The Severity of Symptoms Related to Irritable Bowel Syndrome is a Risk Factor for the Misclassification of Significant Organic Disease

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Background and Aims: The diagnosis of irritable bowel syndrome (IBS) is based mainly on clinical evaluation. The reported incidence of misclassification of significant organic diseases in previously diagnosed IBS patients differs between studies. The aim of this study was to examine the incidence and risk factors for the misclassification of significant organic disease [colon cancer, inflammatory bowel disease (IBD), Celiac disease, and thyroid dysfunction] in a cohort of young patients with symptoms attributed to IBS.

Methods: In this population-based cohort study, we examined the incidence and risk factors for the diagnosis of a new significant organic diseases in a cohort of 2645 IBS patients.

Results: During follow-up, organic disease was diagnosed in 27 subjects (1.03%): IBD in 23, Celiac disease in 2, IBD and Celiac disease in 1, and hypothyroidism in1. The mean interval from the diagnosis of IBS to the diagnosis of an organic disorder was 13.08 ± 8.51 months. Increased symptom severity was the only significant risk factor for the misclassification of an organic disease (hazard ratio, 2.26; 95% confidence interval, 1.01-5.05; $P = 0.047$). The risk ratio for misclassification of organic diseases in moderate to severe IBS was increased by 2.575 (95% confidence interval, 1.10-6.51; $P = 0.027$) as compared with mild IBS.

Conclusions: The incidence of misclassification of major organic disease in IBS patients was low. Increased symptoms severity was the only significant risk factor for the misclassification of organic disorders. Further gastrointestinal evaluation should be considered in patients with moderate to severe symptoms attributed to IBS.

Key Words: irritable bowel syndrome, epidemiology, inflammatory bowel disease, celiac disease

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Irritable bowel syndrome (IBS) is a common chronic functional abdominal dysfunction, expressed by abdominal pain or discomfort and changed stool pattern.[1,2] The reported prevalence of IBS depends upon geographical and cultural factors, as well as on the criteria for IBS diagnosis,[3,4] and is reported to be between 5% and 15% in western countries.[5] IBS causes considerable morbidity and absence from work, and represents a considerable economic burden.[6,7]

The diagnosis of IBS is based mainly on clinical criteria, as specific biomarkers for IBS have not been identified. Guidelines recommend a positive diagnostic strategy for IBS in patients younger than 45 to 50 years.[2,8,9] However, the diagnosis of IBS can be challenging; misdiagnosis of inflammatory bowel disease (IBD), colorectal cancer (CRC), systemic hormonal disturbances, and malabsorptive diseases such as celiac disease are of the greatest concern to the clinician faced with a patient with symptoms suggestive of IBS.

The reported incidence of misclassification of significant organic diseases in previously diagnosed IBS patients differs between studies. In a few reports, the incidence of IBD, CRC, and malabsorption was found to be low even in IBS patients with alarming signs.[10] Moreover, the clinical diagnosis of suspected IBS was not significantly altered even after the performance of colonoscopy or celiac serology.[11,12] In contrast, a higher incidence of IBD (relative risk of 9.42 to 16.3) and positive celiac serology (0.4% to 4%) among previously diagnosed IBS patients were reported in other studies.[13–15]

The aim of this study was to examine the incidence and risk factors for the misclassification of significant organic disease (CRC, IBD, Celiac disease, and thyroid dysfunction) in a cohort of young patients with symptoms attributed to IBS.

METHODS

Population, Definitions, and Follow-up

The study population consisted of Israeli men and women aged 18 to 39 years who were diagnosed with IBS during active military service (mandatory and career service) between the years 2005 and 2012. All participants met the Rome III diagnostic criteria[16] and were evaluated by a gastroenterologist with expertise in IBS to confirm that subjects met symptom-based diagnostic criteria during a medical interview. Normal blood examinations [complete blood count, C-reactive protein, celiac serology (anti tissue transglutaminase antibody or anti endomysial antibodies), and thyroid function tests] were obligatory for the diagnosis of IBS. Normal ileo-colonoscopy and/or small bowel imaging (computed tomography/magnetic resonance enterography or video capsule endoscopy) were required for the exclusion of organic gastrointestinal disease before

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the diagnosis of moderate and severe IBS. The severity of IBS was divided into mild, moderate, and severe categories, based upon the impact of IBS symptoms on everyday activity, as formulated by the Rome Foundation Working Team report on severity of IBS.[17] To diagnose moderate to severe IBS, significant disability had to be confirmed, based on working day loss due to IBS symptoms, as well as the primary physician's opinion based on the severity and frequency of abdominal pain and other symptoms.

We excluded from the study population every case of a diagnosis of a major organic disease established before the diagnosis of IBS (IBD 32, Celiac disease 10, thyroid disease 5).

Follow-up was stopped at the time of the diagnosis of a significant organic disease (IBD, Celiac disease, gastrointestinal malignancy, and thyroid disease), at the discharge from military service or on the December 31, 2012.

Data Collection

We used the central medical record database of the medical corps of the Israel Defense Forces to collect relevant data. We collected demographic, anthropometric, and medical data on our study cohort. Baseline data included country of origin (defined as the father's place of birth or grandfather's place of birth if the father was Israeli-born). All individuals were then grouped into the following categories: Israeli, Middle Eastern (mainly originating from Iran, Iraq, Turkey, and Yemen), African (mainly originating from North Africa and Ethiopia), former Soviet Union, and western origin (Europe\America\Australia). Socioeconomic status was classified according to characteristics of the settlement or city of residence on a 1 to 10 scale by the Central Bureau of Statistics, which we divided into 3 groups (low, medium, and high). Height and weight were measured during the obligatory medical board examination at age 17 years by trained medical personnel using a stadiometer and a beam balance (subjects were barefoot and wore only a shirt and underwear). BMI at the time of examination was stratified into 4 groups: underweight (<5 percentile), normal or healthy weight (5 to <85 percentile), overweight (85 to <95 percentile), and obese (≥ 95 percentile) according to definitions established by the 2000 United States CDC BMI-for-age growth charts.[18,19] The 85th percentile of Israeli adolescents was previously reported to be similar to the 85th percentile US-CDC threshold for men.[20]

Medical data were collected by using the medical profile of each person included in the study cohort. The medical profile is defined as the standards of medical fitness for different jobs and limitations to physical activity due to medical conditions. The medical profile is accordingly constructed by any major medical problem and its severity, and defines any disease condition. In any case of diagnosis of significant medical condition, the medical profile is altered accordingly.

The study was approved by the medical corps ethical committee and registered as ClinicalTrials.gov Number NCT01854060.

Statistical Analysis

Categorical variables were compared between IBS and nonorganic disease and misclassification of organic disease groups with χ^2 test and Fisher exact test as appropriate. T test was used to test mean difference in age at recruitment between the above mentioned groups. Cox proportional-hazards models were used to assess associations between demographic, anthropometric, and clinical characteristics of the participants and time to misdiagnosis of organic disease: hazard ratios and 95% confidence interval (CI) were presented. Log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards, which was confirmed for all variables studied. Cumulative incidence of organic disease in mild versus moderate or severe IBS participants were obtained from Kaplan-Meier survival analysis and compared with Log-rank test. $P < 0.05$ was considered statistically significant.

Analyses were performed with IBM SPSS Statistics for Windows (version 19.0.; IBM Corp, Armonk, NY).

RESULTS

The study cohort consisted of 2645 persons (57.47% males) in whom IBS was diagnosed during the period of the study. During follow-up, significant organic disease was diagnosed in 27 subjects (1.03%) of the IBS cohort: IBD in 23, Celiac disease in 2, combined IBD and Celiac disease in 1, and hypothyroidism in 1. There were no cases of gastrointestinal or other malignancy. The mean age at recruitment for participants with a final diagnosis of an organic disease was 18.91 ± 0.87 years, and for those without an organic disease was 18.85 ± 0.96 years. The mean follow-up period was 13.08 ± 8.51 and 28.55 ± 18.01 months, for participants with and without a final diagnosis of an organic disease, respectively. The demographic, anthropometric, and clinical characteristics of the IBS cohort are summarized in Table 1.

Univariate Cox proportional hazard ratios for the diagnosis of significant organic disease after the diagnosis of IBS are summarized in Table 2. Only increased symptom severity was found to be a significant risk factor for the misclassification of organic disease in IBS patients (hazard ratio, 2.26; 95% CI, 1.01-5.05; $P = 0.047$). The rate of diagnosis of significant organic disorder in patients with mild IBS was 21.45 per 100,000 person years (95% CI, 9.81-40.71), whereas in moderate to severe IBS the rate of diagnosis of significant organic disorder was 55.23 per 100,000 person years (95% CI, 32.73-87.28), resulting in a risk ratio of 2.575 (95% CI, 1.10-6.51; $P = 0.027$) for the misdiagnosis of significant organic disease in moderate to severe IBS.

Cumulative incidence for misclassification of significant organic disease according to severity of antecedent IBS diagnosis is shown in Figure 1.

DISCUSSION

To the best of our knowledge, this is the first study that found that IBS-related symptom severity is a risk factor for the misclassification of significant organic disease. Another important finding is the low incidence of misclassification of significant organic disorders in previously diagnosed IBS patients.

The reported incidence of diagnosis of organic diseases that can mimic IBS symptoms in patients with previous diagnosis of IBS vary between studies. Whitehead et al[10] reported misclassification of significant organic disease in 3% of IBS patients (1% CRC, 1.2% IBD, and 0.7% malabsorption). Similarly, Hamm et al[21] reported a frequency of 1.03% of misclassification of significant organic disease in IBS (4/306 patients: 3 IBD, 1 colonic obstruction), and Tolliver et al[22] reported a similar 1.02% rate of organic disorders that could mimic IBS (1 IBD, 1 CRC out of 196 patients). In a systematic review performed by Cash et al,[15] the prevalence of IBD, CRC, and thyroid dysfunction was

TABLE 1. Demographic, Anthropometric, and Clinical Characteristics of the IBS Cohort

Variables	IBS—No Organic Disease	Misdiagnosis of Organic Disease	Total
Gender (M/F)	1476/1105 (57.41%/ 42.59%)	17/10 (62.96%/ 37.04%)	1493/1105 (57.47%/ 42.53%)
Age at recruitment (mean ± SD) (y)	18.85 ± 0.96	18.91 ± 0.87	18.86 ± 0.96
Weight state [n (%)]			
Underweight	195 (7.59)	3 (11.11)	198 (7.63)
Normal	2009 (78.20)	22 (81.48)	2031 (78.25)
Overweight and obese	365 (14.21)	2 (7.4)	367 (14.13)
Ethnicity [n (%)]			
Jews	2451 (95.33)	26 (96.3)	2477 (95.34)
Other	120 (4.67)	1 (3.7)	121 (4.66)
Origin [n (%)]*			
Israel	236 (9.27)	3 (11.11)	239 (9.29)
Former Soviet Union	510 (20.02)	5 (18.52)	515 (20.01)
Middle East	579 (22.73)	7 (25.93)	586 (22.77)
Africa	514 (20.18)	4 (14.81)	518 (20.12)
Europe/ America/ Australia	708 (27.80)	8 (29.63)	716 (27.82)
Israeli-born/ immigrants	2103/468 (81.80%/ 18.20%)	26/1 (96.30%/ 3.70%)	2129/469 (81.95%/ 18.05%)
Socioeconomic status [n (%)]			
Low	379 (14.78)	2 (7.41)	381 (14.70
Medium	1440 (56.14)	16 (59.26)	1456 (56.107)
High	746 (29.08)	9 (33.33)	755 (29.13)
Symptoms severity [n (%)]			
Mild	1199 (46.64)	9 (33.33)	1208 (46.50)
Moderate-severe	1372 (53.36)	18 (66.67)	1390 (53.50)

*Origin: father's place of birth or grandfather's place of birth if the father was Israeli-born.

IBS indicates irritable bowel syndrome.

TABLE 2. Univariate Cox Proportional Hazard Ratios for the Diagnosis of Significant Organic Disorder in Irritable Bowel Syndrome Patients

Variables	Hazard Ratio	95% CI	*P*
Age at recruitment	1.08	0.77-1.53	0.65
Gender			
Male	1		
Female	0.89	0.40-1.92	0.74
Weight state			
Normal	1		
Underweight	1.38	0.41-4.60	0.60
Overweight and obese	0.50	0.12-2.14	0.35
Ethnicity			
Other	1		
Jews	0.72	0.10-5.32	0.72
Origin*			
Europe/America/Australia	1		
Israel	1.15	0.30-4.32	0.95
Former Soviet Union	0.81	0.27-2.48	0.71
Middle East	1.00	0.36-2.76	1.00
Africa	0.68	0.20-2.25	0.53
Immigration			
Yes	1		
No	0.17	0.02-1.25	0.08
Socioeconomic state			
Low	1		
Medium	2.02	0.48-9.16	0.32
High	2.29	0.49-10.6	0.29
Symptom severity			
Mild	1		
Moderate-Severe	2.26	1.01-5.05	0.047

*Origin: father's place of birth or grandfather's place of birth if the father was Israeli-born.

CI indicates confidence interval.

found to be similar to the general population. The prevalence of Celiac disease was also found to be similar in IBS patients and in the control group in an American multicenter trial.[12] In addition, the prevalence of structural abnormalities of the colon was found to be similar in suspected nonconstipation IBS patients and in healthy controls.[11] In contrast, other reports described higher prevalence of Celiac disease and IBD among IBS patients. The prevalence of Celiac disease was increased 3.6 to 5 folds in patients with a previous diagnosis of nonconstipation IBS than in controls.[23,24] Similarly, in a cohort of previously diagnosed IBS patients, the incidence of IBD was found to be 9 to 16.5 higher than in the general population,[13,14] and prodromal IBS symptoms were found to be responsible for a delayed diagnosis of Crohn's disease and IBS.[25,26]

The diagnosis of a significant organic disease after the diagnosis of IBS can be explained by misdiagnosis, misclassification due to a long prodromal phase of an organic disease, or due to the accidental development of the organic disease in IBS patients. In our study, the mean time for the subsequent diagnosis of organic disease in IBS patients was relatively short (13.08 ± 8.51 mo), therefore most likely indicating misclassification or misdiagnosis due to a prodromal phase of an organic disorder. The low prevalence of misclassification of organic diseases in our cohort is similar to that reported previously.[11,12,15,21,22] This finding can be

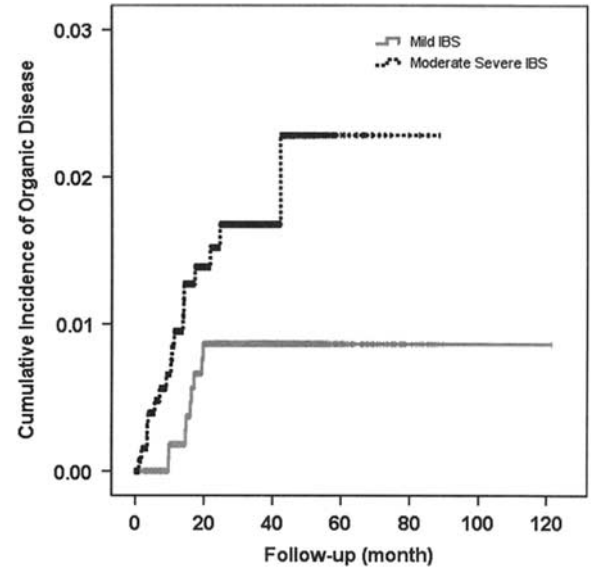

FIGURE 1. Kaplan-Meier survival analysis for the cumulative incidence of diagnosis of organic diseases according to severity of antecedent IBS diagnosis.

attributed to the high yield of positive diagnosis of IBS,[2,8,9] and is similar to a recent prospective study by Begtrup et al[27] who found that a positive strategy toward IBS diagnosis was noninferior to a strategy of exclusion. However, it is also possible that the prerequisite for medical investigations before diagnosing IBS, and particularly in subjects with debilitating symptoms (that had to undergo endoscopy), as well as the fact that the final diagnosis of IBS had to be made by an expert gastroenterologist, also reduced the rate of misdiagnosis of organic disease in our study population.

Interestingly, most of the misclassified cases in our cohort were related to IBD. The requirement for negative celiac serology and normal thyroid function before the diagnosis of IBS may explain the low rates of misdiagnosis of Celiac disease and thyroid disorders. In contrast, there is no actual available biomarker for IBD, although normal blood count and C-reactive protein levels were mandatory for the diagnosis of IBS. Even though colonoscopy and small bowel imagining were performed in subjects with moderate to severe symptoms, small bowel disease possibly could have been missed.[28] The clinical association between IBS and IBD was reported in various studies.[13,14] Furthermore, symptoms compatible with IBS were significantly higher in patients with IBD, even among those in remission, compared with non-IBD controls.[29] These symptoms could represent subclinical inflammation and immune activation that progress in severity toward the clinical expression of IBD. This could be due to abnormal neuronal responses causing hyperalgesia, allodynia, and altered motility.[30,31]

The severity of symptoms in our study was measured by the consequential disability, based on working day loss, as well as the primary physician's opinion (based on the severity and frequency of abdominal pain and other symptoms), and was based on previous reports[32,33] and on the Rome foundation team report on IBS severity.[17] We found that augmented severity of symptoms attributed to IBS increased the risk for diagnosis of organic diseases by 2.26. The fact that this effect was significant even in the small group of misdiagnosed subjects supports the reliability of this finding. Although interpreted with caution, these results may point toward the need for consideration of further gastrointestinal investigation in cases of moderate to severe symptoms attributed to IBS.

The strength of this study includes its large sample size and the multiplicity of data. The period of observation was also reasonably long, reducing the possibility of misdiagnosis of significant organic disease during follow-up of the IBS patients. This study provides important data on the prevalence and risk factors of misclassification of IBS, and supports the recommendations for gastrointestinal evaluation in patients with debilitating symptoms related to IBS. Another fact that supports our results relates to the meticulous medical follow-up during active military service. This reduces the probability of misdiagnosis of significant organic disorders, as most of the organic disorders elicited in this study (IBD, Celiac disease, and any malignancy) are incompatible with military service with immediate discharge.

Our study has few limitations. The first limitation is related to the interval of follow-up. Although the mean follow-up was fairly long, it is possible that new cases of organic disease may have been diagnosed after the cessation of the study. Another limitation relates to the demography of the population. In this study, the population consisted of predominantly young males. This varies from the common western primary or secondary care setting, whereby the majority of patients consulting with symptoms suggestive of IBS are female and of an older age. Furthermore, the demographics of the study population may also account for the low rate of misclassification of organic disease. In addition, the intensive investigation that military personnel undergo may also account for the low misclassification of organic disease, therefore possibly reducing its applicability for clinicians consulting in routine primary or secondary care settings.

In conclusion, in our study population, the incidence of significant organic disorders in previously diagnosed IBS patients was low, as previously described. We found that increased symptoms severity was a significant risk factor for the misclassification of organic disorders. This risk factor can be easily assessed and should be considered in the process of the diagnosis of IBS.

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