hypothesized that a viral gastrointestinal infection such as infection with rotavirus or other RNA viruses that cause gastrointestinal symptoms like coronavirus can lead to the emergence of IBS. Therefore, this study aimed to investigate the above hypothesis and the possible role of rotavirus infection in IBS.

Methods

Sampling

This is a case-control study. Sampling was performed between March 2017 and December 2018. The control group included 40 healthy individuals (10 females and 30 males) and the case group consisted of 40 patients with IBS (14 females and 26 males). The case group participants were selected from IBS patients who had been referred to Mehregan Hospital in Kerman and their disease had been confirmed by a gastroenterologist according to the Rome IV criteria.

Participants in the control group were also selected from those who were referred to Seyed-o-Shohada Hospital (Kerman, Iran) for pre-employment tests. None of the participants in the control group had neither gastrointestinal symptoms nor a history of IBS, IBD, celiac disease, colon cancer, immunodeficiency, or food hypersensitivity. Cases and controls were matched based on age and sex. Before participating in the study, the necessary explanations were provided and informed consent was obtained. Blood samples were collected and, after the serum process, transferred to the laboratory along with stool samples and stored at -40 °C.

ELISA test

Serum samples were taken out of the freezer and, after thawing, were prepared for an ELISA test. All the samples were qualitatively tested according to the kit instructions (Human Rotavirus IgG kit, ZellBio GmbH) for investigating the presence of IgG antibodies against rotavirus. To be able to compare the results, the recorded

optical density values were divided by the cut-off number and recorded as OD/cut-off ratio.

Stool RNA extraction and cDNA synthesis

For this purpose, we used the RNA extraction method (Trizol method) recommended by WHO (28). The extracted RNA was evaluated in terms of quality and quantity and, after cDNA synthesis, it was stored at -40 °C for further steps.

Primer designing

The primers were designed for the rotavirus genome using Primer 3 software (<https://www.bionfo.ut.ee/primer3-0.4.0/>) and checked by Primer-Blast (<http://www.ncbi.nlm.nih.gov/tools/primer-blast/>) and OligoAnalyzer v. 3.1 software (<http://www.idtdna.com/calc/analyzer/>). Growth hormone gene (hGH) primer was also used for the internal control. The sequence of primers used is shown in Table 1.

The primers were prepared with TE buffer and frozen at -20 for later use.

Real-time PCR reaction

Reactions with melting curve analysis were performed using ABI StepOne Real-time PCR instrument (Applied Biosystems, USA). A positive control of rotavirus cDNA and a no template control were included per PCR run. hGH and rotavirus gene amplification were done using polymerase chain reaction and the products were validated in the presence of 140 bp and 358 bp fragments on 2% agarose gel electrophoresis, respectively.

Statistical analysis

The data were analyzed by independent samples t-test, chi-square, Fisher's and Mann-Whitney tests. SPSS v. 22 software was used for data analysis and GraphPad Prism 9 software was employed for drawing the graphs. All the tests were calculated at a 95% confidence interval. All *P* values were two-sided and *P* value < 0.05 was considered statistically significant.

Results

According to the questionnaire, the patients were evaluated for the IBS subtype, the information of which is shown in Table 2.

Also, demographic characteristics, history, and clinical

Table 1. Sequence and specifications of primers used

Primer sequences for qPCR			
Gene	Primer sequence (5'-3')	Annealing temp (°C)	Product size (bp)
Rotavirus	F: CCAACAGTGCTATCAAAGA R: CCTCAACACGCTCCATCC	57	358
hGH	F: TCACGGATTCTGTGTTTC R: TCACGGATTCTGTGTTTC	60	140

information of the participants are reported in Table 3.

Results of the tests and statistical analysis showed that all the patients and controls were positive for IgG antibodies and no difference was observed. Moreover, the comparison of the OD/cut-off ratio in the patients and controls was not significantly different from the control group at a 95% confidence interval (P value=0.413).

Real-time PCR results for detecting rotavirus genome in the stool samples of patients and controls were not statistically significant (P value=0.750) (Figure 1).

Finally, the family history of the participants in the study showed that the relationship between bowel cancer in family members and IBS was not statistically significant (P value=0.531). Also, the presence of colitis and celiac disease among family members was not significantly associated with IBS (P value=0.745).

Discussion

IBS is a common functional gastrointestinal disease of

Table 2. Classification of patients by IBS subgroup

IBS-D	IBS-C	IBS-M	IBS-U	Sum
26 (65%)	0 (0%)	3 (7%)	11 (27%)	4 (100%)

IBS, irritable bowel syndrome.

Table 3. Demographic characteristics, history and clinical information of the participants

Demographic & clinical characteristics	Case (n=40)	Control (n=40)	P value
Demographics			
Age (y) (Mean±SD)	34.35±11.66	36.64±11.90	0.389
Gender, No. (%)			
Male	26 (65.0)	30 (75.0)	0.329
Female	14 (35.0)	10 (25.0)	
Academic education, No. (%)	16 (40.0)	24 (60.0)	0.117
BMI (kg/m ²) (Mean±SD)	22.57±1.73	23.75±2.17	0.009
Current smoking, No. (%)	7 (17.5)	5 (12.5)	0.531
Alcohol intake, No. (%)	11 (27.5)	9 (22.5)	0.606
Physical activity n (%)			
Low	26 (65.0)	20 (50.0)	0.338
Moderate	10 (25.0)	16 (40.0)	
High	4 (10.0)	4 (10.0)	
Family history of IBS n (%)	4 (10.0)	7 (17.5)	0.336
Clinical Symptoms, No. (%)			
Abdominal pain	37 (92.5)	1 (2.5)	<0.001
Bloating	31 (77.5)	2 (5.0)	<0.001
Constipation	9 (22.5)	2 (5.0)	<0.001
Diarrhea	26 (65.0)	0 (0)	
Nausea	3 (7.5)	0 (0)	
Vomiting	4 (10.0)	1 (2.5)	0.359
Depression	18 (45.0)	7 (17.5)	0.015
Anxiety	14 (35.0)	5 (12.5)	0.035

unknown etiology. Although this disease is not life-threatening, it can significantly reduce the quality of life in the patients. Millions of people around the world suffer from this disease and it is more prevalent in women than men.

So far, several factors have been suggested as the possible etiology of this disease. Although IBS is a functional disease, recent studies have shown low-grade inflammation in patients with IBS (29). Recently, a meta-analysis study reported that the frequency of IBS-like symptoms in patients with IBD is higher than in others, which may indicate the role of inflammation in the development of IBS symptoms (30). Another meta-analysis study confirmed the recent finding (31). Many studies have also reported IBS symptoms after a gastrointestinal infection and changes in the composition of the intestinal microbiome (32,33). Using probiotics and prebiotics has been considered effective in reducing the symptoms of the disease (34,35). Researchers have recently drawn attention to the possible role of viruses, especially gastrointestinal viruses, in the development of IBS. In one work, Aalipour et al reported the upregulation of viruses detecting pattern recognition receptors such as RIG-1, TLR 3, and TLR 9 in the intestinal epithelial cells of patients with IBS compared with controls (21). Other researchers have evaluated the changes in the expression of pattern recognition receptors in the intestinal biopsies of patients with IBS, as reported in a systematic review study (21). In the review of post-viral IBS, Shariati et al cited norovirus as the main culprit (36). Marshall et al considered the role of norovirus in the development of IBS symptoms after acute viral food-induced gastroenteritis in a questionnaire study (37). Zanini et al achieved similar conclusions about the development of IBS following an outbreak of viral gastroenteritis caused by drinking water (38). Following the coronavirus pandemic in 2019 and reports of IBS-like symptoms in some patients, as well as exacerbating the symptoms of previous IBS patients, the hypothesis of possible viruses contributing to IBS has been strengthened, although

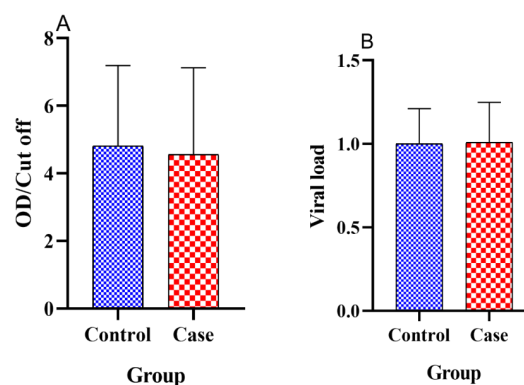


Figure 1. Comparison of the OD/cut-off ratio of serum IgG in the patients and controls (A). Comparing results of stool rotavirus genome Real-time PCR in patients and controls (B)

some researchers have linked these changes to stress and fear of being infected with the virus (39-42). Rotavirus is a genus of the Reoviridae family. The fully infectious rotavirus particle consists of three layers of protein and contains the virus genome, which involves 11 fragments of dsRNA (22). Although rotavirus infection is one of the leading causes of gastroenteritis in infants and children under 5 years of age, there have been numerous reports of adult involvement and even hospitalization (43-45). As mentioned earlier, Mohammadi et al referred to the upregulation of TLR3 and RIG 1 in the intestinal epithelial cells of IBS patients (21). In another study, Camilleri et al found similar results for TLR 3 (46). Since RIG 1 and TLR3 are considered innate immune receptors for detecting viral double-stranded RNA, in this study, we tried to investigate the possible association between rotavirus infection and the onset of IBS through serological and molecular assays.

The result of the qualitative rotavirus IgG test was positive in all the patients and healthy individuals and, in this regard, confirmed previous studies. IgG antibodies showed a history of infection, so it seems that the vast majority of adults had a history of exposure to rotavirus at a younger age. Jiang et al cited previous studies, stating that serum IgG antibody levels in patients can remain above the baseline for a long time and be protective (47). Since most of the studies in this field are old, new works with more participants are recommended.

To quantify the results of the IgG assay, the OD/cut-off ratio was calculated in the case group and compared with the controls. The results were not significantly different from the control group at a 95% significance level (P value = 0.413). Therefore, serological findings in this study showed that a link between rotavirus infection and the onset of IBS seems unlikely. It also seems that the severity of the immune response does not play a role in causing the disease. However, repeating the test with a quantitative method will help make a better judgment. For further investigation, serum IgM, serum IgA, and rotavirus secretory immunoglobulins in duodenal fluid are recommended. Examining rotavirus antibodies in stool specimens will also be helpful.

The difference between the results of the real-time PCR for detecting rotavirus genome in stool samples of the patients and controls was not statistically significant. This finding excluded the association between rotavirus infection and IBS development, although it is recommended to repeat the study on intestinal biopsy specimens of patients with IBS and compare it with the control group. Rizzo et al aimed to search for Epstein-Barr virus DNA in the colonic biopsies of 30 IBS patients by PCR and stated that EBV DNA could not be detected in these samples (48). In another study, Ciccocioppo et al reported the absence of human cytomegalovirus and Epstein-Barr virus DNA copies in both epithelial and

immune cells of the colonic mucosa of IBS patients, while in the patients with IBD, there was clear evidence of high DNA loads of both viruses in either enterocytes or immune cells (49).

According to the results of the questionnaire, no significant relationship was found between intestinal cancer, intestinal ulcer, and celiac disease in patients' families and healthy individuals. There was disagreement about the prevalence of celiac disease in people with IBS. Azimi et al conducted a meta-analysis study and found that the prevalence of celiac disease in Iranian IBS patients was higher than the global estimates, which contradicted the results of the present study (50).

Conclusion

According to the results of serological and molecular studies in this paper, a link between rotavirus infection and IBS seems unlikely. Further research on intestinal biopsy specimens of patients with IBS, as well as further studies on other gastrointestinal and non-gastrointestinal viruses, especially coronavirus, is strongly recommended.

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Competing Interests

We state that the results of the study have nothing to do with the personal interests of the people who participated in the study and the study fund was provided by Kerman University of Medical Sciences.

Ethical Approval

This case-control study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical Code: IR.KMU.AH.REC.1396.2065).

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