American Journal of Emergency Medicine 34 (2016) 871–876

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Usefulness of new and traditional serum biomarkers in children with suspected appendicitis☆,☆☆,☆☆☆

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ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form 5 February 2016
Accepted 5 February 2016

ABSTRACT

Objective: The objective of the study is to evaluate the usefulness of the leukocyte (white blood count [WBC]) and neutrophil (absolute neutrophil count [ANC]) counts; the values of C-reactive protein (CRP), procalcitonin, and calprotectin (CP); and the *APPY*1 Test panel of biomarkers, to identify children with abdominal pain at low risk for appendicitis.

Method: Children 2 to 14 years of age with abdominal pain suggesting acute appendicitis (AA) were prospectively included. Procalcitonin, calprotectin, C-reactive protein, white blood count, ANC, and the new plasma *APPY*1 Test were performed. The final diagnosis was determined by histopathology in cases of AA and telephone follow-up in children discharged without AA.

Results: Between February 2012 and June 2013, 185 children were enrolled with an average age of 9.32 ± 2.7 years. Eighty-nine (48.1%) were finally diagnosed with AA. The *APPY*1 Test panel showed the highest discriminatory power, sensitivity of 97.8 (95% confidence interval [CI], 92.2-99.4), negative predictive value of 95.1 (95% CI, 83.9-98.7), negative likelihood ratio of 0.06 (95% CI, 0.01-0.22), and specificity of 40.6 (95% CI, 31.3-50.5). A negative *APPY*1 Test and ANC less than 7500 per milliliter provided a sensitivity of 100 (95% CI, 95.9-100), negative predictive value of 100 (95% CI, 89.8-100), and specificity of 35.4 (95% CI, 26.6-45.4). In the multivariate analysis, only the *APPY*1 Test and ANC greater than 7500 per milliliter were significant risk factors for AA (odds ratio, 13.76; 95% CI, 3.02-62.57, and odds ratio, 6.37; 95% CI, 2.89-14.28, respectively).

Conclusions: The *APPY*1 Test panel with ANC could be useful in identifying children with abdominal pain suggestive of AA who are at low risk for this disease.

1. Introduction

Acute appendicitis (AA) in children is the primary cause of urgent surgery in pediatric patients. Diagnosis of AA continues to be a challenge, especially in the youngest children, who often present with abdominal pain accompanied by nonspecific signs such as vomiting, lethargy, and irritability.

Acute appendicitis is a progressive disease; in the early stages, there is greater probability that complementary tests available to physicians will be inconclusive. Physicians often face a clinical dilemma on the timing of surgical intervention. Assuming a margin of diagnostic uncertainty, emergency surgery early in the progression of the disease increases the proportion of negative appendectomies (5%-40%). Conversely, postponing surgery until the disease progression leads to further developed clinical signs increases the proportion of perforated appendicitis with peritonitis (5%-30%), which comes with a significant increase in morbidity and mortality [1–3].

Today, imaging techniques constitute the basis of diagnosis in most cases, especially abdominal ultrasound as it is innocuous to the patient. Nonetheless, that technology is not always available, and its performance depends on the experience of the professional using it, which results in sensitivity as low as 80% for some operators [4–6]. Abdominal computed tomographic (CT) scans improve the diagnostic precision but at the expense of exposure to significant ionizing radiation with the resulting consequences that can be assumed in a child; thus, the

☆ Funding source: No external funding was secured for this study.
☆☆ Financial disclosure: The authors have no financial relationships relevant to this article to disclose.
☆☆☆ Conflict of interest: The authors have no conflicts of interest to disclose.
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http://dx.doi.org/10.1016/j.ajem.2016.02.011
0735-6757/

Table 1
Characteristics of the groups

Variables	Appendicitis, n (%)	No appendicitis, n (%)	*P*
	n = 89 (48.1)	n = 96 (51.9)	
Sex			
Males	67 (75.3)	56 (58.3)	.015
Age (y), mean (SD)	9.6 (2.4)	9.17 (2.9)	NS
Weight (kg), mean (SD)	37.5 (13.5)	37.1 (15.1)	NS
Pain duration (h)			
<6	10 (11.4)	15 (15.8)	
6-12	28 (31.8)	15 (15.8)	
12-24	34 (38.6)	29 (30.5)	.01
24-48	10 (11.4)	10 (10.5)	
>48	6 (6.8)	26 (27.4)	
Associated symptoms			
Vomiting	59 (66.3)	38 (39.6)	<.001
Diarrhea	8 (9)	10 (10.4)	NS
Temperature (at home)			
Afebrile	64 (71.9)	67 (69.8)	
37-37.9	17 (19.1)	9 (9.4)	.042
38-38.9	6 (6.7)	11 (11.5)	
>39	2 (2.2)	9 (9.4)	
Pain			
Pain scale, mean (SD)	5,6 (2.1)	5,2 (1.9)	NS
Physical examination			
Distended abdomen	4 (4.5)	0 (0)	.036
Pain on deep palpation	74 (83.1)	75 (78.1)	NS
Psoas positive	31 (34.8)	30 (31.2)	NS
Jump positive	20 (22,4)	19 (19.8)	NS
Blumberg positive	47 (52.8)	30 (31.2)	.025
Peritoneal irritation (psoas/jump/Blumberg positive)	67 (75.2)	48 (50)	.02
Temperature at ED			
Afebrile	52 (58.4)	66 (69.5)	
37-37.9	32 (36)	20 (21.1)	NS
38-38.9	5 (5.6)	6 (6.3)	
>39	0	3 (3.2)	

Abbreviation: NS, not significant.

reduction of its use without a loss of diagnostic efficacy is currently a priority [7–10]. Magnetic resonance image (MRI) may also be used for the diagnosis of appendicitis, with the advantage that it does not entail the radiation exposure, but this study is not usually available in the emergency department (ED) [9].

Besides the clinical signs and imaging, biomarkers have proven in recent years to be a viable diagnostic resource both to support [11–15] and aid in establishing a prognosis of the disease [16].

Various markers have recently been proposed in the scientific literature that are products of the inflammatory reactions as possible markers of AA (procalcitonin [PCT], interleukin 6, interleukin 8, haptoglobin, granulocyte colony-stimulating factor, lactoferrin, calprotectin [CP], etc) [17]. One recent study identified a panel of biomarkers (the *APPY*1 Test) that has the potential to identify, with great accuracy, children with abdominal pain who are at low risk for AA [18].

The primary objective of this study was to determine the diagnostic accuracy of various biomarkers alone and in combination with the purpose of identifying children suspected of having AA who were at low risk for the disease. As a secondary objective, an investigation was performed on clinical and radiologic variables related to the diagnosis of AA and the possible reduction of complimentary tests and hospital stays in those patients with a negative biomarker result.

2. Patients and methods

A prospective study was conducted on cohorts in the pediatric ED of a tertiary hospital with approximately 54 000 annual visits. Informed consent was obtained in writing from the legal guardians of all of the participants and from children 12 years and older. In children 6 years and older, consent was obtained by assent. The study was approved by the local ethics committee (Ethical Committee (EC) of the Basque Country).

A sample of patients aged between 2 and 14 years who visited the ED between February 2012 and June 2013 with abdominal pain suggestive of AA after the evaluation by the attending physician were included. The size and selection of the sample were subject to the presence of the investigators participating in the study. Abdominal ultrasound and basic blood analysis were performed, including white blood cell count (WBC), absolute number of neutrophils (absolute neutrophil count [ANC]), and C-reactive protein (CRP). In addition, the levels of serum PCT and CP as well as the test result of the plasma-based *APPY*1 Test, a biomarker panel that includes a mathematical combination of 3 biomarkers (WBC, CRP, and CP), were determined. The results of PCT, CP, and *APPY*1 were not available to the treating clinicians.

After reviewing the results of the abdominal ultrasound and basic analysis, the attending physician and the pediatric surgeon opted, depending on the degree of the suspicion of AA, for surgical intervention, conducting other tests, hospital observation, or discharging the patient. The diagnosis of AA was based fundamentally on the clinical findings (localized pain in the right iliac and/or the presence of signs of peritoneal irritation) and ultrasound findings. Ultrasound findings were considered to be suggestive of AA if there was an appendicular diameter of greater than 6 mm, the presence of inflammatory changes in the periappendicular tissues, free liquid in the peritoneal cavity, and/or the existence of appendicoliths was observed.

Patients with any of the following conditions were excluded: symptoms lasting more than 5 days, patients who refused to sign the informed consent, children with prior appendectomy, patients with urinary tract infection, oncology patients, patients with inflammatory intestinal disease, and patients undergoing treatment with systemic corticoids.

Demographic data and family histories were collected from patients as well as data on the medical history, a physical examination, and results from the complementary tests performed. All of these data were obtained from the hospital's computer system where they were recorded and later entered by one of the investigators into a database for subsequent analysis. The recruitment was carried out 24 hours a day, 7 days a week. Patient recruitment was performed by the attending physician who was trained on the study protocol.

The presence of AA was determined by the histopathologic analysis of the specimen when surgery was performed. For patients who were discharged without a diagnosis of AA, a telephone follow-up was performed 15 days after the emergency consultation. In cases in which the family could not be contacted, a search was performed through the hospital's computer system and the electronic registries data from the Basque Health System to determine whether the patient returned to the hospital during the monitoring period.

Table 2
Characteristics of ultrasound

Variables	Appendicitis, n (%)	No appendicitis, n (%)	*P*
Ultrasound	n = 89 (48.1)	n = 95[a] (51.9)	
Appendix visible	84 (95.5)	76 (80)	.03
Dimension (mm)			
<6	15 (19.8)	73 (96.1)	
7-8	38 (45.2)	2 (2.6)	<.001
>8	31 (36.9)	1 (1.3)	
Appendicolith	27 (31)	0	<.001
Changes in periappendicial fat	67 (75.2)	1 (1.0)	<.001
Free fluid			
Minimal	32 (36)	25 (26.3)	<.001
Moderate	10 (11.2)	2 (2.1)	
Final report			
Confirmatory for AA	85 (95.5)	1 (1.1)	
Negative for AA	0	80 (84.2)	<.001
Inconclusive	4 (4.5)	14 (14.7)	

[a] One patient did not receive an ultrasound.