Original Article

Neuronal hyperplasia in clinically diagnosed acute appendicitis: A histopathological study in a tertiary care centre

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ABSTRACT

Background: Acute appendicitis is one of the most common general surgical emergencies. Around 20-25% of patients who have an appendectomy done are found not to have acute appendicitis on histopathological examination. There is increasing evidence of the involvement of the enteric nervous system, in the immune regulation and monitoring the inflammatory responses. The present study was done to elucidate if neuronal changes in the appendix could be the cause of clinical acute.

Materials and methods: Hospital records of 60 cases who were diagnosed as acute appendicitis clinically and who underwent appendectomy either laparoscopic or open, were reviewed. Histopathological records of these resected appendices submitted to the department of histopathology, GAIMS, G.K. General Hospital Bhuj were reviewed for one year for the presence or absence of acute appendicitis or neuronal hyperplasia. Routine Haematoxylin and Eosin stain and S-100 protein staining was done on all these 60 cases.

Results: Out of these 60 specimens of appendices received, histopathological examination revealed neuronal hyperplasia in the submucosa and muscularis layer on all the 60 cases. Grading of neuronal hyperplasia was done in all the cases. Out of these 60 specimens of appendices, histopathological examination revealed 48 cases of histopathologically positive acute appendicitis and 12 cases of histopathologically negative acute appendicitis.

Conclusions: Neuronal hyperplasia has an important role in the pathogenesis of appendiceal colic in patients with both histopathologically positive acute appendicitis and histopathologically negative acute appendicitis.

INTRODUCTION

The appendix is an intriguing organ, keeps challenging the clinicians and pathologists. Acute appendicitis is the most common surgical emergency.1

Appendectomy is the most frequently performed operation worldwide. Nearly 20% of patients who undergo appendix resection are found not to have features of acute appendicitis on histopathological examination.2 Obstruction of the lumen, leading to distension and disordered accumulation, lymphoid hyperplasia, and fibrosis are causative factors for the pathogenesis of acute appendicitis. However, microorganism infestation of the appendix is the last event in...
the pathogenesis of acute appendicitis.\(^3\) Even in the absence of acute appendicitis, removal of the appendix relieves pain, suggesting the interaction between local endocrine cells and neural hyperplasia of the enteric nervous system.\(^4\)

Immunocompetent cells like the mast cells, with their important role in hypersensitivity reactions, are closely opposed to the nerves in the gastrointestinal tract. By releasing neurotrophic factors, they might be involved in neuronal hypertrophy of the appendix. In acute appendicitis, the relationship between the enteric nervous system and inflammatory cells has been described.\(^5\)\(^-\)\(^7\)

**MATERIALS AND METHODS**

Appendectomy specimens were received from the department of surgery and fixed in buffered formalin, and sections were taken at three levels, tip, middle, and base. After being embedded in paraffin sections were taken at five micrometers and stained with routine hematoxylin and eosin stain (H&E) and by immunohistochemistry (IHC) S100 protein. The 60 surgically resected appendices with the clinical diagnosis of acute appendicitis were divided into two categories: 1) Histopathologically positive acute appendicitis and 2) Histopathologically negative acute appendicitis

Criteria for diagnosis of histopathologically positive acute appendicitis (at least three out of six) are as follows:

1. Neutrophils infiltrating throughout the muscle layer.
2. Neutrophils present in the submucosa.
3. Epithelial erosion (denudation of the columnar lining epithelium)
4. Suppurative Inflammation (Abscess)
5. Vasodilation and edema.
6. Fibrinous exudate along with acute inflammatory cells over the serosa.

Exclusion Criteria included occasional scattered inflammatory cells within the lumen or serosa, perivascular neutrophils infiltrate, perforated appendix, and Gangrenous Appendix (due to major structural damage to the lamina propria, submucosa, and muscle layer will obscure the neural tissue) and appendiceal fibrosis

Criteria for diagnosis of histopathologically negative acute appendicitis (at least two out of three shall be present) are as follows:

1. Absence of neutrophils in the muscularis propria
2. Intact lining epithelium.
3. Presence or absence of lymphoid hyperplasia.

The ganglion plexus present in the submucosa and muscularis propria was identified. 10 non-overlapping contiguous fields were examined under high power and an average per HPF was calculated and graded:\(^8\)

Grade 1+ (Mild Hyperplasia) : <1/HPF
Grade 2+ (Moderate hyperplasia): 1/HPF
Grade 3+ (Marked hyperplasia) : >1/HPF

**RESULTS**

A total of 60 cases were studied during the study period. Out of the total 60 cases, there were 48 cases (80%) of histologically positive acute appendicitis (HPAA and 12

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**Figure 1**: Photomicrograph showing neural hyperplasia i, a) submucosa and b) muscularis propria (HE stain; a) X100, b) X400).
Neuronal hyperplasia in clinically diagnosed acute appendicitis.

Cases (20%) of histologically negative acute appendicitis (HPNA). Among the total HPAA patients, grade 1 neuronal hyperplasia was observed in 18/48 (37.5%) cases. Grade 2 neuronal hyperplasia was encountered in 22/48 (45.8%) and grade 3 was n 8/48 (16.6%) patients with acute appendicitis. Out of the 12 cases of HPNA, grade 1 neural hyperplasia was seen in 9/12 (75%) cases and grade 2 was seen in 3/12 (25%). Neuronal hyperplasia was observed in both submucosa and muscularis propria (fig. 1 and 2).

DISCUSSION

Appendiceal neuroma or neurogenic hyperplasia of the appendix was first described by Pierre Masson in 1928. It is a relatively common entity characterized by the obliteration of the lumen of the appendix by a proliferation of neural tissue.

Possibly, there is an increase in the number of enteroendocrine cells leading to the hyperplastic proliferation of unmyelinated neurons and Schwann cells. There is increasing evidence supporting the involvement of the enteric nervous system in immune regulation of the body. Lymphocytes and mast cells are in a close functional relationship with the enteric nervous system. Studies have also suggested the presence of receptors for neuropeptides on the immunocompetent cells throughout the gastrointestinal tract (GIT).

Increased nerve proliferation and increased levels of a neurotransmitter (substance P) and vasoactive intestinal peptide has been reported in association with chronic inflammatory bowel disease and appendiceal fibrosis. Appendiceal fibrosis is a fibrotic lesion in which there are more Schwann cells and mast cells as compared to fibroblasts.

In the present study, the neural tissue was highlighted by S100 stain but was equally identifiable in routine HE stains. Inflammatory reactions involving the local endocrine cells and neuro-proliferation may cause repeated and chronic attacks of appendiceal colic.

Grade 1 neural hyperplasia was seen in 37.5% cases of histopathologically positive acute appendicitis and 75% cases of histopathologically negative acute appendicitis. Grade 2 neural hyperplasia was highest and seen in 45.8% of cases of histopathologically positive acute appendicitis. This finding of neural hyperplasia being more common in HPAA was similar to other studies but differed from two other studies.

The pathogenesis of neural hypertrophy in acute appendicitis is still not known. It may represent a form of inflammatory response. The extent of neuronal proliferation seen in the present study is unlikely to develop due to a single attack of acute inflammation. These suggest either repeated bouts and subclinical inflammation or obstruction in the lumen of the appendix. Xiong et al. also supported the above concept of neuronal proliferation.

CONCLUSIONS

Neural hyperplasia may represent an early identifiable morphological feature of inflammation. Hence the present study was conducted and the finding of an increase in neural components in histopathologically positive acute appendicitis suspected a functional link between the enteric nervous system, mast cells, and pathogenesis of the colic in acute appendicitis.

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Conflict of interest: None

REFERENCES


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