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Review

INFLAMMATORY MARKERS IN THE DIAGNOSIS OF COMPLICATED APPENDICITIS IN CHILDHOOD

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ABSTRACT

Acute abdominal pain is challenging because of the nonspecific nature of symptoms and difficulties in physical examination in children. In most of them, it is a manifestation of an urgent surgical or medical condition, where the biggest challenge is a timely diagnosis to start appropriate treatment without any diagnostic delays. There are many conditions that present with abdominal pain in all age groups, ranging from a common viral illness to a life-threatening surgical condition. History, physical examination, laboratory tests, and imaging are initially used to differentiate surgical illnesses categorized as urgent. Their characteristics, age, and physical examination of the patient direct appropriate tests in the context of these differences.

Key words: aplasia, uterus, torsion, ovarian, childhood

In the laboratory tests in the diagnosis of complicated appendicitis in childhood, the blood count revealed leukocytosis with oiliness, accelerated ESR, elevated levels of CRP, and procalcitonin, ferritin, Il-6 and Il-10, and albuminuria and leukocytosis were present in the urine (1, 2). Immature neutrophils are capable of mediating important innate immune functions such as bacterial phagocytosis and killing through the production of reactive oxygen species, albeit less efficiently than mature neutrophils. Immature neutrophils have a longer lifespan and resistance to spontaneous apoptosis and can mature ex vivo (3). Immature neutrophils have a higher basal intracellular tumor necrosis-alpha/interleukin-10 ratio than that of mature neutrophils, suggesting a proinflammatory phenotype. No significant differences were observed between immature neutrophils isolated from patients with OCD.Although at the onset of appendicitis the leukocyte count shows the highest diagnostic sensitivity among laboratory tests, 21% of appendicitis patients have normal levels before appendectomy (4, 5).

Right lower quadrant pain is the most common condition requiring surgical treatment in childhood (1, 2). The majority of cases are due to acute appendicitis or acute mesadenitis (6). The incidence of acute appendicitis is 25/10,000 pediatric patients per year between the ages of 10 and 17 years in the United States (4). Primary acute mesenteric lymphadenitis (AML) is clinically suspected in 7% to 20% of OA diagnoses (7). Treatment tactics for both pathologies differ greatly. In the case of AML, treatment is conservative and does not require hospitalization (1, 8), while in the case of OA, immediate surgical intervention is mandatory (7). Missing the diagnosis in the emergency department can increase the likelihood of perforation as well as other complications (4, 7). The incidence of perforated appendix reaches 10%-20% in children aged 10-17 years (7, 8).

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C-reactive protein (CRP) is a commonly used tool in emergency medicine for febrile patients or when an infectious process is suspected. It was discovered in 1930 and classified as an "acute phase protein" and is an early indicator of an inflammatory state (9). CRP is produced by liver cells in response to cellular damage and inflammation and binds to cellular components that activate phagocytes and macrophages. Interleukin-6 (IL-6) is responsible for CRP synthesis and participation in the acute inflammatory process (10). CRP is a screening test for tissue inflammation, a biomarker of disease activity, monitoring response to therapy, and predicting many acute and chronic diseases. In fact, one cannot distinguish bacterial from non-bacterial infection by the CRP level. Nowadays, it is used as a prognostic factor in infections and inflammatory diseases, and the high variability of the association between elevated CRP and bacterial etiology of infection has a sensitivity of 8% to 99% and a specificity of 27% to 95% (11). CRP controls may be useful for response to therapy. While cytokines are generally seen as destructive, they are also protective when localized. The positive effects of cytokines are investigated, while their role in differentiating surgical emergencies is also investigated. Information is needed on the relationship between cytokines and therapeutic strategies for complicated acute surgical illnesses. It is concluded that CRP level >50 mg/l and leukocyte count >10.4x 10^9 associated with pro-inflammatory markers are important predictors of acute inflammatory diseases in the abdominal cavity, while abdominal ultrasound and CT have significant diagnostic accuracy in emergency abdominal diseases in childhood (12). CRP is a way to judge the effectiveness of therapy in inflammatory abdominal diagnoses.

AA /acute appendicitis /and AML/acute mesenterial lymphadenitis/ in children remain a difficult differential diagnosis. The diagnostic role of some inflammatory variables depends on their etiology and pathogenesis (12, 13). OA arises from an initial luminal obstruction of the appendix and leads to local edema as a result of impaired blood and lymph flow. Soon, the bacterial barrier function of the appendicular epithelium fails and bacterial invasion of the submucosal layers occurs (13). The presence of bacteria leads to the activation of the immune defense and local infiltration by T cells and monocytes. Interleukins and chemokines are released. Cytokines are biologically active substances of polypeptides and glycoproteins with a molecular weight of 8–30 kDa, which participate in cellular immunity in response to a specific inflammatory process. It has been suggested that the serum cytokine response of an OA patient is different from that of an AML patient (14).

Assessment of inflammatory markers is important for predicting severe bacterial infection in children without clinically established focal infectious foci at hospitalization (15). Information from laboratory parameters is particularly useful in determining disease severity. Additional inflammatory markers recommended in the diagnosis of complicated appendicitis in childhood are ESR, C-reactive protein, IL-6, IL-8, TNF-α, ferritin, and procalcitonin (PCT) (16). Early symptoms are non-specific, the combined use of biomarkers is recommended for rapid diagnostic assessment, monitoring of the therapeutic efficacy and improvement of specificity and sensitivity. Elevated levels of IL-6 are more likely to develop complications (pneumonia, multiple organ failure), and on the other hand, decreasing levels are a good indicator of therapeutic efficacy of the antibiotic treatment administered and have positive prognostic value in infectious origin of abdominal pain. Repeated assessment of markers with different half-lives helps to confirm the diagnosis and is suitable for monitoring disease progression. In the longer term, it helps to judge the duration of antimicrobial therapy.

PCT is more likely to help distinguish between viral and bacterial pathologic processes but has limited value in determining the septic process in children compared with adults (17).

Procalcitonin. Numerous studies have been published evaluating the efficacy of PCT concentrations in the diagnosis of acute abdominal pain. It is a peptide undetectable in healthy people. Wanner et al (17, 18) published the largest study (n=405) showing that peak PCT concentrations occur early in patients diagnosed with appendicitis and those with multiorgan dysfunction syndrome (MODS). Among 17

studies evaluating the prognostic value of PCT concentrations in terms of clinical outcome, 12 studies gave positive results and five showed negative or equivocal results. Reith et al. (18) published the largest study of the prognostic use of PCT concentrations (n=246) showing that mean PCT values on postoperative days one, four, and ten were predictive of mortality in patients with acute abdomen and abdominal sepsis ($p<0.01$). Of 14 studies of the utility of PCT concentrations in establishing an infectious cause, 13 were positive and only one was negative. The largest study using PCT concentrations, conducted by Baykut et al. (n=400), evaluated these concentrations in surgical patients with infection and showed that they remained elevated until the fourth postoperative day, with the second elevation occurring between the fourth and sixth postoperative days. In particular, Jensen et al. (n=1200) compared a PCT-directed antibiotic administration strategy with standard of care for sepsis and found no difference in outcomes (50, 51). They found that the PCT group had a longer mean ICU stay, a higher rate of mechanical ventilation, and a reduced estimated glomerular filtration rate in the complicated forms (250, 254). The largest such study by Bouadma et al. (19) (n=621), demonstrated a 4-day reduction in antibiotic duration when PCT concentrations were used to guide therapy relative to the study group given standard of care, with no increase in mortality ($p=0.003$). A PCT above 0.5 ng/ml is seen in cases of perforated or necrotizing appendicitis more than in uncomplicated appendicitis. The sensitivity (46%), specificity (90%) and predictive value of CRP indicate that procalcitonin is a better indicator of severe appendicitis (perforation or peritonitis). An elevated level of PCT alone may help as an adjunct to available clinical laboratory data (68, 93). In children, only the combination of all diagnostic parameters leads to a high diagnostic value.

FERRITIN Ferritin is a protein with an iron storage function that can be abnormally elevated in a wide range of disease states, including malignancy, infection, inflammation, chronic and liver disease. Because of this, a link is made between high ferritin levels and surgical disease, although the expected diagnostic relationship between elevated ferritin levels in determining the specific diagnosis can be challenging. The presentation of these diseases can be easily confused with other conditions such as sepsis with multiple organ failure or malignancies.

It is likely that serum ferritin increases mainly when cells are stressed and damaged (18, 19). This is because serum ferritin levels can increase significantly in response to inflammation and/or various diseases. Serum ferritin appears to be derived from the damaged cells but has iron in it, so it has actually lost or been stripped of most of its normal content. CRP and ferritin levels can be easily integrated into daily clinical practice in children. They are commonly available biomarkers and have wide and varied applications in the clinical world of pediatrics. Based on the available scientific evidence, it is important that biomarkers cannot replace clinical decision making and evidence is complementary to clinical practice. This evidence is based on the literature review (17). CRP and ferritin levels cannot be used in isolation and are only appropriate in clinical situations. Given the diverse literature on elevated CRP and ferritin levels in pediatric practice and the availability of tests in standard clinical laboratories, they can be readily and easily integrated into daily routine (18, 19). Elevated CRP levels in fever may indicate infection, especially in patients with exacerbations of inflammatory bowel disease or pancreatitis, and also be monitored for response to disease treatment.

The combination of elevated CRP and ferritin levels may indicate a severe inflammatory process and impending morbidity. These markers in combination can guide treatment in sepsis and are particularly useful when monitored for signs of response. CRP and ferritin levels remain nonspecific without clinical correlation and other supporting laboratory findings (20). These markers of inflammation are desirable features for clinical decision-making in pediatric surgical emergencies, particularly with regard to the uncontrolled inflammatory response (20).

Cytokines are a large group of proteins, peptides and glycoproteins) control the "behavior" of other cells and themselves (Szczesny TJ, 2007). They are signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis (20). Interleukin-6 (IL-6), tumor necrosis factor α

(TNF-α), interferon-γ, transforming growth factor β (TGF β), interleukin-8 (IL-8) are stimulators of acute phase protein production. IL-6 production is induced by acute inflammatory reactions and is associated with infections and various tissue damage macrophages, B-T-lymphocytes. Necessary for the immune system, through special receptors, cytokines modulate the balance between the human and cell-mediated immune response. They regulate the growth and maturation of cell populations, suppress or enhance the action of other cytokines.

Classification

Interleukin (Interleukin) - cytokines that are produced by lymphocytes. The term means "means of communication". A large part of the interleukins in some rare diseases shows that a deficiency leads to autoimmune diseases or immune deficiency.

Lymphokines (Lymphokines) - are produced by lymphocytes and play a major role in protecting the body during neoplastic transformations.

Chemokines - cytokines mediating intercellular contacts. A functional classification divides them into three types (20).

Type 1 - increasing the immune response - TNF-α;
Type 2 - improve the antigenic immune response - IL-10;
Type 3 - cytokines with proinflammatory function Il-6, IL-12, TNF-α.

Tumor-necrotizing factor alpha –TNF-α. The central role is to synthesize transmembrane cytoplasmic and extracellular protein. It accumulates intracellularly and affects the virus-infected cell. It feedbacks to activate or slow the production of both TNF-α itself and biologically active cytokines (16).

Interleukin 6 (IL-6) is a glycosylated cytokine with a significant role in the acute phase of inflammation. IL-6 is significantly increased during surgery. Its soluble forms activate proteolytic enzymes and suppress the function of hepatocytes, monocytes and lymphocytes.

Interleukin-6 (IL-6) is reported to be one of the most easily measurable cytokines, and its levels found in the blood of patients with acute appendicitis are above 1500 pg/ml, which is consistent with previously reported values. On the other hand, cytokine-related genetic polymorphisms may influence cytokine production or influence their development in appendectomy. Therefore, the genetic aspect of cytokine biology should also be considered in future study (20).

The leukocyte infiltrate in acute inflammation consists of neutrophils, which predominate over monocytes. At certain levels, IL-6 has a protective mechanism, otherwise, it is a pro-inflammatory marker. Therefore, IL-6 is used as a marker in intensive care patients and as a prognostic factor for the outcome of these conditions (15). A decrease in IL-6 from the second day of antibiotic treatment is a marker of treatment effectiveness and is a positive prognostic sign in patients with an infectious etiology (19).

Interleukin-10 is secreted by activated hematopoietic liver cells. Its biological activity initiates a "signaling cascade" of interaction on lymphocytes, NK-cells, macrophages, monocytes, intestinal epithelial cells, astrocytes, etc. Its immunomodulatory effect includes:

- "positive effect", you support phagocytosis and antigen presentation
- “negative effect”, you influence Th1-helper lymphocytes that suppress the pro-inflammatory response

Cytokine profile helps prognostic assessment as well as changes after surgery. (17, 18). Elevated levels of TNF-α and IL-6 correlate with the occurrence of intussusception, and reduction of these levels by inhibition of cyclooxygenase (COX) by indomethacin prevents their formation. Diagnosing the acute abdominal diseases in childhood, as well as the mimicking masks of OHC, is not easy. The nature of the process makes diagnosis and treatment a real urgent task. Early recognition is the first step to reducing complications. Despite the availability of a wide range of laboratory, microbiological and imaging tests nowadays, surgical abdominal emergencies continue to be a cornerstone of surgical practice and reaching a clinical diagnosis is sometimes associated with significant difficulties. Due to the dynamic nature of diseases, evaluation and reevaluation of the results of physical examination and laboratory tests after

hospitalization are necessary not only for early diagnosis, but also for controlling the therapeutic process.

CONCLUSIONS

1. The frequency of diagnosis of emergency surgical diseases in children increases significantly with the confirmation in practice of highly informative laboratory, microbiological and imaging methods.
2. Etiopathogenic (specific) diagnosis remains difficult, which makes differential diagnosis especially important
3. The use of inflammatory markers and predictors of inflammation is determined independently and in combination from the presented literary sources and their method of use.
4. The concentration of the inflammation predictors used: cytokines, ferritin and procalcitonin, are related to the degree of disease manifestation and have high sensitivity and specificity for clinical assessment and differentiation of emergency diagnoses.
5. IL-6, IL-10, TNF-α, ferritin and procalcitonin individually and in combination are statistically proven to be more sensitive in the preoperative period.

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