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Review

Neuroimmunoendocrine peptides on inflammed and morphologically normal appendices removed due to clinical acute appendicitis

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ABSTRACT

Introduction: Despite clinical characteristics and complementary exams indicate acute appendicitis, 15% to 40% of all appendectomies result in removal of appendices with normal macro- and micromorphological aspects. Even so, manifestations of acute abdomen disappear immediately after the appendectomy, and never show back again.

Objective: To assess changes of neuroimmunoendocrine peptides on removed appendices due to clinical presentation of acute appendicitis.

Method: This article presents an updated revision of acute appendicitis, based on references found on PUBMED, LILACS, MEDLINE, WHOLIS and SciELO, using key words “acute appendicitis”, “neuroimmune appendicitis”, “neurogenic appendicopathy”, and “incidental appendectomy”.

Results: Fourteen neuropeptides were analyzed by different authors who suggested the presence of neurogenic appendicopathy in morphologically normal appendices removed from patients with clinical presentation suggesting acute appendicitis.

Conclusion: The etiopathogeny of acute appendicitis continues to be unknown, and there is a great possibility that patients with morphologically normal appendices with clinical presentation of acute appendicitis that heal after appendectomy present a neuroimmunoendocrine disease.

1. Introduction

Despite clinical characteristics and complementary exams indicate acute appendicitis, 15%–40% of all appendectomies result in removal of appendices with normal macro- and micromorphological aspects [1,2]. Even in such condition, the manifestations of acute abdomen disappear immediately after removal of the appendix, without recurrence, suggesting a relationship between the clinical presentation and the removed apparently normal appendix [3].

The appendix is known since Leonardo da Vinci's description, but its function and the pathogenesis of acute appendicitis are still not known [4]. It has been considered as an involuted part of the intestine, but this theory was phylogenetically abandoned [5]. Theories such as that of appendicular lumen obstruction by fecaliths, seeds, and foreign bodies causing wall inflammation are not accepted anymore [6]. Bacterial migration to the appendix wall leading to inflammatory phenomena is also controversial [7].

The amount of the appendiceal lymphatic tissue is proportionally higher than in the rest of the digestive tube suggesting a relation of this organ with the immune system [8]. Another peculiarity of the appendix is the carcinoid tumor, its more frequent type of cancer, which belongs to the neuroendocrine system. The appendix adenocarcinoma has usually origin in the cecum, whose digestive structure is different [9,10].

Another aspect that must be pointed out is the “appendicitis” in the elderly [11]. While in the young appendicitis is demonstrated as an inflammatory disorder, in the elderly, it results from ischemic vascular changes, originated in the mucosa, that evolve to a lesion of the entire wall until perforation in free cavity with consequent peritonitis. The inflammation found in these cases comes from the perforation. Otherwise, the perforation in the youth is usually blocked by the inflammation which started previously and induced adhesions of the appendix to surrounding structures. In these cases, the perforation provokes an abscess restricted to the pericecal region with a benign course [12.13].

Imaging studies contribute for diagnosis when clinical and laboratorial exams are not conclusive. The higher sensitivity and specificity of the imaging exams, with highlights for simple abdominal radiography and computerized tomography that show expansion of the cecum with presence of faecal content, may not be followed by the morphological evidence of appendicitis [14,15].

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Diagnostic imprecision is more frequent in obese individuals, children, and in immunodeppressed patients, including the elderly and patients using immunosuppressant medication [16,17]. In presence of excessive mobile cecum due to lax ligaments leading to appendix abnormal position, such as subhepatic, pelvic, epigastric, and even in the left flank, precise diagnosis is more difficult [1,18,19]. Pain outside of the usual appendix site is found in 24% of cases, especially in pregnant women due to dislocation by the uterus [20].

Maresh and Masson (1910) found neuroendocrine lesions in appendices without signs of acute inflammation indicating association of clinical presentation of appendicitis and disorders of those neuroendocrine peptides, which may or may not evolve to apparent morphological alterations of the appendices. Since then, several works have indicated a real relation between neuroendocrine disturbance and acute appendicitis symptoms [21].

Based on literature studies, the purpose of this article was to assess changes of neuroimmunoendocrine peptides on removed appendices due to clinical presentation of acute appendicitis.

2. Material

This article presents an updated literature review of acute appendicitis, based on references found on PUBMED, LILACS, MEDLINE, WHOLIS and SciELO, using the key words “acute appendicitis”, “neuroimmune appendicitis”, “neurogenic appendicopathy” and “incidental appendectomy”.

3. Results and discussion

The occurrence of endocrine cells in the gastrointestinal submucosa is known since Heidenhein (1870) who observed cells with cytoplasmatic granules stained by chromium salts [22]. Masson (1914) named these enterocromafins cells argentafins because he could stain them selectively with a reducting ammoniacal solution of silver nitrate. The neuroendocrine gastrointestinal cells are scattered among other cells of the mucosa and submucosa, and cannot be differentiated by routine staining with hematoxillin and eosin [23,24]. According to Di Sebastiano et al. (1999), there is a neuroproliferation in the appendix, associated with the increase of substance P (SP) expression and vasoactive intestinal peptide (VIP), in patients with clinical diagnosis of acute appendicitis without inflammatory reaction. These authors described the enhancement of nerve fibers stained by the gene-protein 9.5 (PGP 9.5) in the mucosa of non inflamed appendices, besides the presence of SP and VIP. The increase of SP and VIP in the appendix may cause pain in the right iliac fossa, and both substances are related to inflammatory disturbances [25].

Peptidergic neurons contain other peptides, pro-nociceptive and pro-inflammatory transmitters besides SP and VIP [25]. Olsen and Holck (1987) suggested that SP causes spastic contractions and abnormal peristalsis [26]. SP is associated to sensory nerve fibers involved in antidromic vasodilation, and is released from sensory peripheral nerve endings during chemical and physical stimulation, resulting in neurogenic inflammation. Venous or topic administration of SP may cause vasodilation, plasma overflow, followed by smooth muscle contraction. VIP also causes neurogenic vasodilation on the basal mucosa [25,27].

In the basal mucosa, the neurogenic vasodilation is mediated not only by SP, but also by release of VIP. Kubota et al. (1992) demonstrated that distribution of VIP and its expression change in the presence of inflammatory intestinal disease. According to Di Sebastiano et al. (1999), the changes on peptidergic innervation are related to localized pain in acute appendicitis even without histological manifestation. Neuroproliferation in the *lamina propria* and in the muscular layer was observed in patients with abdominal pain with histologically normal appendices, and this hyperplasia is interrupted when the appendices are removed. The relations of these peptides with right flank pain are reinforced by the expressions of VIP and SP, which are not different from those verified in patients with evident acute inflammation [28].

Bouchard et al. (2001) published that “neuroimmune appendicitis” occurs also in children, upon finding through immuno-histochemical analysis increase in GAP-43, SP and VIP, in presence of pain with histologically normal appendices. Those studies revealed neuronal proliferation and increase in the expression of SP and VIP, in patients with clinical diagnosis of acute appendicitis, even in the absence of appendicular inflammation [25,28].

Xiong et al. (2000) assessed the expression of proteins S100, CNPase, synaptophysin and neuronal enolase which are specific for neurons and Schwann cells, besides tryptase for mastocytes. It was seen an increase of neuronal components and mastocytes, mainly in patients with proven acute appendicitis, suggesting a relation among the enteric nervous system, mastocytes and the pathogenesis of acute appendicitis. The neuronal hypertrophy observed in appendices of patients with clinical presentation of acute appendicitis with histologically normal appendices is similar to other inflammatory responses found in other inflammatory intestinal diseases [29].

Nemeth et al. (2001) observed strong expression of cyclooxygenases 1 and 2, prostaglandin E, nitric oxide synthase and principal complex of histocompatibility class 2 in the mucosa of all inflamed appendices, and also on half of normal appendices removed from patients with clinical presentation of acute appendicitis. Therefore, the inflammation of histologically normal appendices of patients with clinical presentation suggesting acute appendicitis occurs at the molecular level [30].

Whereas the neurogenic disease may not be followed by inflammatory signs, Hofler et al. (1980) suggested the term “neurogenic appendicopathy” for appendices of normal morphological aspects in patients with clinical presentation of acute appendicitis [31]. This concept was revised when it was realized the increased number of neurofibers stained with antibodies against protein S-100, causative of right abdominal pain. According to those authors, as well as to Guller et al. (2001), either neurogenic appendicopathy or morphologically established acute appendicitis reveal the same symptoms, making difficult to distinguish between these two conditions [31,32]. Sesia et al. (2013) revised this concept, adding neuropeptides VIP and SP as agent for the neuronal disturbance [33].

Partecke et al. (2013) while assessing immunohistochemically expressions of S-100 in normal appendices removed from patients with clinical presentation of acute appendicitis found increase of the mediator in nerve fibers of more than half of morphologically normal appendices in comparison with inflamed appendices [34].

Barroso et al. (2015) verified in an immunohistochemical study a more intense staining for VIP in inflamed appendices, followed by on apparent normal appendices with clinical presentation of acute appendicitis, in comparison with normal appendices removed during right colectomies in right colon cancer whose staining was almost inapparent [3]. As there was no correlation with the pathological diagnosis of appendicitis, and the peptides were found also in non-inflamed appendices, the “clinical” disease could have been due to a different etiology, unrelated to the inflammation of the appendix, such as a neuroimmunoendocrine disease.

4. Conclusion

The etiopathogeny of acute appendicitis continues to be unknown, and there is a great possibility that patients with morphologically normal appendices with clinical presentation of acute appendicitis that heal after appendectomy present a neuroimmunoendocrine disease.

Declaration of conflicting interests

The authors declare no conflict of interest with respect to the research, authorship and publication of this article. The author has no

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Author contribution

Thiago Vinicius Villar Barroso, MD - Conceptualization; Data curation; Formal analysis; Methodology; Writing original draft.

Andy Petroianu, MD, PhD, Professor of Surgery – Conceptualization; Data curation; Formal analysis; Project administration; Resources; Supervision; Writing original draft.

Conflicts of interest

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Guarantor

We, Thiago Vinicius Villar Barroso, MD and Andy Petroianu, MD, PhD are the Guarantor of this article and we accept full responsibility for the work and the conduct of the study, we have access to the data, and we control the decision to publish.

CRediT authorship contribution statement

Thiago Vinicius Villar Barroso: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Andy Petroianu:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing - original draft, Writing - review & editing.

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