

## The role of infection in irritable bowel syndrome

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### Abstract

A clinically distinct subset of Irritable Bowel syndrome (IBS) could be induced or exaggerated by bowel infection that is called post-infective IBS (PI-IBS) which is characterized by diarrhea predominant symptoms with less psychiatric illness. The purpose of this work was to study whether some bowel infections contribute to the pathogenesis of IBS and whether the treatment of such infections reduces IBS symptoms.

100 patients with symptoms suggestive of IBS according to Rome II Criteria were chosen from Internal Medicine outpatient clinic-Al Hussein university hospital. They were 64 females and 36 males, aged 18-52 years old with mean age  $38,2 \pm 3,6$  years. They were submitted to: full clinical examination and frequent stool examinations (direct smear and culture) before, soon after and six months after administration of drug therapies for common stool-positive associated bowel infections (diloxanide for *E. histolytica*, metronidazole for *Giardia lamblia*, Ketoconazole for *Candida*, ciprofloxacin for *Salmonella* and neomycin for *Pseudomonas*).

Results obtained showed that 24% of patients had diarrhea predominant symptoms, 13 patients (54%) out of them had history suggestive of acute gastroenteritis.

80 patients had initial positive stool examination and continued the post treatment six months follow up study. Out of them, 13 patients had stool positive for *Salmonella typhi* mixed with *E. histolytica*; ten of them (76.9%) showed a statistically significant persistent clinical and laboratory improvement after ciprofloxacin therapy ( $P < 0.01$ ). So *Salmonella typhi* may be implicated in IBS pathogenesis.

Six patients showed isolated *Giardia lamblia* infection; four of them (66.7%) showed a statistically significant persistent clinical and laboratory improvement after metronidazole therapy ( $P < 0.05$ ). *Giardia lamblia* parasite may be considered in triggering or exaggerating IBS symptoms.

24 patients had isolated *E. histolytica* infection; only one of them (4.2%) showed sustained clinical and Laboratory improvement after diloxanide therapy -statistically insignificant result- ( $P > 0.05$ ). This finding makes the correlation between *E. histolytica* infection and IBS is unlikely.

20 patients had isolated *Candida* overgrowth on stool examination; eight of them (40%) showed a statistically significant clinical and laboratory improvement after Ketoconazole therapy ( $P < 0.05$ ). Therefore *Candida* overgrowth may induce or exaggerate IBS symptoms.

Finally, no growth was noticed for shigella sp. or *E. coli*, this may exclude the role of such organisms in IBS pathogenesis.

### Introduction and Aim of the Work:

Irritable bowel syndrome (IBS) is a group of symptoms of multidetermined pathogenesis. Its symptoms seem to be generated by gut abnormalities in motility, epithelial function and sensory perception (Tornblom *et al.*, 2003). These symptoms include abdominal pain, cramps, bloating and eccentric bowel movement ranging

from diarrhea to constipation. Symptoms are variable in intensity from one patient to another and from one time to another in the same patient. (Neal, *et al.*, 2002). IBS represents 30 – 40% of GIT outpatient visits. It is prevalent among middle age individuals particularly females (Mark *et al.*, 2000).

## The role of infection in irritable bowel syndrome

Nowadays there is an emerging evidence for the role of infection in the pathogenesis of IBS. A clinically distinct subset of IBS is caused by enteric infection that is called post-infectious irritable bowel syndrome (PI-IBS). It is characterized by diarrhea predominant symptoms, less psychiatric illness and increased serotonin-containing enteroendocrine cells (EC) compared to those with non post infective – IBS (Simon *et al.*, 2003). Clinically, their manifestations include abdominal pain, bloating, functional diarrhea, expelling stools, urgency and even stool incontinence (Laurine, 2003).

The purpose of this work was to study whether bowel infections play a role in the pathogenesis of IBS and whether the treatment of such infection reduces IBS-symptom.

### Patients and Methods:

The study was carried out on 100 patients with symptoms suggestive of IBS according to Rome II criteria. They were selected from Internal Medicine out patient clinic at Al Hussien University hospital (from Oct. 2003 to May 2004). They were 36 males and 64 females, aged 18-52 years with mean age  $38.2 \pm 3.6$  years. Patients fulfilled symptoms essential for diagnosis of IBS, reported by Thompson *et al.* (1999) according to Rome II criteria: at least three months of continuous or recurrent abdominal pain or discomfort that has at least two out of three features: (1) relieved with defecation and/or. (2) Onset associated with frequency of stool and/or. (3) Onset associated with a change in the consistency of stool, in addition to other supportive but not essential symptoms such as bloating and passage of mucus.

All patients were subjected to the following:-

\* **Full history taking:** including diet habits, change in bowel habits, bloating, abdominal pain and its relation to defecation; whether these symptoms followed an attack of acute gastrointestinal infection. History of psychiatric troubles was also taken.

\* **Thorough clinical examination:** for palpable or tender colon, gaseous distension and intestinal sounds (exaggerated peristalsis).

\* **Stool examination:** stool were collected from patients in clean cups to be investigated for the presence of microorganisms that may be contributed in IBS pathogenesis; using the following; according to Collee *et al.*, 1997 & Collin *et al.*, 2001:

a - Direct smear examination: saline iodine dissolved stool samples were examined by ordinary microscopy for the presence of *Entameba histolytica*, *Giardia lamblia* parasites and *Candida* overgrowth.

b - Culture of Stools: stools were inoculated on selenite broth medium, incubated at 37°C for 18 hours, then inoculated on MacConky's agar and DCA agar plates which were reincubated at 37C for 24 hours.

Any growth on plates was studied for colonial morphology then gram stained films from colonies were prepared to study morphology of the cultivated organisms and its biochemical reactions.

\* **Courses of specific treatment:** were given for patients with stools positive for various gut microorganisms as follow:

- Diloxanide 500 mg three times a day for 10 days for *E. histolytica*, (Carlos *et al.*, 2001).

- Metronidazole 2000 mg once a day for 3 successive days for *Giardia lamblia* (Carlos *et al.*, 2001).

- Ketoconazole 200 mg once a day for ten days (Shubhada *et al.*, 2001).

- Ciprofloxacin 500 mg twice a day for 21 days for salmonella typhi, paratyphi A & B. (Carlos *et al.*, 2001).

\* **Post treatment clinical evaluation** and stool examination were carried out, soon after termination of specific antimicrobial courses and after six months for only 80 patients out of 100 studied patients with IBS (eight patients had

free stools and 12 patients discontinued the study).

\* **Statistical Methods:** obtained data were analyzed by computer using (a) mean value (b) standard deviation SD±

(c) Chi-square test: to test for significant relation between qualitative variables or percentages.

- Significant values were considered at : P < 0.05.

**Results:**

**Results obtained were analyzed, tabulated and illustrated in: tables (1-4)**

**Table (1):** Groups of Studied IBS patients in relation to bowel habit symptoms.

Group	IBS patients : No. = 100	
	No.	%
Constipation predominant patients	33	33%
Diarrhea predominant patients	24	24%
Alternating constipation & diarrhea patients	43	43%

**Table (2):** Prevalence of patients with history suggestive of acute gastroenteritis prior to occurrence of IBS symptoms and their mood state.

History suggestive of acute gastroenteritis	IBS patients: No. = 100			
	+ve history patients		-ve history patients	
	No.	%	No.	%
	13	13%	87	87%
Mood state	-average mood: 12 patients -anxiety: one patient		-average mood: 48 patients - anxiety: 24 patients - depression:15 patients	

**Table (3):** Initial laboratory findings of stool examination:

Stool examination (direct smear & culture)	IBS patients No.=100	
	No.	%
<b>A) Negative:</b>	8	8%
<b>B) Positive:</b>	92	92%
<b>(i) Single infection</b>		
- E. histolytica.	25	27.1%
- Giardia Lamblia.	6	6.5%
- Candida.	28	30.4%
<b>(ii) Double infection</b>		
- E. histolytica, & pseudomonas.	1	1.1%
- E. histolytica, & S. typhi.	14	15.2%
- E. histolytica, & candida.	4	4.3%
- E. histolytica, & S. paratyphi – A.	1	1.1%
- E. histolytica, & S. paratyphi –B.	3	3.2%
- Candida & pseudomonas.	1	1.1%
- Candida & S. typhi.	6	6.5%
- Candida & S. paratyphi –A.	1	1.1%
<b>(iii) Triple infection</b>		
-E. histolytica, Candida & pseudomonas	2	2.1%

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**Table (4):** Percentages of post-treatment improvement (both clinical & laboratory) in relation to the type of bowel infection among 80 patients with positive stool examination who continued the six months-follow up study.

	Gut infection	Total No. of patients	No. of patients improved	%	P-value
Singl infection	- E. histolytica,	24	1	4.2%	>0.05
	- Giardia L.	6	4	66.7%	<0.05
	- Candida	20	8	40%	<0.05
Double infection	- E. histolytica + pseud.	1	1	100%	<0.001
	- E. histolytica, +S.typhi	13	10	76.9%	<0.01
	- E. histolytica, +Candida	3	0	0.0%	>0.05
	-E.histolytica,+S.paratyphi.A	1	1	100%	<0.001
	-E.histolytica,+S.paratyphi-B	3	2	66.7%	<0.05
	- Candida + S typhi	6	6	100%	<0.001
	Candida+S.Paratyphi-A	1	1	100%	<0.001
Triple infection	- E. histolytica +Candida + pseudomonas.	2	0	0.0%	>0.05
<b>Total</b>		80	34	42.5%	X2:13.95

### Discussion:

Irritable bowel syndrome (IBS) is one of the common gastrointestinal diseases, usually involve middle age population, predominantly females. It is characterized by abdominal pain, cramps and eccentric bowel movement ranging from diarrhea to constipation (Neal; 2002).

A clinically distinct subset of IBS is induced by gut infections that is called post-infective IBS (PI-IBS) which is characterized by diarrhea predominant symptoms with less psychiatric illness (Simon *et al.*, 2003). This goes with results obtained from this study that diarrhea predominant IBS patients were 24% (table 1). 13 patients (54%) out of them had history suggestive of acute gastroenteritis prior to IBS symptoms without clear history of psychiatric illness (Table 2).

In this study, out of 80 stool positive patients who continued the study, 13 patients showed mixed salmonella typhi and E. histolytica infection; ten patients out of them (76.9%) showed a statistically significant clinical and laboratory improvement after Ciprofloxacin therapy ( $P < 0.01$ ) (table 4). Since patients with isolated E. histolytica infection showed a statistically insignificant clinical and laboratory improvement (4.2%), after diloxanide therapy ( $P > 0.05$ ) (table 4), salmonella typhi infection could be

considered in IBS pathogenesis. This goes with the reports of Jonathan *et al.*, 2001 that IBS symptoms may develop in patients after acute salmonella infection.

Six patients out of the 80 stool positive patients had isolated Giardia Lambliia infection, four patients out of them (66.7%) showed a statistically significant sustained clinical and laboratory improvement after metronidazole therapy ( $P < 0.05$ ) (table 4). This finding is consistent with what was published by Rose, 2002 that concurrent Giardia lamblia infection induced exaggerated IBS symptoms in patients with prior IBS, so Giardia lamblia becomes clinically evident by eliciting symptoms of established IBS.

On the other hand; 24 patients out of the 80 stool positive patients showed isolated E. histolytica infection on direct smear examination, only one of them (4.2%) showed sustained clinical and laboratory improvement after Diloxanide therapy -a statistically insignificant result- ( $P > 0.05$ ) (table 4), therefore E. histolytica infection is unlikely to be implicated in IBS pathogenesis. This finding goes with what was reported by Sinha *et al.*, 2003, that bowel symptoms in IBS with concurrent E. histolytica infection were not related to the parasite in their study. Controversially, this finding doesn't go with what was published

by Madanagopalan *et al.*, (1996) that chronic intestinal amebiasis can present in many forms, one of them is characterized by IBS-like symptoms.

20 patients out of the 80 stool positive patients showed candida overgrowth, eight of them (40%) showed a statistically significant sustained clinical and laboratory improvement after Ketoconazole therapy ( $P < 0.05$ ) (table 4). This finding goes with what was published by William, 2003 that intestinal Candidiasis could be associated with allergic reaction to food and symptoms consistent with IBS symptoms including bloating, cramping gut pain, gurgling in the bowel and diarrhea.

No growth for shigella sp. or *E. coli* was noticed on initial stool culture for all IBS studied patients. This may make the role of shigella sp. & *E. coli* in the pathogenesis of IBS is unlikely. Although this finding is controversial to what was reported by Jonathan *et al.*, (2001) that IBS symptoms may develop in patients following acute infection with such organisms.

### Recommendation

\*\* IBS patients should undergo frequent stool examination to rule out associated bowel infections which may contribute in induction or exaggeration of IBS symptoms. Treatment of such infections may reduce these symptoms.

\*\* Large scale studies on IBS patients are recommended for further and precise finding out the role of different gut infections; including *Campylobacter* infection (which needs a special protocol of stool examination for its diagnosis) in IBS pathogenesis.

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## دور العدوى المعوية فى متلازمة القولون العصبى هانى ابو زيد\* - مجدى عبد الكريم\* - محمود موسى بازيد\* - مصطفى يوسف المشد\*\*

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فى الآونة الأخيرة كثر الحديث عن وجود علاقة مباشرة بين العدوى المعوية والإصابة بمتلازمة القولون العصبى والذي يعرف (بالقولون العصبى ما بعد العدوى) والذي يغلب على أعراضه الإسهال المتكرر وتكون أعراض التأثير النفسى فيه غير واضحة. والهدف من هذا البحث هو دراسة الدور الذى تلعبه الميكروبات المعوية فى الأحداث المرضية لمتلازمة القولون العصبى، وعمّا إذا كان علاج هذه الميكروبات يؤدى إلى تحسن أعراضه.

لهذا الهدف تم اختيار مائة مريض بمتلازمة القولون العصبى (حسب تصنيف روما - 2) من العيادة الخارجية للأمراض الباطنة بمستشفى الحسين الجامعى، منهم 64 أنثى و36 ذكر تراوحت أعمارهم ما بين 18 عام إلى 52 عاماً. وقد تم إخضاع المرضى جميعهم إلى الآتى:-

- استقصاء التاريخ المرضى التفصيلى لهم.
- الفحص الإكلينيكى الدقيق الشامل لهم.
- فحص البراز المتكرر قبل وبعد تناول مضادات الميكروبات المعوية التى أظهرها فحص البراز سواء الفحص المباشر لعينات البراز أو من خلال مزارع البراز.

### وقد أظهرت نتائج البحث ما يلى:-

\* وجود عدد أربعة وعشرين مريضاً من المائة مريض بمتلازمة القولون العصبى الذين شملهم البحث غلب على أعراض المرض لديهم الإسهال المتكرر. وقد أفاد ثلاثة عشر مريضاً منهم بأن لديهم تاريخاً مرضياً يرجح حدوث نزلة معوية حادة لهم قبل معاناتهم من هذه الأعراض.

\* هناك ثمانون مريضاً كان فحص البراز لديهم إيجابياً للميكروبات المعوية ممن أكملوا متابعة الدراسة الى نهايتها.

\* أظهرت الدراسة أن ثلاثة عشر من هؤلاء الثمانين (16%) مريضاً كان فحص البراز لديهم إيجابياً لميكروب السالمونيلا التيفودية مختلطة مع طفيل الانتيميبيا هستوليتكا، وأن عشرة مرضى منهم (76.9%) أظهروا تحسناً اكلينيكياً ومعملياً مستمراً ذا دلالة إحصائية بعد العلاج بعقار سبروفلوكساسين مما يشير إلى أن ميكروب السالمونيلا التيفودية قد يكون له دور فى إحداث متلازمة القولون العصبى.

\* كما أظهرت الدراسة أن ستة من هؤلاء الثمانين مريضاً كان فحص البراز لديهم إيجابياً لطفيل الجياردا لامبليا فقط، وأن أربعة منهم (66.7%) أظهروا تحسناً اكلينيكياً ومعملياً مستمراً ذا دلالة إحصائية بعد العلاج بعقار مترونيدازول مما يوحى بدور هذا الطفيل فى إحداث متلازمة القولون العصبى أو إظهار أعراضه وزيادة حدتها.

- \* وكذلك أظهرت الدراسة أن أربعة وعشرين من هؤلاء الثمانين (30%) مريضاً كان فحص البراز لديهم إيجابياً لطفيل الانتاميبيا فقط ولم يحدث تحسن إكلينيكي ومعملي مستمر ذو دلالة إحصائية إلا في واحد منهم فقط (4.2%) بعد العلاج بعقار الدايلوكسانيد مما يضعف إمكانية وجود علاقة سببية بين طفيل الانتاميبيا ومتلازمة القولون العصبي.
- \* وقد أظهرت الدراسة أيضاً أن عشرين من هؤلاء الثمانين مريضاً كان لديهم نمو فوق العادة لفطر الكانديدا في البراز وأن ثمانية منهم قد أظهروا تحسناً معملياً وإكلينيكيًا مستمرًا إذا دلالة إحصائية بعد العلاج بعقار الكتيوكونازول مما يشير إلى وجود علاقة سببية لفطر الكانديدا في إحداث أو إظهار أعراض متلازمة القولون العصبي.
- \* لم تظهر الدراسة أي نمو لميكروب الشيجيلا أو الإي – كولاى فى مزارع البراز المبدئية التي أجريت لجميع المرضى الذين شملهم البحث مما يستبعد وجود علاقة سببية بين هذه الميكروبات ومتلازمة القولون العصبي.

### التوصيات :

- و يوصى بضرورة إجراء مرضى متلازمة القولون العصبي لفحص البراز المتكرر للبحث عن الميكروبات المعوية التي قد تتسبب في إحداث أو إظهار أعراض المتلازمة.
- كما يوصى بضرورة علاج هذه الميكروبات المعوية وخاصة بالنسبة لميكروب السالمونيلا وطفيل الجياردا وفطر الكانديدا إن وجدت، مما يؤدي إلى تحسن أعراض متلازمة القولون العصبي.
- وكذلك يوصى بإجراء الدراسة على نطاق واسع وعلى أعداد أكبر من مرضى متلازمة القولون العصبي لتوضيح دور الميكروبات المعوية المختلفة بدقة في إحداث وإظهار أعراض متلازمة القولون العصبي ولا سيما ميكروب الكامبيلوباكتر الذي يستلزم تشخيصه بروتوكولا خاصا لفحص البراز.