

Original article

C-reactive protein: diagnostic aid in right lower quadrant abdominal pain

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SUMMARY

The aim of this study is to investigate the role of CRP and total leukocyte count in the investigation of right lower quadrant abdominal pain. **Methods:** 537 patients were included in this study who presented at the General Hospital of Amfissa with right lower quadrant abdominal pain, with a median age of 26 years. 335 patients were admitted in the Surgical Clinic and 195 of them underwent surgery. The preoperative laboratory findings were correlated with the histopathology of the excised appendices. **Results:** Patients who were finally diagnosed with non-specific abdominal pain had normal CRP levels, lower than 0.1mg/dl, and normal or slightly elevated white blood cell count, with the exception of 1 patient who had CRP level slightly above 0.1 mg/dl. Patients with uncomplicated acute appendicitis had increased CRP (1-3 mg/dl) and elevated leukocyte count, with the exception of 5 patients who had CRP level less than 1 mg/dl. Finally, patients with gangrenous appendix had CRP values between 3 and 6 mg/dl and elevated leukocyte count, while perforated appendix was correlated with significantly raised levels of CRP (>10mg/dl) and elevated or normal leukocyte count. Sensitivity, specificity, positive predictive value and negative predictive value of CRP in diagnosing acute appendicitis was estimated at 97.27%, 99.34%, 99.44% and 96.79% respectively. **Conclusions:** In patients presenting with right lower quadrant abdominal pain, normal CRP level and total leukocyte count, the diagnosis of acute appendicitis is extremely rare. Furthermore, CRP value above 10mg/dl is correlated with perforated appendix.

Keywords: CRP, leukocytes, acute appendicitis

INTRODUCTION

Accurate preoperative diagnosis of acute appendicitis still remains elusive, while the overall negative laparotomy rate remains at about 20%. It must be stressed that acute appendicitis is essentially a clinical diagnosis. Yet, laboratory measurements such as leucocyte count and C-reactive protein concentration are commonly used as diagnostic aids in patients with right lower quadrant abdominal pain. A polymorphic leukocytosis is stressed as an important feature for diagnosing acute appendicitis. An elevated level of C-reactive protein (CRP), an acute phase protein, is one of many downstream indicators of inflammation. Physiologically, CRP enhances cell-mediated immunity by promoting phagocytosis, accelerating chemotaxis, and activating platelets. The test for CRP is a simple and effective screening test for occult bacterial infection or tissue injury. The aim of this study is to investigate the role of these inflammatory markers in diagnosing acute appendicitis.

SUBJECTS AND METHODS

A single center, observational study was conducted from September 2001 to January 2009. A total of 537 patients were included in this study who presented at the General Hospital of Amfissa with right lower quadrant abdominal pain and were treated in the Emergency Department and the Surgical Clinic. The age range was 8-80 years, with a median age of 26 years. Blood samples were obtained for C-reactive protein and leukocyte analysis at the time of presentation. Physical examination and laboratory investigation, including total leukocyte count and CRP level, were normal in 202 patients, who were discharged without being admitted to the Surgical Clinic. On the other hand, 335 patients were admitted to the Sur-

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gical Clinic for further evaluation. 140 of them (Group A, 41.8%) were finally diagnosed with atypical right lower quadrant pain (nonspecific abdominal pain) and they did not undergo surgery whereas 195 patients (Groups B, C, D, E) were diagnosed with acute appendicitis and underwent surgery. Decision to operate was not influenced by the preoperative levels of these tests. All the patients were operated for appendicitis on the basis of history, physical findings and relevant clinical data.

Based on histological features of the removed appendix, the patients who underwent surgery were divided into four groups (Table 1), as follows:

Group B: negative macro-microscopical findings for acute appendicitis (normal appendix)

Group C: inflamed appendix (simple appendicitis)

Group D: gangrenous appendicitis and

Group E: perforated appendix.

A review of their preoperative total leucocyte count (TLC) and CRP levels was made. The normal values for white cell count and CRP levels were taken as 6.000-10.000/ μ L and <0,1mg/dl, respectively. The laboratory findings were correlated with the histopathology of the excised appendices.

Non-categorical findings were assessed by the student t-test. P values < 0.05 were considered significant.

RESULTS

The results of our study are shown in Table 1. Mean CRP values were calculated for each group, and compared with the standard value of 0.05 mg/dl, which was determined as normal.

Patients of Group A had normal CRP levels, lower than 0.1mg/dl, with a mean CRP value of 0.047, and normal or slightly elevated white blood cell count. The difference between the mean CRP value of this group and the normal value was not statistically significant ($P>0.05$). Those re-

sults in combination with physical examination excluded the diagnosis of acute appendicitis.

A total of 195 patients underwent surgery in this study of whom 12 had a normal appendix histopathologically (Group B), giving an overall negative appendectomy rate of 6.2%. They had normal values of CRP, with a mean CRP value of 0.052, and normal or slightly elevated white blood cell count. Only 1 patient of this group had CRP level slightly above 0.1 mg/dl. The difference between the mean CRP value of this group and the normal value was not statistically significant ($P>0.05$).

Among the 183 patients who had appendicitis, 72 had an inflamed appendix (Group C, simple appendicitis), 85 had a gangrenous appendix (Group D) and 26 had perforated appendix (Group E).

Patients of Group C had slightly increased CRP (1-3 mg/d l), with a mean CRP value of 1.74, and elevated TLC, with the exception of 5 patients who had CRP level less than 1 mg/dl. Patients of Group D had CRP values between 3 and 6 mg/dl, with a mean CRP value of 4.42, and elevated TLC. Finally, patients of Group E, with perforated appendix, had significantly raised levels of CRP (>10 mg/dl), with a mean CRP value of 12.85, and elevated or normal TLC. Differences between the mean CRP values of groups C/D/E and the normal value were statistically very significant ($P>0.001$).

Sensitivity, specificity, positive predictive value and negative predictive value of CRP in diagnosing acute appendicitis was estimated at 97.27%, 99.34%, 99.44% and 96.79% respectively.

DISCUSSION

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. Acute-phase proteins are a class of proteins whose plas-

Table 1. Laboratory investigations in patients with symptoms and signs of acute appendicitis.

GROUP	NUMBER OF PATIENTS	CRP (mg/dl) (<i>mean\pmSD</i>)	LEUKOCYTES (μ L) (<i>mean\pmSD</i>)
A	140	0.09 \pm 0.16	7807 \pm 1031
B	12	0.13 \pm 0.18	8250 \pm 866
C	72	2.01 \pm 0.64	11819 \pm 1142
D	85	4.61 \pm 0.85	16223 \pm 1158
E	26	14.85 \pm 4.46	18384 \pm 3188

ma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the acute-phase reaction (also called acute-phase response).^{1,2}

The physiological role of CRP is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via C1q. CRP is synthesized by the liver in response to factors released by fat cells (adipocytes). It is a member of the pentraxin family of proteins.^{1,2}

CRP was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C polysaccharide of pneumococcus. Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer, however discovery of hepatic synthesis demonstrated that it is a native protein.³

The CRP gene is located on the first chromosome (1q21-q23). CRP is a 224-residue protein with a monomer molar mass of 25106 Da. The protein is an annular pentameric disc in shape and a member of the small pentraxins family.^{1,2}

CRP is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. CRP binds to phosphocholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages (opsonin mediated phagocytosis), which express a receptor for CRP. It is also believed to play another important role in innate immunity, as an early defense system against infections.^{1,2}

CRP rises up to 50,000-fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hours. Its half-life is constant, and therefore its level is mainly determined by the rate of production (and hence the severity of the precipitating cause).¹

In surgical diseases CRP levels increase postoperatively and peak at the 3rd postoperative day. In uncomplicated cases serum CRP concentration returns to normal by the 7th-10th postoperative day. Acute surgical diseases are characterized by mild elevation of CRP levels, while significant rise is observed in cases of infectious complications.⁴ In acute appendicitis CRP levels may be within normal limits or slightly elevated during the first hours, but perfo-

rated or gangrenous appendix is almost always connected with significant elevation, as shown by our study. Acute appendicitis is a very rare diagnosis when both total leukocyte count and CRP levels are within normal limits.⁵⁻⁷

The first studies concerning the use of CRP in diagnosing acute appendicitis were conducted by Russian surgeons in 1967, in which diagnostic and prognostic role of CRP were evaluated. Since then, several similar studies, many of which concern children, have been conducted, giving varying results.⁸

As far as Greek bibliography is concerned, it seems that there is no well documented record of the importance of CRP in acute surgical diseases, with the exception of studies concerning children and the work of the authors of this study.⁵⁻⁷

Dueholm et al, in 1989, suggested that only the triple combination of CRP, total white blood cell count and total neutrophil count is of diagnostic value in acute appendicitis, indicating that acute appendicitis is unlikely when these three tests are simultaneously negative.⁹

In 1997, Hallan and Asberg reviewed 22 eligible articles including 3436 patients on the accuracy of CRP in patients with suspected appendicitis. Sensitivity and specificity varied considerably from 40-99% and 27-90%, respectively. They concluded that CRP is a test of medium accuracy and it was not possible to draw firm conclusion on its usefulness.¹⁰

Yokoyama et al reviewed 150 patients who underwent appendectomies and had pathologically confirmed appendicitis, between May 1, 1999 and September 31, 2007, in attempt to clarify the role of C-reactive protein (CRP) as a surgical indication marker for appendicitis. This study showed that the white blood cell counts and neutrophil percentage are not useful for surgical indication, whereas univariate analysis indicated that only CRP was significantly different between the surgery necessary group and unnecessary group, and multivariate analysis showed that only CRP was an independent marker for necrotic appendicitis.¹¹

In 2003, Salem et al. prospectively evaluated patients admitted with nontraumatic, acute, abdominal pain to the surgical department of a large referral hospital over a period of 1 year. Patients were divided into 3 groups: non-specific abdominal pain (NSAP), surgical non-operative and surgical operative group. Despite statistically significant differences between the groups, the authors could not identify a useful level of CRP to differentiate between patients with NSAP and those requiring operative and non-operative management.¹²

The sensitivity and specificity of CRP in diagnosing acute appendicitis was estimated by Khan et al. (2004) at 75,6% and 83,7% respectively.¹³

In 2004, Andersson reviewed 28 different diagnostic variables in the assessment of patients with acute appendicitis in 24 eligible primary articles. The author found that each element of history, examination and laboratory markers of inflammation is of weak discriminatory and predictive capacity. However a combination of more than one variable would make the diagnosis more likely.¹⁴

Shafi et al conducted a study, in 2007, on 110 patients who were operated for acute appendicitis to determine the role of total leucocyte count (TLC), C-reactive protein (CRP) and percentage of neutrophil count in the diagnosis of acute appendicitis. According to the results, CRP had a sensitivity, specificity and positive predictive value of 95.6%, 77.77% and 95.6% respectively. The authors concluded that the above inflammatory markers, (TLC, CRP and neutrophil count) can be helpful in the diagnosis when measured together as this increases their specificity and positive predictive value.¹⁵

In general, most authors agree that acute appendicitis is unlikely in adult patients with normal leukocyte count and CRP value, even if clinical symptoms and signs indicate acute appendicitis. Consequently these patients should not undergo surgery. Furthermore several studies have shown that combining total leukocyte count with CRP value enhances the accuracy of both tests. Both these results are in agreement with those of our study. However a normal leukocyte count and CRP value do not effectively exclude appendicitis in children.¹⁶⁻¹⁸

CONCLUSION

The investigation of right lower quadrant abdominal pain and the diagnosis of acute appendicitis is sometimes difficult and complicated, so that the measurement of CRP and white blood cells are not enough or safe. In effect, there is need for more diagnostic methods. The results of our study show that in acute appendicitis the values of CRP could be normal or slightly elevated at the beginning of the disease (first hours) and in cases of gangrenous or perforated appendicitis CRP values are almost always significantly elevated. When WBC and CRP values are normal, acute appendicitis is rarely the diagnosis for right lower quadrant pain.

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