Chronic Pelvic Pain and Irritable Bowel Syndrome: Is Subclinical Inflammation Bridging the Gap?

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Selection of candidates for study: 40 female patients with confirmed IBS (Rome III), aged under 45 years were consecutively recruited during hospitalization and freely joined this cross-sectional, exploratory study. They were assigned into 2 equal groups, as matched pairs, based upon the presence or absence of CPP (EAU, 2014): 20 patients CPP negative vs. 20 patients CPP positive. A lot of diseases and conditions were ruled out as a result of an integrated, interdisciplinary approach.

Conclusions. Young female IBS patients with concurrent CPP symptoms often experienced other associated functional pain conditions like FM and migraine along with anxiety, more severe abdominal complaints as well as higher gut DB and consecutively subclinical pro-inflammatory status. Strong positive correlations of gut DB to inflammatory markers as well as to CPP symptoms give the relationship IBS-CPP a new perspective.

Keywords: CPP, IBS, inflammation, gut dysbiosis

Irritable bowel syndrome (IBS) is characterized by a multitude of symptoms digestive and extra-digestive that need at some point a multidisciplinary approach. This study aimed at profiling IBS associated with chronic pelvic pain (CPP) in young females. A cross sectional observatory study on 40 consecutive young female patients (under 45 years) with IBS (Rome III) was performed. Patients were assigned in two groups, as matched pairs, based on the presence of chronic pelvic pain (CPP) symptoms: cystalgia, urinary urge and dyspareunia: CPP(+) vs. CPP(-) and undertook clinical examinations with special protocols related to migraine disability, fibromyalgia, temporo-mandibular joint dysfunction, as well as assessment of anxiety and severity of abdominal pain. Laboratory work-up (blood, urine and stool) as well as multiple exams: digestive endoscopy, abdominal and pelvic ultrasound/CT were performed. Results: CPP (+) group displayed higher CRP, TNF-alpha, gut dysbiosis (DB) and abdominal pain severity, as well as assoctated fibromyalgia, migraine and anxiety mood disorder. DB positively correlated with inflammatory markers and symptoms characterizing CPP. In conclusion, young female IBS patients with concurrent CPP symptoms often experienced other associated functional pain conditions like FM and migraine along with anxiety, more severe abdominal complaints as well as higher gut DB and consecutively subclinical pro-inflammatory status. Strong positive correlations of gut DB to inflammatory markers as well as to CPP symptoms give the relationship IBS-CPP a new perspective.

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IBS was diagnosed according to Rome III criteria: 3 months of continuous or recurrent symptoms of abdominal pain or discomfort eventually relieved with bowel movements, associated or not with changes in frequency of defecation or in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> 3 bowel movements per day or < 3 per week); obvious differences in stool appearance (hard, loose, watery or poorly formed stools); presence of mucus in stools; bloating and feeling of abdominal distension; or sensation of incomplete evacuation, straining, or urgency [7]. CPP diagnostic criteria in women patients relied on persistent pain in structures related to the pelvis, often associated with negative cognitive, behavioral, sexual and emotional consequences, as well as various symptoms suggesting lower urinary tract, bowel, pelvic floor or gynecological issues, according to EAU, 2014 [8]. Migraine diagnostic and severity assessment were based on international headache consensus IHC-2 and migraine disability MIDAS scores: 0-5 as minimal, 6-10 as mild, 11-20 as moderate, and 21 or more, as severe disability [9,10]. GAD was scored minor, under 5, moderate, 6-10 and severe, 11-21 [11]. TMJD was assessed as present or absent [12]. FM assessment was based on a protocol examination of painful points, according to ACR, 2010 and scored as 1, minor, 2, moderate and 3 severe [13]. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. Graph Pad Prism 8 software (Graph Pad Software, Inc., La Jolla, CA, USA) was used to perform statistical analysis. Quantitative variables were expressed as mean values (MV) ± standard deviation (SD) and qualitative variables were expressed as percentages. Chi-squared test for comparison of two groups, in cases of categorical analyzed variables, as well as unpaired t test were performed; p values were interpreted with confidence interval CI= 95%, p ≤ 0.05 being considered statistically significant. Nonparametric Spearman correlation test with the calculation of r coefficient and consecutively linear regression equation were realized. Graph representation was performed accordingly.

**Results and discussions**

Demographic and biological baseline data are depicted in Table 1. There were no statistically significant differences related to age or location, marital status, education, CBC and standard biochemistry tests. However, inflammatory markers like HS-CRP (p=0.0132) and TNF-alpha (p=0.001), as well as DB (p=0.0001) were statistically significant higher in CPP positive group.

Clinical characteristics in study population are summarized in Table 2. There were no statistical differences concerning alcohol drinking, cigarettes smoking, oral contraception, occupational stress or previous pelvic surgery. Statistically significant differences were observed in CPP positive group related to more severe scores for abdominal pain (p=0.0025), FM (p=0.0001), MIDAS (p=0.05) and GAD (p=0.03).

Each symptom characterizing CPP associated to IBS was separately analyzed concerning possible link to top clinical and biological parameters which at initially descriptive data distribution demonstrated a significant statistical difference. As seen in Figure 1, cystalgia was strong positive correlated to abdominal pain (r=0.59; p=0.005) and gut DB (r=0.44; p=0.04)
Study of dyspareunia correlations are depicted in Figure 2. We noted a strong positive correlation of dyspareunia to FM (r=0.48; p=0.03) and gut DB (r=0.48; p=0.02).

As illustrated in Figure 3 urinary urge was strong correlated to FM (r=0.45; p=0.04) as well as to gut DB (r=0.53; p=0.01).

As seen n figure below (Figure 4), there is a close positive correlation between DB ranges and inflammation markers, respectively TNF-alpha (r=0.9; p<0.0001) and CRP (r=0.8; p<0.0001).

IBS is well known as intestinal disorder often associated to other functional pain conditions and various extra-intestinal co-morbidities [14-16] Several pelvic floor conditions are reported by multiple studies as co-morbidities associated to IBS: pelvic organ prolapse, urinary urgency, latency or incontinence [17,18], as well as sexual dysfunctions[19,20]. Many researchers observed that there is a greater possibility of associated conditions like IBS, FM and chronic fatigue syndrome in women with interstitial cystitis or painful bladder syndrome and also in those with higher levels of anxiety or depression [21]. The question whether these disorders have some common underlying pathways is still open to debates [22-24]. There is indeed a crosstalk between the bladder and bowel and a lot of overlap between CPP and overactive bladder symptoms [25,26]. There is also a complex physiology of urologic and gastrointestinal functions based on the convergence of dorsal root ganglia neurons, resulting in multiple pelvic organs sensors, located in diverse organs from pelvic area, such as: colon, bladder and gynecologic organs. Gut microbiota DB could alter this inter-organ dialogue by corruption of many pathways to the normal existing brain-gut connection. Moreover, it is by now demonstrated that gut DB could trigger inflammatory pathways that could manifest not only local, as an interstitial cystitis, in these cases, but also in different area, far from pelvic location [27, 28]. In this view, our study observations showed positively good correlations between DB ranges and inflammatory markers, as well as between DB and all pelvic assessed symptoms, such as: urinary urge, dyspareunia and cystalgia. Based on these preliminary data, next question in line is: could probiotics represent a possible alternant tool to alleviate pelvic inflammation, triggered by gut DB? If these findings are validated by prospective studies, it could provide an interesting new perspective on the relationship IBS-CPP.
Conclusions
Young female IBS patients with concurrent CPP symptoms often experience other associated functional pain conditions like FM and migraine, along with anxiety, more severe abdominal complaints as well as higher gut DB and consecutively subclinical pro-inflammatory status. Strong positive correlations of gut DB to inflammatory markers as well as to CPP symptoms give the relationship IBS-CPP a new perspective.

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