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A low frequency of post infection-IBS in patients attended in a tertiary referral center in México

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ABSTRACT

Background: PI-IBS prevalence is around 10.1%-14.5% ≥ 12 months after infectious gastroenteritis in North America, Europe and Asia. However, there are no studies from Latin America. Two previous studies in Mexico suggest a low incidence of 5%.

Aims: to determine the prevalence of PI-IBS in patients attended in a tertiary-care center, as well as IBS subtypes, severity, other digestive symptoms and red flags *vs* nPI-IBS.

Methods: seventy IBS patients screened for immunological research completed the Rome III, Spiller's for PI-IBS and IBS-SSS questionnaires. PI-IBS prevalence was determined according to three criteria sets. C1: ≥ 2 episodes of sudden onset, onset while traveling,

initial illness with any of the following symptoms, fever, vomiting, bloody diarrhea and a positive stool culture. C2: sudden onset and > 2 episodes of fever, diarrhea, vomiting and bloody diarrhea. C3: sudden onset after an infectious episode such as a positive culture or onset with ≥ 2 episodes of fever, vomiting, diarrhea, rectal bleeding and foreign travel. Items were dichotomized as present or absent and compared using the Fisher's exact and Mann-Whitney U tests.

Results: PI-IBS prevalence was as follows. C1: 5.7%, C2: 0 and C3: 1.4%. There were no IBS-C or IBS-M cases. In the C1 group, one case was mild and three were moderate IBS, which was similar to the non PI-IBS group. One case in the C3 group had mild IBS. There were no differences in the frequency of esophageal, gastroduodenal, anorectal, bloating/distension and red flags between PI-IBS and non PI-IBS groups (analyzed only for C3).

Conclusions: in Mexico, there is a very low prevalence of PI-IBS in patients from a tertiary-referral center. However, it varies according to the surrogate-criteria used. The later needs to be taken into account when performing PI-IBS studies.

Key words: Post infection IBS-(PI-IBS). Prevalence. Surrogate diagnostic criteria. Mexico.

INTRODUCTION

Irritable bowel syndrome (IBS) is considered as one of the most frequent functional gastrointestinal disorders (FGID), which are known worldwide as disorders of gut-brain interaction (DGBI) (1,2). However, its prevalence varies significantly due to different diagnostic criteria, surveys and sample methods of the studies (2). IBS is a multifactorial disorder with several described etiological factors, including an increased epithelial permeability, dysbiosis, inflammation, visceral hypersensitivity, epigenetics and genetics and altered gut-brain interactions (3). In addition, a group of patients develop IBS after an enteric infection, so called post infection-IBS (PI-IBS) (4). In fact, it has been proposed that a previous gastrointestinal infection, together with female sex and a younger age are the most important single factors for developing IBS (3). There is currently no validated

definition for PI-IBS. However, the recently published Rome Foundation Working Team proposed to diagnose PI-IBS as new-onset, Rome IV criteria-positive IBS following an episode of acute gastroenteritis in individuals who did not suffer from IBS prior to the infection (5). The incidence of PI-IBS has been reported in the range of 3% to 30% (4). Although there are more studies of PI-IBS following bacterial enteritis, as many as 41.9% of the cases of PI-IBS were related to previous parasitic infections, compared to only 13.8% following bacterial infections (4,6-9). Furthermore, PI-IBS can also emerge after a viral gastroenteritis such as a norovirus infection.

Reports of PI-IBS prevalence vary not only according to the involved pathogen but also the geographical region, the suspicion of infectious gastroenteritis, clinical and laboratory proof of an infection, patient follow-up after the acute episode and the criteria that were used to diagnose IBS (10). In a systematic review of 45 studies, the pooled prevalence of PI-IBS was found to be 10.1% and 14.5% more than 12 months after the infectious episode (11). Interestingly, this systematic review only identified studies performed in North America, Europe and Asia, whereas no studies from Africa or Latin America were identified (11). Another study was recently published based on a very large internet survey and reported that 13.3% of cases met the criteria for PI-IBS (12). This survey provided questionnaires in eight languages including two versions in Spanish, one for Spain and one for Mexico. However, 74% of the subjects were from Europe and the majority were from Italy, The Netherlands, Germany and Spain. In fact, there was at least one return from another 107 countries (12). The study also concluded that PI-IBS was significantly associated with living in Northern Europe and North American.

To the best of our knowledge, PI-IBS has not been studied in the Latin America population and it is scarcely seen in the clinic, at least in Mexico. In fact, two previous small studies performed for other reasons in tertiary referral centers in Mexico found a prevalence of PI-IBS of 5.8% and 4.8%, respectively (13,14). Accordingly, the prevalence of PI-IBS in Mexico seems to be lower than that reported in other parts of the world (11,12). Therefore, this study aimed to analyze the frequency of PI-IBS in IBS Rome III patients from a tertiary referral center in Mexico, based on different surrogate diagnostic criteria.

In addition, the IBS subtypes, IBS severity and the frequency of other gastrointestinal symptoms and red flags were compared between PI-IBS and non-PI IBS patients.

METHODS

IBS patients that presented for the first time the Coloproctology Service at the Hospital General de México Dr. Eduardo Liceaga, in Mexico City, who were screened to participate in immunological research studies in IBS were included in this study. The hospital is a national referral center and the main hospital of the public health system. Patients were between 18 to 65 years of age. Patients with a previous history of celiac disease, inflammatory bowel disease or with an acute infectious disease were excluded. In addition, patients are routinely given a flexible sigmoidoscopy as part of the consultation in the Coloproctology Service. Therefore, cases with any organic finding such as mucosal ulcerations or signs of inflammatory or infectious diseases were also excluded. Subsequently, all patients answered the Rome III Adult Questionnaire for FGIDs (RIIIAQ) (15), the IBS-Severity Scoring System (IBS-SSS) (16) and a questionnaire based on Spiller's criteria for PI-IBS (17). In addition, a questionnaire including epidemiological characteristics and recall of IBS-symptom onset was also administered.

The RIIIAQ, which has been previously translated into Mexican Spanish (18), was used to diagnose IBS and to determine IBS subtypes: IBS with constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M) and non-subtyped (IBS-U), as well as for the presence of other gastrointestinal symptoms and red flags. The IBS-SSS is an IBS severity scale that is easy to use, has reasonable psychometric validity and reproducibility and can therefore be used to assess severity in research and clinical care (19). It is based on patient experience over the previous ten days in five issues, including the severity and the number of days with abdominal pain, severity of abdominal distension, satisfaction with bowel habits and general interference of IBS symptoms in patients' lifestyle. It can be mild, moderate and severe as indicated by scores of 75 to 175, 175 to 300 and > 300, respectively. The maximum achievable score is 500 (16). This questionnaire has been translated into Spanish and has been used in previous cross-cultural studies that have included patients

from Mexico (20).

The Spiller questionnaire has been used as a surrogate for the diagnosis for PI-IBS (17). Accordingly, three sets of criteria were used to determine the prevalence of PI-IBS:

– Criteria 1: patients were considered to have PI-IBS if they fulfilled Rome III criteria for IBS with normal laboratory tests and two or more of sudden onset episodes, onset while traveling or an initial illness characterized by fever, vomiting, bloody diarrhea or a positive stool culture (17).

– Criteria 2: in the presence of a sudden onset episode (with or immediately after an infectious illness or during or immediately after foreign travel) and more than two of the following symptoms: fever, diarrhea, vomiting or bloody diarrhea. This questionnaire was used in one of our previous studies (14).

– Criteria 3: PI-IBS prevalence was also determined according to the criteria used in the recent internet survey by Card et al. (12) as follows: a sudden onset of IBS and when it occurred suddenly, whether an infectious illness was also noted. Supporting evidence for the diagnosis of PI-IBS included sudden onset after an infective episode diagnosed either by a positive stool culture or acute onset of new bowel symptoms associated with two or more of the following: fever, vomiting, diarrhea, rectal bleeding or onset during foreign travel (12). Cases that did not fulfill the criteria for PI-IBS are referred to herein as non PI-IBS.

Statistical analysis

Categorical and continuous variables were expressed as percentages and mean and standard deviation (SD), respectively. The frequency of PI-IBS and non PI-IBS as well as the severity (mild, moderate and severe) were expressed as percentages. Patients' recall of symptom onset in years was reported as the mean ± SD, median and mode due the small number of patents. Furthermore, the PI-IBS item scores were dichotomized as present or absent and were compared with the exact Fisher's test and Mann-Whitney U test, when appropriate. In addition, other gastrointestinal symptoms included in the RIIIAQ were sub-grouped according to their target organs as esophageal, gastroduodenal and anorectal

symptoms, while bloating or distension was left as an independent group. In addition, the prevalence of each red flag included in the RIIIAQ was reported in PI and non PI-IBS. These gastrointestinal symptom groups and the red flags were analyzed as dichotomized data using the independent bilateral proportion test. Analyses were performed using the IBM SPSS Statistics for windows version 21.0, Armonk, NY: IBM Corp.

This study is part of a larger research project of the immunological aspects in IBS that was approved by the Institutional Review Board of the Hospital General de México "Dr. Eduardo Liceaga" (DI/15/107/04/020) and the Research Division of the Faculty of Medicine of the Universidad Nacional Autónoma de México (117/2014). All of the patients signed and informed consent.

RESULTS

Seventy Rome III-IBS patients with a mean age of 43.3 ± 14.8 years, including 53 (75.7%) females and 17 (24.3%) males, were included in the study. The prevalence of PI-IBS varied according to the three sets of criteria used. The highest prevalence found was 5.7% with criteria 1, whereas no PI-IBS patients were identified with criteria 2 and only one patient was found with criteria 3. In terms of IBS subtypes, there were no IBS-C or IBS-M among our PI-IBS patients, which included two IBS-D and two IBS-U patients. In contrast, the non PI-IBS group included all subtypes of IBS with the most predominant one being the IBS-C. However, there were no differences in the subtype distribution due to the small number of patients in the PI-IBS group. Furthermore, the majority of the PI-IBS reported a moderate IBS similar to the non PI-IBS patients and there were no differences in the recall of symptom onset between the PI and non-PI groups (Table 1).

With regard to the prevalence of other gastrointestinal symptoms of the Rome III Questionnaire among the PI-IBS, we only reported this for criteria 1 patients, taking into consideration that there were no PI-IBS patients identified based on criteria 2 and only 1 patient based on criteria 3. We also reported the prevalence of these symptoms in the non PI-IBS group (Table 2). Accordingly, there were no differences in the frequency of esophageal, gastroduodenal, anorectal symptoms, bloating/distensions or red flags

between the criteria 1 PI-IBS patients *vs* the non PI-IBS group.

DISCUSSION

A very low prevalence of PI-IBS of 5.7% was found in this cohort of IBS patients according to Rome III criteria that were attended in the main public tertiary-referral center in Mexico. However, this rate varied based on the surrogate criteria used and was as low as 1.4% to zero, accordingly. In addition, there were no differences in the symptom severity according to the IBS-SSS questionnaire, the recall of years of IBS symptom onset or the presence of extraintestinal symptoms or red flags included in the RIIIAQ, between the PI and non PI-IBS patients. To the best of our knowledge, this is the first study to determine the prevalence of PI-IBS in Mexico in a well-characterized patient cohort that attended a national referral hospital and the first one in a Latin American population. Two important issues should be discussed herein: the low prevalence of PI-IBS in a Latin American population and the different rates according to the surrogate criteria used.

The prevalence of PI-IBS using the Rome III criteria is very low in Mexico and similar to that found in two other studies, which were not specifically designed to determine the frequency of PI-IBS in patients diagnosed with Rome I and Rome II criteria (13,14). The 5.7% to 1.4% rate found in this study are much lower than the 10.1% to 14.5% rate reported by Klem et al. in their systematic review of studies from North America, Europe and Asia. Furthermore, there were no significant differences in the prevalence of PI-IBS according to the geographical region in that review. In Europe, the prevalence was 13.0% (95% CI: 8.1-20.3), 12.2% (95% CI: 9.9-14.8) in Asia and 7.5% (95% CI: 3.8-14.1) in North American with studies from the US and Canada (11). The later one being the closest prevalence-rate of PI-IBS to that found in the current study. However, this figure is still higher than that found in Mexico, which considered the southernmost country of North America, although a Latin American one, with different cultural and hygiene factors that may influence the prevalence of DGBI (20,21). Interestingly, one study that was included in the systematic review by Klem et al. (11) was performed by Okhuysen et al. to determine the prevalence of PI-IBS in 169 students when they returned to the US after

five weeks in Mexico (22). Sixty-one (63%) developed diarrhea while in Mexico, mostly due to enterotoxigenic and enteroaggregative *Escherichia coli*. Of these, six were newly diagnosed with PI-IBS six months later (22).

On the other hand, the Klem et al. systematic review also reported that 41.9% of patients with enteritis caused by protozoa or parasites developed IBS (22). We were not able to determine the etiological factor of the enteritis causing PI-IBS in our patients. However, the high rate of parasitic etiologies by Klem et al. is in contrast with a study performed in an open population in Central America, where no differences were found in the parasite carriage between subjects that fulfilled the criteria for IBS and controls (16.6% *vs* 15.4%). Thus, suggesting that IBS in our region is not related to parasites (23). However, a previous parasite infection was reported by 16% of those fulfilling IBS-Rome III criteria *vs* 5.07% of controls in a study of an indigent population in the US-Mexico border area of El Paso-Texas, 90% of whom were born in Mexico (24). The differences between the two previous reports suggest that living in a more "clean" environment may predispose to the development IBS in the presence of parasitic infections. Although, this needs to be investigated further.

As discussed elsewhere, it is possible that the hygiene hypothesis (25) may explain the lower frequency of PI-IBS in Mexico compared to that reported in other countries (11,12). This hypothesis proposes that improved sanitation and a decreased exposure to enteric infections early in childhood may lead to a greater susceptibility to develop an inappropriate immunologic response upon exposure to new antigens (e.g., gastroenteritis) later in life. Thus, predisposing to allergic and inflammatory conditions (26). However, an increased exposure to microbial factors in childhood may stimulate the immunological system, providing a protection upon exposure to enteric organisms in adulthood. Thus decreasing the onset of PI-IBS, which may be the case in Mexico and other underdeveloped countries. In contrast to this theory, Koloski et al. found in a random population sample from Sydney, Australia, that PI-IBS was present in 20% of those who developed IBS. In general, IBS in adulthood was associated with a shorter duration of breastfeeding, sharing a bedroom, exposure to herbivore pets and hygiene factors up to

five years of age. However, PI-IBS was only associated with a previous bout of gastroenteritis and antibiotic use with no association with overseas travel, exposure to pets or bedroom sharing up to the age of five. Thus, they proposed that rather than the hygiene hypothesis, the data provided indirectly support the "disappearing microbiome theory". According to this theory, IBS development may result due to an impaired gut-microbiota colonization and immunoregulation early in life, as a consequence of factors such as a cesarean section, shorter breastfeeding, the maternal use of antibiotics and formula feeding babies, among others (27). It is possible that in Mexico, the absence of "disappearing microbiome" factors such as lower rates of cesarean sections, gastric suctioning at birth and longer breastfeeding periods protect later in life against IBS when exposed to enteric infections (PI-IBS). Furthermore, "non-hygiene" factors due to lower socioeconomical conditions such as sharing a bedroom early in life, pet exposure and living in rural areas may also play a protective role (27,28). Recently, Bloomfield et al. recommended that strategies to restore the microbiome should be implemented, including natural childbirth, breast feeding, increased social exposure through sports and other outdoor activities, diet and an appropriate or rational antibiotic use (28).

The second issue to discuss is the differences in the prevalence-rates of PI-IBS according to the three sets of surrogate diagnostic criteria. This is an important issue as many of the epidemiological studies on PI-IBS are based on similar methods (12,27,29-31), unless populations can be followed-up after the infectious enteritis outbreaks (32-35). The absence of PI-IBS using the more strict criteria 3 is an interesting one, as these were also used by Card et al. in their recent large internet survey. In this study, the majority of subjects were from Europe (12), a contrast that strengthens our results and the concept that PI-IBS is very scarce in Mexico. In addition, the different rates of PI-IBS based on the various surrogate criteria should be taken into consideration when performing epidemiological studies with a retrospective diagnosis of PI-IBS. This aspect deserves further investigation. The currently ongoing Rome IV Global Epidemiological study may shed light on this issue.

The current study has some limitations. First, it is a retrospective study of consecutive patients and recall bias may influence the low prevalence of PI-IBS in this Rome III-IBS population. However, as mentioned earlier, the current results are in agreement with two previous studies from Mexico using the Rome I and Rome II criteria for IBS. Secondly, this is a small study sample and considers the low prevalence of PI-IBS in Mexico. A much larger sample is needed to make comparisons between the PI-IBS and the non PI-IBS patients. However, this is a well-characterized set of patients from a tertiary referral center. Therefore, findings such as the absence of IBS-C patients among the PI-IBS are in agreement with other studies that found a predominance of IBS-D and an absence of IBS-C subtypes in PI-IBS patients (5,12,27), even though the sample group was extremely small. Third, as this is a patient sample, the currently found prevalence rates of PI-IBS may not be applicable to the general population. The ongoing global epidemiological study of DGBI using the Rome IV criteria may shed light on the population-based frequency on PI-IBS, not only in Mexico, but in other Latin American Countries such as Argentina, Brazil and Colombia. Finally, we did not assess the health related quality of life to compare it between the PI and non-PI IBS patients.

In conclusion, we found a very low prevalence of PI-IBS among a well-characterized group of IBS-Rome III patients that attended a tertiary referral center in Mexico. To the best of our knowledge, this is the first specific study to determine the prevalence of PI-IBS patients in Mexico and Latin America. Although the study sample and the number of PI-IBS patients was small, the data is consistent with that suggested in two previous studies in Mexico. Furthermore, there were no IBS-C patients identified among them. The later one is in agreement with that reported in other epidemiological studies on PI-IBS. Finally, the prevalence-rates varied according to the surrogate diagnostic criteria used. This issue needs to be taken into consideration when performing prevalence studies of PI-IBS and is a subject that deserves further investigation.

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Table 1. Prevalence of PI-IBS, subtypes and severity, according to different diagnostic criteria

		Criteria 1			*Criteria 2*		*Criteria 3*	
		PI-IBS	Non PI-IBS	p-value	PI-IBS	Non PI-IBS	PI-IBS	Non PI-IBS
Prevalence n (%)		4 (5.7)	66 (94.3)		---	70 (100)	1 (1.4)	69 (98.6)
Age Mean (SD)	Years	38.25 (24.66)	43.61 (14.24)	0.317	---	43.3 (14.8)	24	43.58 (14.72)
Sex n (%)	F	3 (75)	50 (75.8)	0.973	---	53 (75.7)	1 (100)	52 (75.4)
IBS-subtypes n (%)	IBS-C	---	21 (31.8)	0.281	---	21 (31.8)	---	21 (31.8)
	IBS-D	2 (50)	17 (25.8)		---	19 (28.8)	---	19 (28.8)
	IBS-M	---	10 (15.2)		---	10 (15.2)	---	10 (15.2)
	IBS-U	2 (50)	18 (27.3)		---	20 (30.3)	1 (100)	19 (28.8)
Severity IBS-SSS n (%)	Mild	1 (25)	18 (27.3)	0.963	---	19 (28.8)	1 (100)	18 (27.3)
	Moderate	3 (75)	45 (68.2)		---	48 (72.7)	---	48 (72.7)
	Severe	---	3 (4.5)		---	3 (4.5)	---	3 (4.5%)
Recall of symptom onset mean (SD)	Years	6.75 (6.65)	5.4 (6.07)	0.720	---	5.48 (6.06)	1.00	5.54 (6.08)
Recall of	Years	5 (1)	4 (1)	0.720	---	4 (1)	1.00 (1)	4 (1)

symptom onset median (mode)								

PI-IBS: post infection-irritable bowel síndrome; IBS-C: irritable bowel syndrome with constipation; IBS-D: irritable bowel syndrome with diarrea; IBS-M: mixed irritable bowel síndrome; IBS-U: unsubtyped irritable bowel síndrome; IBS-SSS: Irritable Bowel Syndrome-Severity Scoring System; F: female; n: number; %: percentage; SD: standard deviation.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Table 2. Other gastrointestinal symptoms in PI and non PI-IBS

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ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Target organ	*Gastrointestinal symptoms*	*Criteria 1* *n (%)*		
		PI-IBS	*Non PI-IBS*	*p value*
Esophageal	Feeling of a lump, fullness or something stuck in the throat*	2 (50)	28 (42.4)	0.648
	It hurts to swallow when eating or drinking	-	13 (19.7)	
	Pain or discomfort in the middle of the chest (not related to heart problems)	1 (25)	28 (42.4)	
	Chest pain, that felt like burning	1 (25)	20 (30.3)	
	Heartburn (a burning discomfort or burning pain in the chest)	4 (100)	46 (69.7)	
	Food or drinks get stuck after swallowing or go down slowly through the chest	1 (25)	27 (40.9)	
Gastroduodenal	Feeling uncomfortably full after a regular-sized meal	1 (25)	41 (62.1)	0.401
	Feeling unable to finish a regular-sized meal	1 (25)	35 (53)	
	Having pain or burning in the middle of the abdomen, above the belly button but not in the chest	3 (75)	41 (62.1)	
	Having bothersome nausea	2 (50)	39 (59.1)	
	Vomiting	1 (25)	21 (31.8)	
	Make yourself vomit	-	4 (6.1)	
	Having food come back up into the mouth	1 (25)	22 (33.3)	
	When food came back up into the mouth, it usually stays in the mouth for a while before swallowing it or spitting it out	-	10 (15.2)	
	Retching (heaving) before food came up into the mouth	-	7 (10.6)	
	Vomiting or feeling sick to the stomach when food came up into the mouth	-	11 (16.7)	
	Experiencing bothersome belching	1 (25)	41 (62.1)	
Anorectal	Need to press on or around the bottom or remove stool in order to complete a bowel movement	-	26 (39.4)	
	Having difficulty relaxing or letting go to allow the stool	1 (25)	33 (50)	

*During the last three months. PI-IBS: post infection-irritable bowel syndrome.