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CHALLENGES IN COLOPROCTOLOGY

The PNEI holistic approach in coloproctology

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Abstract The psycho-neuroendocrine-immune approach relies on the concept of considering diseases from a holistic point of view: the various components (psyche, nervous system, endocrine system, and immune system) control the diseased organ/apparatus and in turn are influenced by a feedback mechanism. In this article, we will consider the psycho-neuroendocrine-immune approach to coloproctological disorders, by providing clinical cases and discussing them in light of this approach.

Keywords Coloproctology · Constipation · Psyche · Enteric nervous system · Immune system · PNEI approach

Introduction

The psycho-neuroendocrine-immune (PNEI) system is at the same time a very old and a very modern concept [1]. Old, because it relies on the paradigm of homeostasis, i.e., "the tendency to stability in the normal internal environment of the organism" [2]. Modern, because it goes beyond the mechanistic viewpoint of a disease considered only as the dysfunction of a single organ or organ system, and evaluates the patient using a holistic approach, i.e., by "considering the person as a functioning whole, or relating to the conception of a human being as a functioning whole" [2].

In general, the PNEI system may be graphically represented as a rhombus, at the center of which lies the organ or organ system of interest, in this article the large bowel and the pelvic floor. The relationship between the organ and the vertices of the rhombus is similar to a cybernetic system. In fact, each point controls the organ/organ system and in turn is influenced by it via a feedback mechanism (Fig. 1).

In the present paper, we provide and discuss some practical examples of the clinical usefulness of the PNEI holistic approach (PHA) in coloproctology. We feel that this approach is more comprehensive than the mechanistic one often adopted by coloproctologists, and may yield more useful information leading to a better understanding of the patients' problems.

"P" for psyche

Clinical case

A 38-year-old woman came to our attention complaining of difficulty having a bowel movement. She had been previously evaluated elsewhere, but reported that the symptoms remained unchanged after a 2-month trial of fiber supplements and increased water input. Her past history was unremarkable, and biochemical screening did not reveal secondary causes for constipation. Physical examination revealed a slight increase of perineal descent during straining and good anal sphincter tone. On further questioning, she reported straining at stools and spending excessive time on the toilet. Although the patient was

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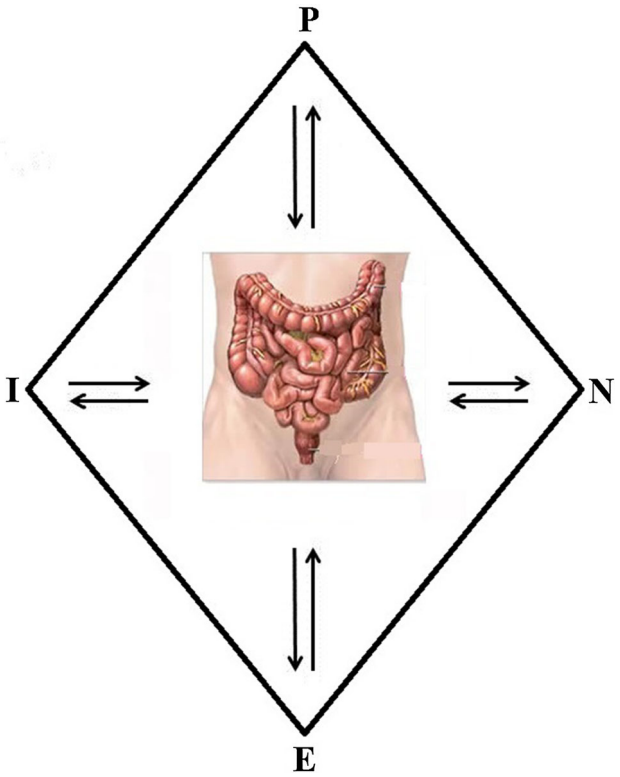

Fig. 1 *Graphic* representation of the PNEI system in coloproctology

scheduled to undergo diagnostic evaluation (anorectal manometry and defecography), she did not turn up but after a couple of months she returned for consultation. She said she had tried homeopathic therapies without success and asked to be treated without further investigations. We scheduled a 2-month trial with macrogol, but the patient said that although it was effective she did not want to take medications for long periods of time. After several other appointments, she agreed to undergo anorectal manometry and defecography. The results of both examinations were obstructed defecation (OD). Therefore, we suggested pelvic floor rehabilitation using biofeedback therapy, but this was definitely refused by the patient. However, she agreed to psychotherapy, and after a few months, she was more confident, more prone to discuss possible therapeutic options, and eventually she underwent five sessions of biofeedback therapy with almost complete resolution of her symptoms.

"P" for psyche is particularly important in patients with OD. This condition occurs in about 7 % of the general population [3] and is often characterized by a normal number of bowel movements associated with straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, and the use of manual maneuvers to facilitate defecation more than 25 % of the time. Paradoxical contraction of or failure to relax pelvic floor muscles during attempts to defecate is observed on anorectal manometry and defecography [4]. It is worth noting that about one-third of the patients with OD have an altered mental pattern [5], and a story of physical or sexual abuse may be elicited from a subset of patients [6]. The importance of a psychological evaluation in at least a subset of constipated patients has been repeatedly highlighted [7, 8]. However, this is usually neglected in studies on OD patients, and only recently has the importance of including a psychological evaluation of these patients been emphasized [9].

Straining at stools, one of the main symptoms complained of by OD patients, may in the long term cause pudendal nerve stretch injury and, eventually, descending perineum syndrome and fecal incontinence [10, 11]. Chronic strain may also cause prolapse or deformation of the rectum, such as rectocele, internal mucosal prolapse, peritoneocele, descent of the pouch of Douglas, and enterocele [12]. These are all organic lesions resulting from long-lasting straining at defecation, even though they are often mistaken by the surgeon for the causes of the patient's symptoms and thus become the target of surgical interventions that can be costly and often useless, or even dangerous.

"N" for enteric nervous system

Clinical case

A 51-year-old woman came to our attention because of proctalgia and rectal bleeding associated with constipation. She was also very anxious about her symptoms. Physical examination revealed that she had a sigmoidostomy and a parastomal hernia, believed to be one reason for difficult defecation. Her previous medical history was remarkable for a stapled transanal rectal resection (STARR) carried out t2 years before in another hospital because of symptoms of OD attributed to recto-rectal intussusception or invagination. After STARR, her constipation did not improve and the patient started to complain of chronic proctalgia, which she described as quite severe. Another surgical consultation led to the construction of a sigmoidostomy. However, the subsequent development of a parastomal hernia pressing on the stoma prevented adequate bowel emptying. In addition, the post-STARR pain persisted. Proctoscopy revealed diversion colitis, characterized by mucosal fragility, bleeding upon contact with the instrument and multiple ulcers. Due to the refractory constipation, two deep surgical biopsies, one in the posterior rectal wall and one in the afferent sigmoidostomy loop, were taken and showed a normal colon but rectal aganglionosis. On repeated questioning, it turned out that none of the previous surgeons who had treated the patient had carried out in-depth diagnostic studies.

This case illustrates quite well the second letter of the acronym. The enteric nervous system (ENS) is considered the true "brain of the gut" [13], and, through a complex network composed of two main ganglionated plexi, it regulates all gut activities [13]. To date, abnormalities of the ENS, such as a reduced number of interstitial cells of Cajal, enteric neurons, and enteric glial cells, have been repeatedly reported in constipated patients [14, 15], and therefore, there is enough objective evidence to suggest that some so-called "functional" disorders may have organic causes [16].

For this reason, a thorough clinical, laboratory, and instrumental evaluation is mandatory in all patients with constipation before considering a surgical approach [17]. Moreover, conventional anorectal manometry can provide evidence for a strong suspicion of rectal aganglionosis and allows aganglionosis to be distinguished from other forms of megarectum, even in doubtful cases [18]. In the above instance, such a simple evaluation could have spared the patient unnecessary surgery. Furthermore, the immediate approach with STARR, without any investigations, to a putative OD syndrome since it reduced the rectal volume probably prevented the clinicians who treated the patient afterward from documenting rectal dilation related to the underlying aganglionosis, further delaying the correct diagnosis. Indeed, although the STARR approach to OD is an effective one, at least in the short and medium term [19, 20], it is very dependent on accurate patient selection [21, 22] and long-term results tend to be disappointing [23]. Moreover, a substantial number of patients remain symptomatic [24] and, should the procedure fail, the outcome is poor [25].

"E" for endocrine system

Clinical case

A 62-year-old man came to our attention due to persistence of an anal fissure for 2 years. He had tried all sorts of conservative treatments, including topical creams (lidocaine, nitroglycerin, calcium antagonists) and a high-fiber diet. However, these approaches were unsuccessful: The fissure either did not heal or recurred soon after the end of treatment. The pain after defecation became frequent and often unbearable and was sometimes accompanied by rectal bleeding. The patient turned to us for advice about local botulinum toxin A injection or internal anal sphincterotomy. Digital rectal examination and anorectal manometry revealed normal sphincter function, without anal hypertonus. We then looked for other causes of impaired fissure healing. Since there is evidence in the literature that growth hormones play an important role in wound healing [26, 27], we looked for endocrine causes. A computed tomography scan of the brain showed an empty sella, a rather common incidental finding, which may be associated with hypopituitarism of varying degrees [28].

We hypothesized that a lack of pituitary growth factors had caused delayed or absent wound healing and we treated the patient with an amino acid-based scarring agent, to stimulate the release of growth hormone [29]. This approach led to complete healing of the fissure and resolution of symptoms within a month. After more than a year of follow-up, there was no recurrence.

This case serves as an effective example of the importance of the third letter of the acronym. Too often in daily clinical practice, the fact that the endocrine system may play an important role in the homeostasis of the gut and that it may be responsible for symptoms other than diarrhea is forgotten or downplayed [30]. For instance, thyroid [31] or parathyroid [32] dysfunction can cause constipation or intestinal pseudoobstruction that may mimic organic bowel occlusion [33]. Thus, when symptoms do not respond to treatment, or when even extensive investigations fail to show an underlying cause, an assessment of the patient's endocrine system may provide the clue to a better understanding of the patient's symptoms and more effective treatment [34], as in the case reported above.

"I" for immune system

Clinical case

A 35-year-old woman came to our attention because of chronic abdominal pain. She started to complain of crampy pain 3 years prior to presentation, and the evaluations performed elsewhere revealed questionable biliary sludge, for which reason she underwent laparoscopic cholecystectomy. However, the pain reappeared with the same characteristics shortly after surgery, and the patient underwent several upper and lower endoscopic procedures (including endoscopic retrograde cholangiopancreatography), all yielding negative results. Several pain treatments (including a course of opioids) had little or no effect. The patient was mildly anxious, and physical examination revealed tenderness upon palpation of the lower abdominal quadrants. She admitted that the pain: (a) was not present during the night, but only when she was awake; (b) often decreased or disappeared after bowel movements. On further questioning, it was evident that these symptoms, accompanied by alternating bowel habits, had first appeared about 3 months after a trip to Mexico, where the patient experienced diarrhea that persisted after returning home and was subsequently diagnosed as *Campylobacter jejuni* enteritis. On these grounds, a diagnosis of post-infectious irritable bowel syndrome (IBS) was made, and the patient was appropriately treated with almost complete resolution of symptoms.

Thus, even the fourth letter of the acronym ("I") fits in the general picture. In fact, to date, there are no doubts that the interaction between the immune system and the gut is extremely strong, and likely to influence all aspects of intestinal function. This is particularly true for the so-called "functional" disorders [35], even though there is evidence that several other pathologies may be influenced [36–38]. IBS has been repeatedly investigated in this regard. For instance, it is well known that this condition is preceded by an acute event of infectious origin in about 10 % of cases [39]. However, it is not known whether specific pathogens have unique effects on long-term alterations in gut physiology or different pathogens converge to cause common alterations resulting in similar phenotypes. The role of microbial virulence and pathogenicity factors in development of post-infectious IBS is also largely unknown [40].

There are several studies demonstrating mucosal immune system activation in patients with IBS; an increased number of lymphocytes [41] and of activated mast cells [42] has been demonstrated in the terminal ileum, jejunum, and colon of these patients, as well as elevated plasma levels of proinflammatory interleukins, that are mediators of immune responses [43]. Moreover, it is becoming increasingly evident that the complex intestinal ecosystem containing an enormous number of bacteria and other microorganisms that reside in the gut (microbiota) is able to influence to a great extent several physiologic variables, such as decision-making processes, learning, and memory. This ecosystem protects the host against pathogens, metabolizes complex lipids and polysaccharides, neutralizes drugs and carcinogens, modulates intestinal motility, and makes visceral perception possible [44]. The bidirectional signaling between the brain and the intestine, the so-called "microbiota-gut-brain-axis," is of paramount importance for maintenance of gut homeostasis, and it is involved in the pathogenesis of several conditions, including IBS [45].

Using the PHA in coloproctology: a diagnostic refinement

Although the above examples are only few of the myriad clinical situations occurring daily in the coloproctological field, we have selected them to illustrate the importance of the PHA approach for appropriate diagnosis and treatment. In fact, by focusing only on a specific symptom, the physician often fails to see the whole picture, and this may be misleading and potentially a cause of error. Especially in surgical settings, if we only focus on "repairing" a damaged organ or tissue, but do not focus on the why this damage appears, the risk of recurrence or, worse, of further impairment or damage is very high, even when the patient is in the hands of a skilled and experienced surgeon.

Indeed, the old reductionist model of disease in which physicians tried to identify a single underlying biological factor as responsible for a patient's symptoms has been progressively replaced by a more integrated, biopsychosocial model of illness and disease [46]. Investigation of this new model, with the help of experimental animal models, has provided evidence suggesting that the mind and the body are so interrelated that their dysregulation can produce illness (the person's experience of ill health) and disease. For instance, anxiety and fear are common aggravators of pain [47, 48].

It is important for a physician to remember that the patient is a person, not a disease. Healing involves a close relationship and, often, a high degree of confidence and trust, between the patient and doctor, and often all aspects of a patient's life need to be addressed. Thus, the "picky" doctor will most likely take a detailed clinical history including all the potential factors that may be causing the patient's illness, such as other health problems, diet and sleep habits, stress and personal problems.

Treatment involves dealing with the cause of the condition, not just alleviating the symptoms, and not infrequently requires a tailored approach. Of course, we realize that in this era of super-specialization it is often difficult to have in-depth knowledge of different fields. However, it is also true that it is not difficult to have competent specialists available for each area of the PNEI system. As in most fields, the key to success is to develop a multidisciplinary team, able to face every complex, even apparently simple, situation, and offer patients the best possible treatment options.

Conflict of interest None.

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