

# Clinical evidence on visceral pain. Systematic review

## Evidência clínica sobre dor visceral. Revisão sistemática

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Visceral pain is induced by abnormalities of organs such as stomach, kidneys, bladder, gallbladder, intestines and others and includes distension, ischemia, inflammation and mesenteric traction. It is responsible for physical and psychic incapacity, absenteeism and poor quality of life. This study aimed at discussing major aspects of visceral pain with regard to prevalence, etiology and diagnosis.

**CONTENTS:** According to Evidence-Based Medicine concepts, visceral pain etiology, diagnosis and prognosis were reviewed in LILACS, EMBASE and Pubmed databases. Therapeutic studies were not selected. The following terms were used as search strategy: (“visceral pain”[MeSH Terms] OR (“visceral”[All Fields] AND “pain”[All Fields]) OR “visceral pain”[All Fields]). Only studies published in Portuguese, English or Spanish were included. Narrative reviews with opinionated content and specific therapeutic procedures of medical specialties were excluded. Studies on visceral pain related to heart, cancer and musculoskeletal diseases and pregnancy were also excluded.

**CONCLUSION:** Visceral pain is a heterogeneous condition where most frequent presentation is abdominal pain in the course of irritable bowel syndrome. Other diseases induce visceral pain and adequate diagnosis is critical for effective treatment.

**Keywords:** Chronic pain, Systematic review, Visceral pain.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** A dor visceral é causada por anormalidades de órgãos como o estômago, rim, bexiga, vesícula biliar, intestinos ou outros e inclui distensão, isquemia, inflamação e tração do mesentério. É responsável por incapacidade física e psíquica, absentismo do trabalho e má qualidade de vida. O objetivo deste estudo foi discutir os principais aspectos da dor visceral relacionados a prevalência, etiologia e diagnóstico.

**CONTEÚDO:** Foram revisados segundo os preceitos da Medicina Baseada em Evidência os enfoques etiológicos, diagnóstico e prognóstico da dor visceral nas bases de indexações biomédicas, LILACS, EMBASE e Pubmed. Não foram selecionados os estudos terapêuticos. Utilizou-se como estratégia de busca os termos: («visceral pain»[MeSH Terms] OR (“visceral”[All Fields] AND “pain”[All Fields]) OR “visceral pain”[All Fields]). Somente foram incluídos os estudos publicados em português, inglês ou espanhol. Foram excluídas as revisões narrativas de conteúdo opinativo e procedimentos terapêuticos específicos das especialidades médicas. Também foram excluídos os estudos sobre dor visceral relacionada às doenças do coração, neoplásicas, musculoesqueléticas e a gestação.

**CONCLUSÃO:** A dor visceral é uma condição heterogênea, cuja apresentação mais frequente é de dor abdominal no curso de síndrome do intestino irritável. Outras doenças cursam com dor visceral e o diagnóstico adequado é fundamental para o tratamento eficaz.

**Descritores:** Dor crônica, Dor visceral, Revisão sistemática.

### INTRODUCTION

The International Association for the Study of Pain (IASP) has updated in 2011 visceral pain taxonomy and identification among chronic conditions, according to anatomic location in abdominal viscerae, chest and neck<sup>1</sup>.

Visceral pain is characterized by painful subjective perception in the abdomen or chest, and may be referred to somatic structures. So, it is difficult to diagnose visceral pain, especially if it is long-lasting, recurrent and without specific pathophysiological abnormality.

Functional chronic visceral pain is one of the most common causes of morbidity among general population. Functional chronic visceral pain (FCVP) and functional gastrointestinal disorders (FGID) have different definitions:

- FCVP is defined as pain coming from internal organs (visceral) such as stomach, kidneys, gallbladder and others, and

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lasting more than three months. The term functional describes a symptom or complex of symptoms in the absence of any structural or tissue abnormality.

- FGID is defined as digestive system disorder where symptoms cannot be explained by the presence of structural or tissue changes, based on clinical symptoms.

Visceral pain causes depend on the nature of triggering stimulation. Symptoms characteristics are: 1) abrupt onset; 2) widespread and difficult to locate pain, more often perceived along trunk midline; 3) pain referred on superficial tissues; 4) presence of hyperalgesia; 5) motor, autonomic and affective responses activation<sup>2</sup>.

Other authors have added more characteristics: 1) it is not evoked by all viscerae (solid organs such as liver, kidneys, pulmonary parenchyma are not sensitive to pain); 2) it is not always associated to visceral injury. A low threshold stimulus may activate visceral sensory afferents, such as intraluminal gas pressure; 3) it is referred in other sites, probably related to visceral and somatic nervous fibers convergence when connecting in spinal cord dorsal horn<sup>3</sup>.

Based on the importance of the subject, the Brazilian Society for the Study of Pain (SBED), in 2013, which has been the international year against visceral pain, tried to gather best scientific quality material to sensitize healthcare system researchers, clinicians and managers for the impact and consequences of lack of adequate diagnosis and management of this syndrome.

This document updates systematic reviews of Pubmed, EMBASE and LILACS databases on Visceral Pain, carried out by SBED in the year 2013. The objective of this study is limited to the publication of articles indexed just as visceral pain.

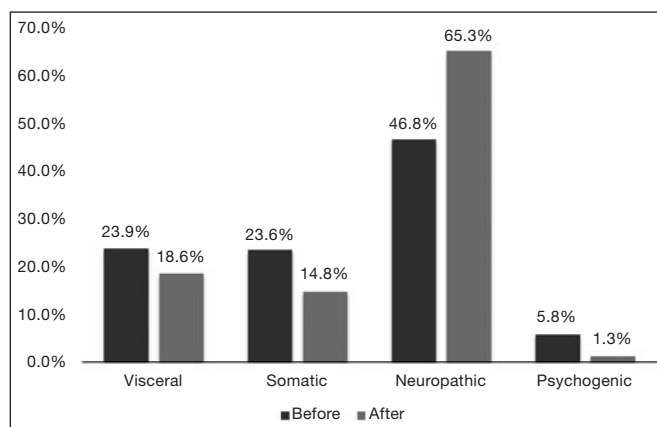
## CONTENTS

According to Evidence-Based Medicine concepts, etiologic and prognostic visceral pain approaches were reviewed in the two largest biomedical databases, Pubmed and EMBASE, and in LILACS database for being the one with the highest number of Brazilian publications. Original diagnostic or therapeutic studies on peculiarities of different specialties related to the subject and which moved away from the interest of general informative and educational aspects were not included. Although not including original articles on diagnosis and therapy in the primary search of this review, a complementary Pubmed search was carried out to recover systematic reviews of diagnostic and therapeutic studies on primary and more frequent types of visceral pain. Query strategy has contemplated visceral pain descriptors with regard to health education, information dissemination, patients' participation, patients' education, patients' preference, patient-centered assistance, evaluation of results, etiologic and prognostic aspects. Only studies published in Portuguese, English or Spanish were included in the review. Exclusion criteria were narrative reviews with opinionated contents, diagnostic or therapeutic procedures specific to medical specialties, such as clinical consequences of surgical interventions, hormonal treatment, antibiotic therapy, alpha-adrenergic blockers, radiofrequency ablation, immunobiologic, neural plexus blocks, transcranial magnetic stimulation,

myelotomy, botulinum toxin injection, acupuncture, homeopathy and alternative practices. Studies on visceral pain related to heart, cancer, musculoskeletal diseases and gestation were also excluded.

The following strategy was adopted for complementary Pubmed query: ("visceral pain"[MeSH Terms] OR ("visceral"[All Fields] AND "pain"[All Fields]) OR "visceral pain"[All Fields]) AND ("2013/01/01"[PDAT]: "2015/11/30"[PDAT]). Scientific quality of publications was evaluated as A (high), B (moderate), C (low) and D (very low), by the GRADE system<sup>4</sup>.

Words visceral, somatic, neuropathic and psychogenic were considered to evaluate the proportion of studies on pain. We ended up with 16337 quotations until 2013. After adding the filter corresponding to most recent studies from 1/1/2013 to 11/30/2015, we have obtained 4461 quotations, being visceral pain the second most studied from the four types of pain. Figure 1 shows increased number of recent publications as compared to somatic and psychogenic pain, although neuropathic pain was the one with the highest growth rate in number of quotations, probably due to the interest of pharmaceutical industries.



**Figure 1.** Quotations on Pubmed database, according to type of pain, before and after January 2013

In the first search, in 2013, 105 scientific articles were selected from 1793 recovered quotations. From these, 37 quotations were selected by the group to continue with the process. Evidence synthesis corresponded to the evaluation of 34 full text articles, presented in the literature quotation format in Vancouver style, publication quality evaluated by the GRADE system and text of primary results in the language originally used for the article or translated into Portuguese. Fifteen articles with children and infants and nine low quality articles according to the group of specialists were excluded. So, 10 articles were considered for description.

Similarly, in these last three years, 1106 quotations were recovered, corresponding to 20% of the total of 5541 quotations on visceral pain indexed since 1956. Following, there is qualitative and descriptive synthesis of the evidences of 29 articles meeting inclusion criteria and of 10 more of the first systematic search. Heterogeneity of studies has prevented any meta-analysis-type quantitative synthesis.

## CHRONIC ABDOMINAL PAIN AND IRRITABLE BOWEL SYNDROME (IBS)

A systematic review of 14 studies on the prevalence of chronic abdominal pain observed in primary care has shown that mean grouped frequency of consultations for this type of complaint was 2.8%. In approximately one third of patients, underlying cause of abdominal pain could not be identified. Most common etiologies were gastroenteritis (7.0-19.2%), IBS (2.6-13.2%), urologic cause (5.3%) and gastritis (5.2%). Approximately one out of 10 patients had acute disease such as appendicitis (1.9%), diverticulitis (3.0%), cancer (1.0%), biliary or pancreatic disease (4.0%) needing immediate treatment<sup>5</sup> (A).

Another study carried out in Canada with 2382 chronic pain patients has shown that visceral pain corresponded to 5.4% of the sample. Among 128 visceral pain patients, etiologic diagnoses were endometriosis, IBS, chronic pancreatitis, refractory angina, vulvodynia, post-cholecystectomy syndrome and post-herniorrhaphy pain<sup>6</sup>. Visceral pain has affected individuals with mean age of 44 years and was often related to depressive symptoms. On the other hand, a review of 58 epidemiologic studies involving 196472 children between 4 and 8 years of age, suggested a global prevalence of 13% (CI<sup>95%</sup> 12-15%) of abdominal pain. IBS was more frequently reported with approximately 9% (CI<sup>95%</sup> 6-12%). Highest rates were reported for South America and Asia, with approximate value of 16% as compared to 10% in Europe. Abdominal visceral pain has affected more females and was associated to the presence of anxiety, depressive disorders, stress and traumatic events<sup>7</sup> (A). IBS was also common among 120 female students of the Warsaw University, aged between 19 and 27 years. Abdominal pain or discomfort was more frequent in the group of students considering their practice of physical activity as low and was reason for school or work absenteeism<sup>8</sup> (B).

It is important to remember that IBS prevalence depends on studied population. A meta-analysis of epidemiologic studies estimates global prevalence of 11.2% being lower in South-eastern Asia and India. There are many risk factors, such as being female and the presence of depression, post-traumatic stress, daily life stress, family history and bacterial gastroenteritis epidemics<sup>9</sup> (B). Also, early manifestation of gastrointestinal symptoms, socioeconomic level during childhood, prenatal, trauma during childhood as well as disease behavior reinforcement and modeling (behavioral) are potential risk factors<sup>10</sup> (A).

IBS is a functional gastrointestinal tract disorder characterized by abdominal discomfort, pain and change in intestinal habits, often associated to psychological or psychiatric disorders. The development of the syndrome may be related to body response to stress and to the interaction between visceral perception and bowel motility. In addition, there might be serotonin receptors changes (5hydroxytryptamine, 5HT)<sup>11</sup> (C) and regional decrease of anterior and insular cingulate cortex gray matter. In addition, neuroplastic changes in female patients were related to symptoms severity<sup>12</sup> (A), favoring the

hypothesis that females have stronger connectivity of brain networks related to pre-frontal regions modulators of medial and dorsolateral cortex<sup>13</sup> (A).

Similarly in a fear model with different conditioning visual stimuli and with rectal pain as non-conditioning stimulus, healthy males and females were compared with the aid of functional nuclear resonance, with regard to neural responses during aversive visceral learning, in extinction and with the reactivation or reestablishment of fear memory. Positive response to conditioning stimulus has further reactivated females' hippocampus, thalamus and cerebellum. This suggests differences between genders with regard to neural processes mediators of aversive visceral learning, being that reactivation reinforcement of the anterior fear memory trait in females could justify the predominance of females among chronic abdominal visceral pain patients<sup>14</sup> (A).

On the other hand, IBS may induce specific abnormalities in the attention, anxiety, hypersurveillance and visceral hypersensitivity network test<sup>15</sup> (B). So, anxiety disorder may induce visceral hypersensitivity<sup>16</sup> (D) and psychological factors increased the perception of painful sensations only in hypersensitive patients to bowel inflation tests<sup>17</sup> (B).

Chronic pain, chronic abdominal pain and IBS are associated to increased psychiatric comorbidity. In chronic pain populations, there is significantly increased risk for depression and anxiety, regardless of pain location. With regard to IBS, there are more than 20 studies measuring the overlapping of IBS and psychiatric disorders. Authors have concluded that approximately half of IBS patients meet criteria for one or more psychiatric disorders. In addition, the prevalence of comorbid psychiatric disorders is higher among patients looking for hospital care, where up to 90% suffer of psychiatric disorders. Data indicate that no psychiatric disorder is solely associated to IBS, but that most common comorbid conditions are depression, followed by widespread anxiety disorder.

IBS is then marked by a high load of psychiatric comorbidity. Several studies have found that suicide behavior rates in chronic abdominal pain have increased even after psychiatric disorder control. Depression is probably the most powerful predictor of suicide behavior through a variety of populations, including chronic pain groups; however, it is not the only significant psychosocial predictor. Chronic abdominal pain and IBS are known for significantly affecting a wide variety of quality of life variables, including extraintestinal chronic stress symptoms and "vital exhaustion", so it is possible that this is also linked to increased suicide behavior<sup>18</sup> (C);

## IRRITABLE BOWEL SYNDROME AND ASSOCIATED DISEASES

Specific IBS somatic comorbidity conditions are:

**Fibromyalgia:** the association between IBS and fibromyalgia (FM) has been studied more than any other comorbidity. FM is present in approximately 32.5% (interval of 28-65%) of IBS patients and IBS is present in approximately 48% (interval of 32-77%) of FM patients.

**Chronic fatigue syndrome (CFS):** the prevalence of CFS in general population is estimated in 0.4%. Six studies have examined the presence of IBS in chronic fatigue patients and have reported high level of overlapping, varying from 35 to 92% (mean of 51%). The only study to date informing about the prevalence of CFS among IBS patients has concluded that 14% have reported CFS.

**Chronic pelvic pain:** IBS is a common comorbidity, affecting 29-79% (mean of 49.9%) of females with chronic pelvic pain.

**Temporomandibular joint disorder:** IBS was present in 64% of 25 patients with temporomandibular joint pain (TMJ) and TMJ pain was present in 16% of 270 IBS patients.

**Other disorders:** IBS was reported by 30.2% of 2045 respondents with interstitial cystitis, as compared to IBS prevalence in general population of 9.4%. It was observed that 38% of IBS patients have reported back pain, 18% premenstrual syndrome and 10% dysmenorrhea; all these rates are significantly higher as compared to patients with other gastrointestinal disorders. IBS was common among gynecological references, in patients with dyspareunia (52.4%), dysmenorrhea (50%), urinary symptoms (44.4%) and non-menstrual hemorrhage (40%). Global rate of IBS patients in a sample of 798 gynecologic patients was 37.3%, significantly higher than that observed in patients with skin, ear, nose or throat disease. IBS was present in 22.7% of individuals with bronchial hyper-responsiveness.

**Symptoms of non-gastrointestinal comorbidity:** urinary symptoms compatible with detrusor hyperreflexia (that is, increased micturition frequency, urinary urgency, nocturia) or bladder output dysfunction (that is, incomplete bladder emptying) are also common in IBS patients.

Described conditions and which are strongly associated to IBS share some clinical features: 1) all are substantially more common in females; 2) may be triggered or worsened by stress and; 3) are associated to fatigue, difficulty to sleep, anxiety and depression. It would seem probable that disorders with so many similarities and overlaps would share a common etiology, however, evidence is not convincing.

Pathophysiological mechanisms considered for IBS symptoms are:

1. Visceral hypersensitivity;
2. Autonomous nervous system deregulation;
3. Smooth muscle hyperreactivity;
4. Neurotransmitters level abnormalities, such as serotonin or neurotransmitters receptors;
5. Sustained activation of the immune system after infection, stress or other psychological factors;
6. History of sexual trauma.

IBS comorbidity with other functional gastrointestinal disorder is even more impressive than its overlapping with somatic non-gastrointestinal conditions and the overlapping of functional gastrointestinal disorders is so important that some have proposed that terms such as "irritable bowel", should be used for all of them, and that drugs effective for one of these disorders should also be effective for the others<sup>19</sup> (B).

On the other hand, it is possible that patients with kidney stone are at higher risk of developing IBS<sup>20</sup> (C).

### Irritable bowel syndrome diagnosis

A systematic review including 110 publications has found a huge number of standardized tools to evaluate chronic abdominal pain in IBS patients. Single domain methods, such as validated 10 points scale (NRS) and gastrointestinal symptoms severity questionnaires, primarily focus on abdominal pain intensity evaluation. Among validated questionnaires, the Symptom Severity Scale (IBS) has presented broader pain-related aspects. General pain questionnaires and electronic evaluation tools for current symptoms are still waiting for validation. Evidences for the use of challenge tests, such as balloon distention, are weak due to the low correlation with retrospective questionnaires<sup>21</sup> (A).

With regard to additional exams, IBS patients often complain of symptoms worsening after meals. Standardized meal challenge test has observed differences as compared to healthy controls with regard to abdominal pain, distention, discomfort, gases and feeling of fullness. Test was carried out with the ingestion during breakfast of food with 540 kcal, being 8g fiber, 36% fat, 15% proteins and 49% carbohydrates. Authors have concluded that the test is useful to define the approach and follow up the effect of interventions<sup>22</sup> (A).

Endoscopic capsule to evaluate small bowel (SBCE) is considered a noninvasive exam to help the diagnosis of patients with chronic non-explained abdominal pain. A systematic review with 1520 patients participating in 21 studies has shown low grouped diagnostic yield (20%; CI<sup>95%</sup> 16-26%). Among patients with positive results, inflammatory injuries are the most common (78%), followed by tumors (9%). Wide heterogeneity observed among studies may be explained by variable pain duration and by different previous exams performed before SBCE<sup>23</sup> (A).

A predictive model was derived from a study with 160 healthy females with IBS, who had volume, mean curvature, surface area and cortical thickness calculated for each brain region. Results have shown that algorithms developed as from regional brain morphometry had no predictive capacity for the diagnosis of the syndrome. However, it was possible to identify relevant neurobiological markers to be used together with other clinical manifestations, in broader diagnostic criteria to be studied in the future<sup>24</sup> (B).

Notwithstanding the large number of diagnostic tests, there are no convenient methods to differentiate patients with predominance of moor gastric dysfunction or visceral hypersensitivity. A total of 120 patients with functional dyspepsia and 30 healthy volunteers were included in a cross-sectional study to evaluate ultrasound combined with the ingestion of up to one liter of water. Test was useful to differentiate patients with predominant postprandial fullness from those where epigastralgia has prevailed, helping the therapeutic decision-making process<sup>25</sup> (B).

The development of new biomarkers and the identification of specific psychological patterns have helped the differential diagnosis of visceral pain common to IBS, intestinal inflammatory syndrome and other functional gastrointestinal diseases. Biological markers and psychological patterns have been as-



sociated to clinical and demographic information to generate automated algorithms allowing the differential diagnosis of visceral pain associated to bowel diseases<sup>26</sup> (B).

A systematic literature review to identify diagnostic studies for IBS in adult populations has found 22 articles in a total of 7106 patients. Positive and negative likelihood ratio meta-analysis of Rome III criterion, current gold standard, has shown values of 3.35 (CI<sup>95%</sup> 2.97-3.79) and 0.39 (CI<sup>95%</sup> 0.34-0.46), similar to other symptoms-based criteria. Eleven individually evaluated biomarkers had no better results than symptoms-based criteria.

Psychological patterns had good performance in just one study. Five different combinations of criteria were evaluated and the best in terms of positive likelihood ratio was fecal calprotectin associated to bowel patency and to Rome I criterion with LR+ of 26.4 (CI<sup>95%</sup> 11.4-61.9). In terms of negative likelihood ratio, the association of serum biomarkers and psychological patterns with LR- of 0.18 (CI<sup>95%</sup> 0.12-0.25). Authors have concluded that combined criteria of symptoms, biological markers and psychological pattern have better diagnostic performance than when considered separately<sup>27</sup> (A). Repeated noninvasive electromagnetic stimulation has modulated visceral sensitivity in study with healthy volunteers and IBS patients, increasing healthy limits of rectal pain for up to one hour after intervention. The study helps justifying the use of neurostimulation to control functional gastrointestinal disorders<sup>28</sup> (B).

### Chest pain

Pain is becoming a clinical complication for chronic pulmonary obstructive disease patients (CPOD). A review of 358 studies has selected five of them considered of good quality where combined prevalence of moderate to very severe pain and CPOD was 66% (CI<sup>95%</sup> 44-85%). Most severe pain was associated to increased dyspnea, fatigue, worse quality of life and more specific comorbidities<sup>29</sup> (A).

Conversely, visceral pain predominates among causes of chest pain identified in the review of 11 studies with 3900 patients. In decreasing order of prevalence, there were cardiovascular disease (14 to 16%), respiratory disease (10 to 18%), gastrointestinal disorders (6 to 10%) and esophageal diseases (6 to 7%). Other pains were costochondritis (25 to 50%) and psychogenic pain (10 to 18%). Authors call the attention to the fact that such percentages should accurately estimate the pretest probability to guide procedures indicated during diagnostic process<sup>30</sup> (A).

Non-cardiogenic chest pain (NCCP), also called non-cardiac chest pain, is the angina-type retrosternal pain of non-cardiogenic origin. Its prevalence is high; in the United States, for example, up to one fourth of the population refer such complaint. On the other hand, among patients submitted to coronaryography to investigate chest pain, 10 to 13% have normal results. The Rome III Consensus has considered the application of the "functional chest pain of presumable esophageal origin" to patients with episodes of retrosternal chest pain of visceral quality without apparent explanation, being previ-

ously ruled out cardiac origin and diagnostic hypotheses of gastroesophageal reflux disease (GERD) and esophageal motility disorders.

NCCP prevalence is not known in most Latin-American countries, but because it is often associated to GERD, it is worth evaluating the prevalence of the latter. In Latin-America, the prevalence of GERD varies from 12 to 25%. NCCP pathophysiology is not totally explained. Proposed etiopathogenic factors include GERD, esophageal motor disorders, esophageal mechanical and physical properties, visceral hypersensitivity, abnormal central esophageal stimulation processing, abnormal autonomic activity and psychological comorbidities.

NCCP may significantly affect quality of life. It is interesting to observe that notwithstanding the heart disease having been ruled out by previous exams, patients still have modifications and limitations in their lifestyle. This may often worsen the presentation due to persistent belief that patients have heart disease. NCCP implies considerable costs due to work absenteeism, chronic use of cardiovascular drugs, repeated hospitalizations for investigation and substantial anxiety.

It is important to highlight that esophageal evaluation of NCCP patients is indicated just after cardiologic investigation having effectively ruled out the possibility of heart disease as the cause of the symptom. This is necessary because the isolated analysis of the clinical presentation may not provide the perfect distinction between chest pain of esophageal origin and of cardiac origin, and morbidity and mortality of both are totally different. Options for diagnostic aid are: 1. Therapeutic test with proton pump inhibitor (PPI); 2. Esophageal manometry; 3. Prolonged pHmetry, telemetric pHmetry and esophageal impedance; 4. High digestive endoscopy; 5. Challenge tests; and 6. Psychological evaluation<sup>31</sup> (D).

A systematic review of diagnostic tests used for non-cardiovascular chest pain has included 28 studies, being that 20 have investigated gastroesophageal reflux disorder (GERD), three musculoskeletal chest pain and 5 psychiatric conditions. Quality of studies was good in 15 and moderate in 13. GERD diagnosis was more probable with typical disease symptoms or when using proton pump inhibitor. Grouped sensitivity and specificity of the six studies was 89 and 88%, respectively. Findings of clinical musculoskeletal pain results had low yield. Panic and anxiety disorders were not frequently diagnosed and should always be considered in differential chest pain diagnosis. Questionnaires for panic syndrome and anxiety disorder screening have accurately identified individuals needing further tests to close the diagnosis<sup>32</sup> (A).

It should be highlighted that thoracic spine disc protrusion might mimic visceral pain syndrome and should be taken into account in situations of symptoms with characteristics of digestive or urologic affection which are not confirmed by specific diagnostic tests. This observation was obtained in a case-control study involving 200 people<sup>33</sup> (C).

### Other chronic pains

Functional abdominal pain syndrome (FAPS) is a debilitating disorder with constant or almost constant abdominal pain,

lasting for at least six months. Prevalence estimates are 0.5 to 1.7% and tend to predominate among females.

Few pathophysiological studies were carried out specifically in FAPS patients, so there are few available data. FAPS pathophysiology seems to be the only one where pain is especially caused by amplified central sensory perception of normal visceral sensory input. FAPS diagnosis is according to Rome III symptoms-based diagnostic criteria. These criteria are oriented to identify patients with severe symptoms and how they represent constant or almost constant abdominal pain, with loss of daily functions (work/school leave, family and social activities limitations) and are differentiated from IBS based in their non-association with changes in intestinal habits or other bowel-related events.

Physicians should obtain specific pain characteristics, especially whether there is association with bowel movements, eating and menstrual cycle. If abdominal pain is associated to bowel movements (changes in frequency or consistency, and relief after evacuation), IBS should be considered. In patients with right upper quadrant or epigastric pain, epigastric pain syndrome should be considered and differential diagnosis should include functional gall bladder syndrome. If pain is associated to eating, especially in cases of pain of recent onset in elderly patients with history of vascular disease, chronic mesenteric ischemia should be evaluated. Finally, if pain is associated to menstruation, gynecologic diseases, such as endometriosis, or dysfunctional uterine bleeding should be evaluated by a gynecologist.

FAPS patients may manifest symptoms reported by typical behaviors, which may provide important hints for diagnosis. In addition to their contribution for diagnosis, recognizing and addressing such behaviors may play a critical role in the establishment of physician-patient therapeutic relationship, as well as in the development of a treatment plan<sup>34</sup> (D).

Referred visceral pain may justify the higher intensity of symptoms associated to low back pain. Ambulatory study with 2974 low back pain patients has shown that 19.6% of them have also reported chest, abdomen and groin pain. These patients, as compared to isolated low back pain patients, had higher levels of pain and functional incapacity which, however, have not impaired low back pain clinical course and recovery<sup>35</sup> (A).

Visceral agioedema abdominal pain is an uncommon complication and often not recognized in the anti-hypertensive treatment with angiotensin converting enzyme inhibitors, which more often induces cough and respiratory angioedema. In addition to widespread abdominal hypersensitivity, computerized tomography may show widespread thickening of the intestinal wall. Symptoms improve in 48 to 72h after drug withdrawal<sup>36</sup> (C).

There is consensus that symptomatic kidney stones should be treated. Kidney stones diagnosis is relatively easy when evaluated by ultrasound. As opposed, establishment of symptoms of patients which could be attributed to gallstones is a major challenge for medical diagnosis in primary care. Seven abdominal symptoms suggestive of gallstones were evaluated in a meta-analysis of 24 studies about diagnostic accuracy of ab-

dominal symptoms for gallstones. Methodological quality of included studies was low. Evaluators were blind for reference standards for abdominal symptoms in just eight studies, only eight studies were adjusted by age and gender and in hospital studies, the extension of gallstone disease of included patients was poorly described.

This lack of methodological quality, however, does not explain the heterogeneity of diagnostic accuracy of abdominal symptoms. Biliary colic, defined as “constant pain in right upper abdominal quadrant lasting more than half an hour”, “pain irradiation” and “administered analgesics” were the only three symptoms consistently related to gallstones, although non-adjusted estimates of diagnostic precision were kept low. These three symptoms had better diagnostic precision in referred patients, although without statistical significance for pain irradiation, which may be explained by the small number of studies included in the evaluation of such symptom. Biliary colic, described as “severe and episodic constant pain lasting more than 15 minutes” is considered a diagnostic symptom.

Although our analysis confirms this relationship, discriminative biliary colic capacity was low. Biliary colic was present in 20% of patients with gallstones and 6% of patients without stones. Eighty percent of patients with gallstones were referred with other abdominal symptoms. Discussion is whether patients have asymptomatic gallstones or their gallstones induce other symptoms different from biliary colic<sup>37</sup> (A).

Cyriax syndrome is a subluxation of the distal part of 8<sup>th</sup>, 9<sup>th</sup> and 10<sup>th</sup> ribs, in general secondary to trauma. It is predominantly manifested by high abdominal pain, with possibility of confusion with visceral pain. Diagnostic is clinic and should be present as differential diagnosis, thus avoiding numerous investigations contributing to patients' distress. Its etiology is in general trauma of variable intensity, such as: 1) single right trauma (fall, car accident, martial sports, use of surgical separators); 2) repeated right trauma (cobblers chest, weight load on chest, postman); 3) indirect trauma (sudden traction, example: practice of tennis, golf, lifting heavy loads). Pain is in general violent and may last from minutes to some hours, being related to movements<sup>38</sup> (D).

Interstitial cystitis (IC) is a visceral pain syndrome with deep impact on quality of life; it is a devastating bladder condition characterized by pelvic pain, urinary frequency and urgency and nocturia. Recently, investigators started to use the term “painful bladder syndrome” to describe cases with painful micturition which may not fit the stricter IC definition.

Real IC prevalence rate is unknown and estimates widely vary from 67 per 100 thousand to 575 per 100 thousand cases, based on diagnostic criteria and methods used to estimate the rate. IC is primarily diagnosed among Caucasian females, with mean age at diagnosis of 42-46 years.

Although being known since 1836, IC etiology and pathogeny are still not clear. So, it is not surprising that patients suffer from IC from 5 to 7 years, in average, and very often visit eight physicians before having the correct diagnosis.

Debilitating IC symptom makes many patients unable to deal with daily life functions. In severe cases, patients often need to

empty the bladder more than 60 times per day and experiment severe pelvic pain and dyspareunia, which may impact several quality of life domains and result in severe depression<sup>39</sup> (C). IC patients have widespread hypersensitivity to deep tissue stimulation with lower thresholds, as compared to healthy individuals. In addition, there are evidences that IC patients have perception of poorer health, increased somatic complaints and added surveillance to sensations<sup>40</sup> (B). History of sexual abuse is estimated in approximately 40% of all adult patients with chronic abdominal pain or gastrointestinal complaints. Data on the prevalence of sexual abuse in children with chronic abdominal pain are, however, scarce. Systematic review of studies investigating the prevalence in children has resulted in 269 articles, of which just two have met inclusion criteria. Abuse condition was found in 2.1 and 8.0% of patients with chronic abdominal visceral pain between 4 and 21 years of age. Major limitation of the studies was sample size (48 and 50) and lack of control group<sup>41</sup> (B). Visceral pain associated to functional syndromes is among different clinical manifestations which may also be attributed to hysteria. According to the North-American manual for diagnosis of mental disorders, the new approach is due to the lack of pathologic substrate and the physiologic and expressional nature of such condition<sup>42</sup> (C).

## CONCLUSION

Visceral pain is a heterogeneous condition, the more frequent presentation of which is abdominal pain with IBS. IBS is a complex disease involving still not explained pathophysiological mechanisms. The strategy for diagnosis still needs literature consensus. Visceral pain requires well developed propeudetics to avoid inadequate etiologic diagnosis and treatment.

## REFERENCES

- Merskey H, Bogduk N. International association for the study of pain (IASP) classification of chronic pain. [Internet]. Seattle, Washington; 1994. Available from: <http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf>.
- Austin PD, Henderson SE. Biopsychosocial assessment criteria for functional chronic visceral pain: a pilot review of concept and practice. *Pain Med*. 2011;12(4):552-64.
- Kraychete DC, Guimarães AC. [Visceral hyperalgesia and chronic abdominal pain: diagnostic and therapeutic approach]. *Rev Bras Anestesiol*. 2003;53(6):833-53. Portuguese.
- Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64(4):380-2.
- Viniol A, Keunecke C, Biroga T, Stadje R, Dornieden K, Bösner S, et al. Studies of the symptom abdominal pain—a systematic review and meta-analysis. *Fam Pract*. 2014;31(5):517-29.
- Giladi H, Scott W, Shir Y, Sullivan MJ. Rates and correlates of unemployment across four common chronic pain diagnostic categories. *J Occup Rehabil*. 2015;25(3):648-57.
- Kortelerink JJ, Diederik K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One*. 2015;10(5):e0126982.
- Niemyska S, Ukleja A, Ławiński M. Evaluation of irritable bowel syndrome symptoms amongst Warsaw University students. *Pol Przegl Chir*. 2015;87(5):252-9.
- Bokic T, Storr M, Schicho R. Potential causes and present pharmacotherapy of irritable bowel syndrome: an overview. *Pharmacology*. 2015;96(1-2):76-85.
- Chitkara DK, van Tilburg MA, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. *Am J Gastroenterol*. 2008;103(3):765-74.
- Stasi C, Bellini M, Bassotti G, Blandizzi C, Milani S. Serotonin receptors and their role in the pathophysiology and therapy of irritable bowel syndrome. *Tech Coloproctol*. 2014;18(7):613-21.
- Jiang Z, Dinov ID, Labus J, Shi Y, Zamanyan A, Gupta A, et al. Sex-related differences of cortical thickness in patients with chronic abdominal pain. *PLoS One*. 2013;8(9):e73932.
- Labus JS, Gupta A, Coveleskie K, Tillisch K, Kilpatrick L, Jarcho J, et al. Sex differences in emotion-related cognitive processes in irritable bowel syndrome and healthy control subjects. *Pain*. 2015;154(10):2088-99.
- Benson S, Kattoor J, Kullmann JS, Hofmann S, Engler H, Forsting M, et al. Towards understanding sex differences in visceral pain: enhanced reactivation of classically-conditioned fear in healthy women. *Neurobiol Learn Mem*. 2014;109:113-21.
- Hubbard CS, Hong J, Jiang Z, Ebrat B, Suyenobu B, Smith S, et al. Increased attentional network functioning related to symptom severity measures in females with irritable bowel syndrome. *Neurogastroenterol Motil*. 2015;27(9):1282-94.
- Chen ZL, Zhang XC, Pan GR, Sun Y, Xu M, Li XQ. Clinical features and therapeutic options for isolated visceral artery dissection. *Ann Vasc Surg*. 2015;30:227-35.
- Grinsvall C, Törnblom H, Tack J, Van Oudenhove L, Simrén M. Psychological factors selectively upregulate rectal pain perception in hypersensitive patients with irritable bowel syndrome. *Neurogastroenterol Motil*. 2015;27(12):1772-82.
- Spiegel B, Schoenfeld P, Naliboff B. Systematic review: the prevalence of suicidal behavior in patients with chronic abdominal pain and irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007;26(2):183-93.
- Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology*. 2002;122(4):1140-56.
- Erdem E, Akbay E, Sezgin O, Doruk E, Canpolat B, Cayan S. Is there a relation between irritable bowel syndrome and urinary stone disease? *Dig Dis Sci*. 2005;50(3):605-8.
- Mujagic Z, Keszthelyi D, Aziz Q, Reinisch W, Quetglas EG, De Leonardi F, et al. Systematic review: instruments to assess abdominal pain in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2015;42(9):1064-81.
- Posserud I, Strid H, Störsrud S, Törnblom H, Svensson U, Tack J, et al. Symptom pattern following a meal challenge test in patients with irritable bowel syndrome and healthy controls. *United Eur Gastroenterol J*. 2013;1(5):358-67.
- Xue M, Chen X, Shi L, Si J, Wang L, Chen S. Small-bowel capsule endoscopy in patients with unexplained chronic abdominal pain: a systematic review. *Gastrointest Endosc*. 2015;81(1):186-93.
- Labus JS, Van Horn JD, Gupta A, Alaverdyan M, Torgerson C, Ashe-McNalley C, et al. Multivariate morphological brain signatures predict patients with chronic abdominal pain from healthy control subjects. *Pain*. 2015;156(8):1545-54.
- Kugler T. The usefulness of water-drinking ultrasonography combined test for evaluating patients with functional dyspepsia. *Korean J Gastroenterol*. 2015;66(2):92-7.
- Sood R, Law GR, Ford AC. Diagnosis of IBS: symptoms, symptom-based criteria, biomarkers or “psychomarkers”? *Nat Rev Gastroenterol Hepatol*. 2014;11(11):683-91.
- Sood R, Gracie DJ, Law GR, Ford AC. Systematic review with meta-analysis: the accuracy of diagnosing irritable bowel syndrome with symptoms, biomarkers and/or psychological markers. *Aliment Pharmacol Ther*. 2015;42(5):491-503.
- Algladi T, Harris M, Whorwell PJ, Paine P, Hamdy S. Modulation of human visceral sensitivity by noninvasive magneto-electrical neural stimulation in healthy and irritable bowel syndrome. *Pain*. 2015;156(7):1348-56.
- Lee AL, Harrison SL, Goldstein RS, Brooks D. Pain and its clinical associations in individuals with COPD: a systematic review. *Chest*. 2015;147(5):1246-58.
- Haasenritter J, Biroga T, Keunecke C, Becker A, Donner-Banzhoff N, Dornieden K, et al. Causes of chest pain in primary care - a systematic review and meta-analysis. *Croat Med J*. 2015;56(5):422-30.
- Domingues GR, Moraes-Filho JP. Dor torácica não-cardiogênica. *Arq Gastroenterol*. 2009;46(3):233-40.
- Wertli MM, Ruchti KB, Steurer J, Held U. Diagnostic indicators of non-cardiovascular chest pain: a systematic review and meta-analysis. *BMC Med*. 2013;11:239.
- Lara FJ, Quesada JQ, Ramiro JA, Toledo RB, Del Rey Moreno A, Muñoz HO. Chronic abdominal syndrome due to nervous compression. Study of 100 cases and proposed diagnostic-therapeutic algorithm. *J Gastrointest Surg*. 2015;19(6):1059-71.
- Sperber AD, Drossman DA. Review article: the functional abdominal pain syndrome. *Aliment Pharmacol Ther*. 2011;33(5):514-24.
- Panagopoulos J, Hancock MJ, Kongsted A, Hush J, Kent P. Does anterior trunk pain predict a different course of recovery in chronic low back pain? *Pain*. 2014;155(5):977-82.
- Mutnuri S, Khan A, Variyam EP. Visceral angioedema: an under-recognized complication of angiotensin-converting enzyme inhibitors. *Postgrad Med*. 2015;127(2):215-7.
- Berger MY, van der Velden JJ, Lijmer JG, de Kort H, Prins A, Bohnen AM. Abdominal symptoms: do they predict gallstones? A systematic review. *Scand J Gastroenterol*. 2000;35(1):70-6.
- Pinto Devia J, Michel H. Síndrome de Cyriax. 54 casos y revisión de la literatura. *Rev Med Surg*. 1990;15(2):102-5.
- El Khoudary SR, Talbott EO, Bromberger JT, Chang CC, Songer TJ, Davis EL. Severity of interstitial cystitis symptoms and quality of life in female patients. *J Womens Health*. 2009;18(9):1361-8.
- Ness TJ, Powell-Boone T, Cannon R, Lloyd LK, Fillingim RB. Psychophysical evidence of hypersensitivity in subjects with interstitial cystitis. *J Urol*. 2005;173(6):1983-7.
- Sonneveld LP, Brilleslijper-Kater SN, Benninga MA, Hoytema van Konijnenburg EM, Sieswerda-Hoogendoorn T, Teeuw AH. Prevalence of child sexual abuse in pediatric patients with chronic abdominal pain. *J Pediatr Gastroenterol Nutr*. 2013;56(5):475-80.
- Medeiros De Bustos E, Galli S, Haffen E, Moulin T. Clinical manifestations of hysteria: an epistemological perspective or how historical dynamics illuminate current practice. *Front Neurol Neurosci*. 2014;35:28-43.