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Review Article

Pathophysiology of Acute Appendicitis

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Abstract

Background: Acute appendicitis, the most common abdominal emergency that requires surgical treatment, shows a lifetime risk of 7%. Its overall incidence is approximately 11 cases per 10,000 individuals per year, and may occur at any age, although it is relatively rare at the extremes of age.

Method: This article presents a recent-year-review of acute appendicitis, based on a study of references found in the PUBMED, using the key word of "pathophysiology of acute appendicitis" as research limitation.

Results: The function of the appendix is not clearly understood, although the presence of lymphatic tissue on it suggests a role in the immune system. The primary pathogenic event in most of patients with acute appendicitis is believed to be due to luminal obstruction. Although being logical and likely to be true, this theory has not been proven. There is strong epidemiologic evidence supporting the proposition that perforated and non-perforated appendicitis are separate entities with a different pathogenesis. Recently, with the advent of neurogastroenterology, the concept of neuroimmune appendicitis has evolved. Considering that neurogenic disease may not include inflammatory signs, the name "neurogenic appendicopathy" seems to be a more appropriate term for appendices of morphological normal aspect in patients with clinical symptoms of acute appendicitis.

Conclusion: As it can be perceived, based on the large number of studies related to acute appendicitis, it is not yet established the pathophysiology of this disease More research is in need to understand this still mysterious disease.

INTRODUCTION

Acute appendicitis, the most common abdominal emergency that requires surgical treatment, shows a lifetime risk of 7%. Its overall incidence is approximately 11 cases per 10,000 individuals per year, and may occur at any age, although it is relatively rare at the extremes of age. Between 15 and 30 years of age there is an increase of 23 cases per 10,000 population/year, and then a decline of cases with aging [1-6]. Most of patients are whites (74 %), and it is very rare in blacks (5 %) [5,6]. Some authors have described a seasonal variation in the incidence of appendicitis, a higher incidence occuring at summer time, or at spring and autumn, or even in raining whether [7,8]. This finding however is controversial and not uniform [7]. Reginald Fitz in 1886 was the first physician to write about the pathophysiology of acute appendicitis, accurately describing the aetiology of this disease [9].

While the clinical diagnosis may be straightforward in patients presenting classic signs and symptoms of the disease, atypical presentations may result in diagnostic confusion and delay in treatment [5,9,10] This article presents a recent-year-review of acute appendicitis, based on a study of references found in the PUBMED, using the key word of "pathophysiology of acute appendicitis" as research limitation.

Pathophysiology of acute appendicitis

The function of the appendix is not clearly understood, although the presence of lymphatic tissue on it suggests a role in the immune system. In humans it is regarded as a vestigial organ, but this idea is erroneous because the role of the appendix has been established as a neuroendocrine and immunological structure. Its acute inflammation is classified as: [1,5]

- not complicated appendicitis - inflamed appendix, in the absence of gangrene, perforation, or abscess around the appendix;

- complicated appendicitis - perforated or gangrenous appendicitis or the presence of periappendicular abscess.

The primary pathogenic event in most of patients with acute appendicitis is believed to be due to luminal obstruction [10]. This may result from a variety of causes, which include fecaliths, lymphoid hyperplasia, foreign bodies, parasites, and

by both primary (carcinoid, adenocarcinoma, Kaposi sarcoma, and lymphoma) and metastatic (colon and breast) tumors. Fecal stasis and fecaliths characterize the most common cause of appendiceal obstruction, followed by lymphoid hyperplasia, vegetable matter and fruit seeds, barium from previous radiographic studies, and intestinal worms (especially ascarids) [11-13]. The prevalence of appendicitis in teenagers and young adults suggests a pathophysiologic role for lymphoid aggregates that exist in abundance in the appendix of this age group [5,9,14]. According to this theory, obstruction leads to inflammation, rising intraluminal pressures, and ultimately ischemia. Subsequently, the appendix enlarges and incites inflammatory changes in the surrounding tissues, such as in the pericecal fat and peritoneum.

If untreated, the inflamed appendix eventually perforates. True appendiceal calculi (hard, noncrushable, calcified stones) are less common than appendiceal fecaliths (hard but crushable concretions), but they have been associated more commonly with perforating appendicitis and with periappendiceal abscess. This aetiology of occlusion appears to be more common in younger individuals, in whom lymphoid tissue is more abundant than in older persons [1,2,5,9,14].

Rapid distension of the appendix ensues because of its small luminal capacity, and intraluminal pressures can reach 50 to 65 mm Hg [1,3,4,10]. This appendiceal condition leads to enlargement of the cecum due to the cecal localised ileum, caused by the inflammatory process. The cecal content is stored and is not conducted to the right colon. The presence of fecal loading inside a large cecum is identified in the plain abdominal radiography as a specific sign of acute appendicitis [4,5,12,13].

As luminal pressure increases, venous pressure is exceeded and mucosal ischemia develops. Once luminal pressure exceeds 85 mm Hg, thrombosis of the venules that drain the appendix occurs, and in the setting of continued arteriolar inflow, vascular congestion and engorgement of the appendix become manifest. Lymphatic and venous drainages are impaired and ischemia develops. Mucosa becomes hypoxic and begins to ulcerate, resulting in compromise of the mucosal barrier, and leading to invasion of the appendiceal wall by intraluminal bacteria. Most of bacterias are gram-negative, mainly *Escherichia coli* (present in 76 % of cases), followed by *Enteroccocus* (30 %), *Bacteroides* (24 %) and *Pseudomonas* (20%) [1,3,10].

Although being logical and likely to be true, this theory has not been proven. In the most recent review on aetiology and pathogenesis, several studies showed that contrary to common thinking, obstruction of the appendix is unlikely to be the primary cause in the majority of patients [1,4,10,11]. An investigation that measured the intraluminal pressures in the appendix showed that in 90% of patients with phlegmonous appendicitis, there was neither raised intraluminal pressure nor signs of luminal obstruction. There were signs of obstruction of the appendiceal lumen, expressed as an elevated intraluminal pressure, in all patients with a gangrenous appendix, but not in patients with phlegmonous appendix [15,16]. These data suggest that obstruction is not an important factor in the causation of acute appendicitis, although it may develop as a result of the inflammatory process. On the basis of available evidence, it is likely that there are several aetiologies of appendicitis, each of which leads to the final pathway of invasion of the appendiceal wall by intraluminal bacteria [5,17,18].

The inflammation extends to serosa, parietal peritoneum, and adjacent organs. As a result, visceral afferent nerve fibres that enter the spinal cord at T8 - T10 are stimulated, causing referred epigastric and periumbilical pain represented by the correspondent dermatomes. At this stage, somatic pain supersedes the early referred pain, and patients usually undergo a shifting on the site of maximal pain to the right lower quadrant [19,20]. If allowed to progress, arterial blood flow is eventually compromised, and infarction occurs, resulting in gangrene and perforation, which usually occurs between 24 and 36 hours. Anorexia, nausea, and vomiting usually follow as the pathophysiology worsens [1,5,6].

There is strong epidemiologic evidence supporting the proposition that perforated and non-perforated appendicitis are separate entities with a different pathogenesis. Patients with a short duration of symptoms had a predominantly neutrophil infiltrate that changed to a predominant lymphocytic infiltrate with evidence of granulation tissue as the duration of symptoms became longer. These findings support the contention that a mixed infiltrate of lymphocytes and eosinophils represents a regression phase of acute appendicitis. Fibrous adhesion formation and scarring of the appendix wall also have been demonstrated and are consistent with resolution of a previous attack of appendicitis. In old people, the usual manifestation of the so called “appendicitis” is perforation without or with little inflammation. In these cases, an ischemic appendix perforates, differently from those of young people, in whom the perforation is due to the evolution of an inflammation with severe infection [19].

The immune role of the appendix involves local and systemic responses to recognize the microbe molecular patterns and to initiate the local response that attracts and activates leukocytes, increases vascular permeability, elicits pain, and enhances blood flow to the infected tissue. Many features of this immunity are characteristic of acute appendicitis, as a common form of moderately severe, yet localized, bacterial infection. The important elements of the immunity are linked to the genome, responding to microbial signals without further gene modification. Allelic polymorphisms in various innate immunity genes have been associated however with increased risk of acquiring infectious diseases. Complicated appendicitis is associated with the IL-6 −174 C-allele and TNF-α that might influence the severity of inflammation in appendicitis. Increased TF expression and decreased tissue factor pathway inhibitor expression contribute to local microvascular thrombosis, tissue necrosis, and gangrene [21,22].

Recently, with the advent of neurogastroenterology, the concept of neuroimmune appendicitis has evolved [23-25]. After a previous minor bout of intestinal inflammation, subtle alterations in enteric neurotransmitters are seen, which may result in altered visceral perception from the gut; this process has been implicated in a wide range of gastrointestinal conditions [8,26-28].

About 95% of serotonin in the body is in the gastrointestinal tract, located mainly in the mucosal neuroendocrine cells [29,30]. Appendixes with inflammation are markedly depleted of serotonin in the epithelium (enterochromaffin cells) and *lamina propria* [30]. Local increase in serotonin secretion in the appendix may play an important role in the pathogenesis of inflammation. The initial event in appendicitis is thought to be luminal obstruction with various etiologies. Once obstruction occurs, epithelial mucosal secretions increase the luminal pressure. It has been suggested that enterochromaffin cells have pressure receptors that, upon sensing luminal pressure, release 5-HT into the *lamina propria*. It may be postulated that local serotonin release exacerbates intraluminal secretion, venous engorgement, vasoconstriction and smooth muscle contraction, which divert the congestive process to an inflammatory one. Abundant 5-HT3 receptors on vagal and other splanchnic afferent neurons and on enterochromaffin cells have a significant role in inducing nausea and emesis. However, a cause and effect relationship between subepithelial neurosecretory cells and appendicitis, if any, remains to be established [28-33].

There is neural proliferation on the appendix associated with the increased immunologic reaction to substance P and to the vasoactive intestinal polypeptide (VIP) in patients with clinical diagnosis of acute appendicitis without inflammatory reaction. Increase of these mediators in the appendix may cause pain on the right iliac fossa in the presence of acute appendicitis, and are related with inflammatory intestinal diseases and appendicular fibrosis, containing Schwann cells, mastocytes and fibroblasts [24,28].

Most of these studies were performed in adults, and the pathophysiologic investigation must be extended to children in order to identify the real origin of appendiceal inflammation, mainly in the early years. A more adequate comprehension of this disorder is necessary to justify any new therapeutic proposal.

Considering that neurogenic disease may not include inflammatory signs, the name "neurogenic appendicopathy" seems to be a more appropriate term for appendices of morphological normal aspect in patients with clinical symptoms of acute appendicitis. Either neurogenic appendicopathy or acute appendicitis present the same symptoms and signs; it is hard to distinguish between these two conditions previously to the surgical procedure. Despite the increase of protein S-100 on the neural fibres of morphological normal appendices compared to those on inflamed appendices, the difference is not significant [23,25,28,32,34].

As it can be perceived, based on the large number of studies related to acute appendicitis, it is not yet established the pathophysiology of this disease [35,36]. There is not doubt that all these phenomena are related to appendicitis, and they are part of the genesis of this inflammation [37,38]. More research, however, is in need to understand this still mysterious disturbance.

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