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RESEARCH ARTICLE

MORPHOLOGY AND SERUM IGE LEVELS IN RECURRENT ACUTE APPENDICITIS.

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Abstract

The pathophysiology and morphology of recurrent appendicitis has not been well studied. This study was conducted to examine the subtle morphological changes in recurrent appendicitis and to compare the serum IgE levels with appropriate controls. The clinical, laboratory and morphological findings of the appendicitis were compared between the three groups namely, acute, recurrent and control. No significant differences were found in the clinical, laboratory, and morphological parameters between acute appendicitis presenting for the first time and recurrent appendicitis. Repeated attacks in recurrent appendicitis may indicate a predisposition to type I hypersensitivity. The appendix in recurrent appendicitis does not undergo chronic or reparative changes to any significant extent.

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Introduction:-

Significance of eosinophils in acute appendicitis is now a well-defined feature (Aravindan et al., 2010). In a large proportion of cases, acute appendicitis is recurrent, and it is considered as a differential diagnosis in patients with recurrent pain in the iliac region. It is defined as recurring right iliac fossa pain with acute appendicitis confirmed at the time of operation. Therecurrent pain completely subsides after surgery. In a retrospective study conducted by Chang and Chang (2004) in 290 patients with appendicitis over a two-year period, about 11% had recurrent appendicitis. Many other studies had also reported the presence of acute appendicitis in patients, within a year of conservative treatment and required surgery (Eriksson and Grandstorm, 1995; Barber et al., 1997).

Surgery is usually done for recurrent appendicitis in the acute phase as an emergency or in the non-acute phase as interval appendicectomy. Acute appendicitis is characterized by increase in eosinophils, mast cells, nerves and ganglion cells in mucosa, submucosa, and muscularis propria (Singh et al., 2008). The subtle morphological changes in these appendicectomy recurrent appendicitis specimens are not well studied. It is hypothesized that these are cases in which repeated allergen induced and IgE mediated mast cell degranulation occur – similar to chronic asthma. Yet, the pathophysiology and the morphological changes in recurrent inflammation of the appendix is unclear. There is a speculation that recurrent appendicitis is caused by partial obstruction of the appendiceal lumen or excessive mucus production in the appendix (Chang and Chang, 2004; Seidman et al., 1991). There is negligent data available on the morphological features and serum IgE levels in patients with this condition. This study aims to fill the gap with respect to IgE levels and the morphological changes in recurrent appendicitis.

Methodology:-

Detailed clinical and histological examination of 15 cases of recurrent appendicitis was carried out and compared with 16 cases of acute appendicitis. Acute appendicitis cases were either presenting for abdominal pain for the first time or with appendix removed for suspected appendicitis that turned out to be histologically normal. Blood sample

for both cases and control were collected immediately on admission and stored. Cases had histologically proved acute appendicitis, either presenting for the first time (n=16) or those with a history of at least one previous hospitalization for clinically suspected appendicitis (n=15). Controls included patients with appendectomy specimens that are histologically normal, healthy volunteers with no history of allergy (n=17), and those with acute bronchial asthma (n=10). Allergic diseases like skin conditions, asthma and allergic disorders other than those with bronchial asthma were excluded from the study.

Personal information including dietary habits, history of allergy, symptoms and its duration, onset of symptoms, surgical details, and clinical diagnosis were collected. Sample with 2 ml blood was collected from cases and controls by venipuncture in vacutainers. The tubes were kept undisturbed for 90 min and serum separated by centrifuging at a speed of 2500 rpm for 5 mins. These serum samples were then stored at -20°C till IgE assay. Specimens were examined for the following features: Length, circumference (cm) surface exudates, luminal contents and presence/absence of pus. Appendectomies were classified on the basis of histological features. Total serum IgE was estimated using an automated chemiluminescence assay (IMMULITE total IgE, DPC Diagnostics Products Corporation, Los Angeles, USA).

Results:-

Clinical and laboratory variables of the different groups namely, recurrent appendicitis, first-time acute appendicitis and normal appendix are given in **Table 1**.

Table 1:-Clinical and Laboratory parameters in the three groups -- recurrent appendicitis, first-time acute

Clinical and Laboratory parameters in the three groups						
Parameter	Acute first-time appendicitis (A)	Normal appendix (N)	Recurrent appendicitis (R)	p		
				A vs N	R vs N	A vs R
Mean age (yrs)	26.8	23.8	25.9	>0.05	>0.05	>0.05
Males (%)	87.5	50	60	>0.05	>0.05	>0.05
Emergency surgery (%)	93.8	30	73.3	0.001	0.04	>0.05
Absolute neutrophil count (Mean/mm ³)	11668	7767	10575	0.018	>0.05	>0.05
Absolute lymphocyte count (Mean/mm ³)	2462	2967	2806	>0.05	>0.05	>0.05
Absolute eosinophil count (Mean/mm ³)	440	171	300	>0.05	>0.05	>0.05
Absolute monocyte count (Mean/mm ³)	136	185	198	>0.05	>0.05	>0.05
Eosinophils/10 hpf in muscle	58.9	6.3	66	<0.001	<0.001	>0.05

appendicitis, and normal appendix

The mean total leucocyte count and absolute neutrophil count are higher in acute first-time appendicitis and recurrent appendicitis. A statistically significant relationship can be noted between these parameters in case of classical acute appendicitis. Results also show that none of the clinical or laboratory parameters are significantly different between first time and recurrent appendicitis. Eosinophil infiltration of the muscle layer also is greatly increased in these two types of appendicitis, when compared to normal.

Gross and microscopic parameters of the three groups are given in **Table 2**. Presence of neutrophils in lamina propria, submucosa, and serosa was significantly higher in first time and recurrent appendicitis when compared to normal. So was mucosal ulceration and edema in the submucosa and muscle, though the values were significant only in case of first time appendicitis. Fibrosis, moderate to severe, was higher in the two appendicitis group when compared to normal. There was no significant difference between first time appendicitis and recurrent appendicitis in this regard. Similarly, though Schwann cell and neural hyperplasia was seen only in three cases, all belonging to recurrent appendicitis group, the differences were not statistically significant. Eosinophil infiltration of the muscle

layer was greatly increased in acute first time appendicitis as well as recurrent appendicitis. Lymphocytes or macrophage collections were not significantly increased in either type of appendicitis. Organized serosal exudates were seen in 37.5%, and 40% of cases of first time appendicitis and recurrent appendicitis, respectively. The difference between the two were not significant.

Table 2:-Gross and microscopic parameters in the three groups -- recurrent appendicitis, first-time acute appendicitis, and normal appendix.

Gross and microscopic parameters in the three groups						
Parameter	Acute first-time appendicitis (A)	Normal appendix (N)	Recurrent appendicitis (R)	p		
				A vs N	R vs N	A vs R
Length	5.9	6.5	5.6	>0.05	>0.05	>0.05
Circumference	1.4	1.2	1.6	>0.05	>0.05	>0.05
Surface exudates (%)	43.4	0	53.3	0.017	0.006	>0.05
Muscular ulceration (%)	93.8	40	80	0.005	>0.05	>0.05
Neutrophils in lamina (%)	68.8	10	93.3	0.005	<0.001	>0.05
Submucosal edema (%)	100	30	66.7	0.046	>0.05	>0.05
Submucosalneutrophils (%) ¹	100	0	93.3	<0.001	<0.001	>0.05
Muscle edema (%)	100	30	93.3	0.046	>0.05	>0.05
Lymphocytes >1/hpf in muscle (%)	12.5	0	13.3	>0.05	>0.05	>0.05
Serosal neutrophils (%)	81.3	0	86.7	<0.001	<0.001	>0.05
Eosinophils/10 hpf in muscle	58.9	6.3	66	<0.001	<0.001	>0.05
Serosal organized exudates (%)	37.5	0	40	0.035	0.028	>0.05
Moderate to severe fibrosis (%)	37.5	10	46.7	0.139	0.065	>0.05
Macrophage collections (%)	0	10	6.7	>0.05	>0.05	>0.05
Neural hyperplasia	0	0	20	>0.05	>0.05	>0.05

Serum IgE levels in the different categories are given in **Table 3**.

Table 3:- Serum IgE levels in different categories.

Category	No.	Range	Mean	Median	p (vs Normal volunteers)
Normal volunteers	17	46-2271	391	181	—
Chronic asthma	10	787-3774	1811	1550	0.0001
Normal appendix	10	344-1784	790	583	0.0139
Acute first-time appendicitis	16	256-2269	713	540	0.0077
Recurrent appendicitis	15	1034-5316	2462	2395	<0.0001

Serum IgE levels were significantly higher in recurrent appendicitis, higher than that found in chronic asthma. Mean values of eosinophils in acute first-time appendicitis and normal appendix were also elevated when compared to normal volunteers.

Discussion:-

Recurrent appendicitis is often considered as a differential diagnosis in patients with recurrent right iliac fossa pain (Chang and Chan, 2004). In many cases, acute appendicitis is found to be more common than recurrent appendicitis (Crabbe et al., 1986), while recurrent form was reported to be more common than any other inflamed appendicitis in one of the studies (Kolar et al., 2014). The mean age group for recurrent appendicitis was found to be around 26 years. Eosinophil infiltrate in appendicitis was described earlier in the study conducted by Stephenson and Snoddy (1961), but was categorized as subacute appendicitis without mentioning the clinical correlation of the term. Acute appendicitis with eosinophilic infiltration was mentioned as eosinophilic gastroenteritis rather than a variant of appendicitis (Jona et al., 1976). Eosinophil infiltration of muscle layer in acute appendicitis was reported as a widespread phenomenon in few studies (Aravindan, 1997; Singh et al., 2008). The presence of acute eosinophilic appendicitis is suggested as an early marker of acute appendicitis (Rajeswari et al., 2015). Acute eosinophilic appendicitis, as it is called, occurs when there is no infection. According to Aravindan (1997), eosinophil infiltration is an early event, possibly triggered by Type I hypersensitivity, and infection of appendix is considered as a later occurrence. Studies had reported that acute appendicitis may not have an obstructive etiology (Carr, 2000). This was in contrary to the widespread belief that eosinophil infiltration is an evidence of chronic inflammation (Stephenson and Snoddy, 1961; Crabbe et al., 1986). The allergic theory of appendicitis is supported by the fact that mast cell counts are higher in acute appendicitis (Mysorekar et al., 2006).

Recurrent appendicitis, or the occurrence of repeated episodes of abdominal pain, the origin of which can be traced to appendix, is a contentious entity as the origin of previous pain cannot be associated with morphological changes of appendix. There were no significant clinical or morphological differences between acute first-time appendicitis and recurrent appendicitis. The proposition of non-surgically treated acute appendicitis having morphological sequelae like fibrosis and neural hyperplasia with propensity to recurrent appendicitis thus becomes untenable. As per this study, most cases of recurrent appendicitis are no different from ordinary acute appendicitis and hence they merely reflect repeated attacks of acute inflammation without morphological evidence of chronicity.

The mean eosinophil count was found to be highest in acute eosinophilic appendicitis, and the value was higher than that of recurrent appendicitis (Kolar et al., 2014). The mean eosinophils/10 hpf in muscle was 66 in recurrent appendicitis when compared to 6.3 in normal appendix. Norman J Carr suggests that an eosinophil count in excess of 10 per mm² (25 per 10 HPF) could be abnormal. It is possible that a bigger sample size could have given a slightly different value with regard to the eosinophil count in muscles. But in this study, the number of people with recurrent appendicitis must have been underestimated to a certain extent, as many patients are either ignorant or have forgotten about the earlier occurrence of the pain/symptom. Many patients do not consider an earlier episode of pain as relevant to the present condition and that it should be reported. Further, serum samples from this study were stored for a period of time until analysis at a different site. It is not clear whether this also have added to a small percentage of difference in the eosinophil count in muscles of the specimens.

The serum IgE levels of eosinophils were also found to be very high in this type of appendicitis. It can be hypothesized that persistently high serum IgE levels may lead to recurrent appendicitis as seen in bronchial asthma. In fact the levels are even higher than in bronchial asthma. It is possible that repeated allergen-induced and IgE mediated mast cell degranulation may occur in these cases, similar to that of conditions like bronchial asthma. Mean

values of eosinophils were elevated in normal appendix and acute-first time appendicitis when compared to normal volunteers. But this is due to an occasional high value and not due to a generalized increase in the parameter. In addition, there were few cases of normal appendix with high serum IgE values with a history of recurrent abdominal pain. It is possible that these are cases in which near complete resolution has occurred by the time of surgery. The repeated attacks in recurrent acute appendicitis may be due to the predisposition to type I hypersensitivity. The appendix in recurrent appendicitis, thus, does not undergo chronic or reparative changes to any significant extent.

Conclusion:-

Repeated attacks in recurrent acute appendicitis may be due to the predisposition to type I hypersensitivity. The appendix in recurrent appendicitis does not undergo chronic or reparative changes to any significant extent.

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