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Original Article

Hyponatremia as a Biochemical Marker of Complicated Acute Appendicitis: A Retrospective Cohort Study

Adel Ahmed Alfayez[1], Jamal Al-Hudhaif[1], Abdullah M. Zahi[1], Nawaf Mushabab Al-Hassan[2], Saad Ahmed Aldohaim[2], Mohammed Ali Hejji[2], Osama Khalid Al-Harbi[2], Nawaf Abdullah Alsaadi[2]

[1]Prince Sultan Military Medical City, Department of Pediatric Surgery, Riyadh, Saudi Arabia
[2]King Saud Medical City, College of Medicine, Riyadh, Saudi Arabia

ABSTRACT

Aim: Acute appendicitis is a frequent surgical emergency which affects the lower right quadrant of the abdomen. Failure to diagnose this condition might result in perforation, abscess development, or peritonitis if not tackled. Hyponatremia was the focus of our retrospective cohort investigation because it may serve as a biochemical indicator for spotting serious forms of acute appendicitis in our patient group.

Materials and Methods: All pediatric patients aged up to 14 years who were admitted to the Prince Sultan Military Medical City, under our service between 2020 and 2023 were retrospectively reviewed. Data of interest were retrieved from the medical files of our study subjects and entered into Excel sheets, including medical history, age, sex, type of referral, and associated comorbidities, as well as clinical data such as abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent histories of upper respiratory tract infection.

Results: Thirty-one (19%) patients were found to have a complicated acute appendicitis, confirmed by the presence of gross or micro-perforation and segmental gangrenous segment on histopathological analysis. Statistically significant differences were observed in those patients with the complicated form, compared to others with the non-complicated form of acute appendicitis in terms of preoperative sodium levels, along with intra-operative findings of perforated appendices. Compared to the non-complicated patients, those with complicated acute appendicitis had a much lower mean blood sodium level.

Conclusion: This study suggests the use of hyponatremia as a potential biomarker for complicated cases. Early diagnosis and appropriate response can assist medical and surgical practitioners in providing more focused and effective management plans for complicated cases, which would improve patient outcomes.

Keywords: Acute appendicitis, pediatrics, hyponatremia, biomarkers, and sodium level

Introduction

When blood salt levels drop too low, a condition known as hyponatremia develops. Excessive perspiration, nausea, vomiting, diarrhea, and the side effects of several drugs are among the potential causes of this disease (1). Common surgical emergencies affecting the lower right quadrant of the abdomen include acute appendicitis, characterized by pain, nausea, and vomiting. Standard methods for

Address for Correspondence
Jamal Al-Hudhaif, Prince Sultan Military Medical City, Department of Pediatric Surgery, Riyadh, Saudi Arabia
Phone: +966505440091 **E-mail:** hudhaif@gmail.com **ORCID:** orcid.org/0009-0002-1551-4955
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diagnosing acute appendicitis include clinical examination, imaging techniques, and the presence of inflammatory markers, such as C-reactive protein, neutrophil shift, and white blood cell (WBC) count. If untreated, complicated acute appendicitis (CAA) may progress to perforation, abscess development, or peritonitis. The fact that the symptoms of this condition might overlap with those of non-CAA (NCAA) and cause unusual presentations makes diagnosis difficult (2). Recent research suggests that hyponatremia may also be a sign of CAA (2).

An important area of study is the development of an accurate and practical molecular marker for early identification of CAA. Adults with complex appendicitis may show signs of hyponatremia, as reported by Sheen et al. (3). Conversely, hyponatremia was investigated in a meta-analysis by Anand et al. (4) for its possible use as a diagnostic indicator of CAA in children. Hyponatremia and CAA were shown to be significantly correlated in a prospective evaluation of diagnostic accuracy (5). Shuaib et al. (6) studied hyperbilirubinemia, hyponatremia, and their combined use in diagnosing CAA prior to surgery. Taken together, these studies suggest that hyponatremia may be a useful diagnostic indicator, particularly in those patients with CAA.

This retrospective cohort study aimed to examine the correlation between CAA and hyponatremia. We aimed to thoroughly examine the medical records of eligible patients in order to determine whether hyponatremia could be a valuable addition to the existing diagnostic criteria for predicting CAA prior to surgery. By incorporating blood sodium levels as dependable indicators, their integration into diagnostic algorithms has the potential to improve accuracy, shorten the time required for surgical intervention, assist clinicians in anticipating surgical complexities, and enhance patient outcomes.

Materials and Methods

The objective of our study was to examine and either corroborate or challenge the findings of previous studies on this subject. One of our primary goals was to determine whether hyponatremia could be used as a biochemical marker to identify complicated forms of acute appendicitis in our group of patients.

Study Design

All pediatric patients aged up to 14 years who were admitted to the Prince Sultan Military Medical City under our service between 2020 and 2023 were retrospectively reviewed. Patients aged <14 years who had a clinical versus radiological picture of acute appendicitis and underwent appendectomy (open or laparoscopic) met the inclusion criteria (n=162). Patients older than 14 years of age, those with chronic metabolic or endocrine problems, and those who underwent incidental appendectomy were excluded (n=0).

Informed consent not applicable in this study as such study is not requiring patients consent, instead The Prince Sultan Military Medical City (Ethical Board Committee) accepted our study (IRB approval no.: E-2130).

Data Collection

The data of interest were retrieved from the medical files of our study subjects and entered into Excel sheets, including their medical history, age, sex, type of referral, and associated comorbidities, as well as clinical data such as abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent history of upper respiratory tract infection (URTI). Laboratory data included WBC count, absolute neutrophil count, creatinine, blood urea nitrogen (BUN), and glucose. The electrolytes used included sodium (Na), potassium (K), and chloride. Radiological investigations included the modality and findings. Intra-operative data covered any findings and/or complications.

Definitions

NCAA is evident on histopathological examination, with features of inflammation alone.

CAA is evident on histopathological examination, with necrotic segments in a completely gangrenous or perforated appendix.

Laboratory Findings

Hyponatremia was defined as blood serum concentration ≤135 mmol/L; leukocytosis as a WBC count >12-16×10^9 (depending on the reference ranges based on the patient's age); neutrophilia as an absolute neutrophil count >7×10^9 and creatinine, BUN, glucose, potassium, and chloride, all of which were within their normal ranges. All laboratory investigations were performed when the patients presented to the emergency department before medical management was initiated.

Statistical Analysis

Microsoft Excel 2010 was used for data collection, storage, and management. We used SPSS® version 21.0 (IBM Inc., Chicago, Illinois, USA) to analyze the data and create the figures. The results of the descriptive analysis

are presented as percentages and figures for the categorical variables. We used the Shapiro-Wilk test and Q-Q plots to check whether the continuous variables were normal. The median (interquartile range) with box-and-whisker plots was used to display the data which were not normally distributed. Therefore, for continuous variables, the Mann-Whitney U test was used to compare the groups with and without perforated appendicitis. Odds ratios (OR) were obtained by comparing the proportions of categorical variables across groups using the chi-square test. The results were considered statistically significant if the p value was <0.05.

Results

A total of n=162 patients were analyzed, along with their socio-demographic data, associated comorbidities (Tables I, II) and with their type of referral (Figure 1). From a total number of 162 patients, 31 (19%) were found to have a CAA confirmed by the presence of gross or micro-perforation and segmental gangrenous segments on histopathological analysis.

Clinical data were analyzed between both groups, CAA versus NCAA, including abdominal pain, nausea/vomiting, anorexia, fever, changes in bowel movement, dysuria, and any recent history of URTI (Table III). A 5% level of significance was observed for nausea, vomiting, and fever (p=0.029 and 0.036 respectively).

Table I. Socio-demographic characteristics

Characteristic	Group I complicated acute appendicitis (n=31)	Group II non-complicated acute appendicitis (n=131)	p value
Age in years, median (IQR)	11 (9-13)	10 (8-12)	0.266
Age group			
2-5, n (%)	4 (12.9)	9 (6.9)	0.271
6-8, n (%)	3 (9.7)	31 (23.7)	0.086
9-14, n (%)	24 (77.4)	91 (69.5)	0.385
Gender, n (%)			
Male	18 (58.1)	73 (55.7)	0.813
Female	13 (41.9)	58 (44.3)	
Length of stay in days, median (IQR)	4 (3-6)	1 (1-2)	<0.001*

*Statistically significant at the 5% level of significance
IQR: Interquartile range

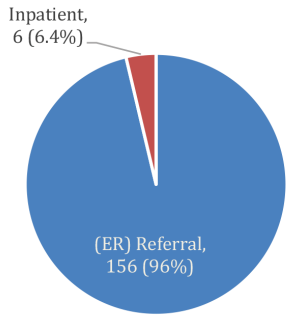

Figure 1. Type of referrals

Table II. Associated comorbidities

Associated comorbidities	ALL	Group I complicated acute appendicitis (n=31)	Group II non-complicated acute appendicitis (n=131)
Asthma	7	2	5
Obesity	2	0	2
Allergic to nuts	2	1	1
Celiac disease	1	0	1
Autism	1	0	1
Esophageal stricture causing GERD*	1	0	1
Gastroenteritis	1	0	1
Cow milk allergy	1	0	1
Iron deficiency anemia	1	0	1
ADHD* not on meds, urethral stenosis	1	0	1
Adrenal insufficiency**	1	0	1
Anxiety disorder	1	0	1
Central precious puberty	1	0	1
Epilepsy, GDD*, chromosome 16p 11 microdeletion syndromes	1	1	0
Known to have chronic constipation	1	0	1
Large PDA* (post catheter closure), not on meds	1	0	1
Sickle cell anemia, nephrocalcinosis, dental caries	1	0	1

*GERD: Gastroesophageal reflux disease
**Patient was compliant to treatment, and had not been admitted to hospital with electrolyte disturbances for long time (therefore this patient was not excluded) ADHD: Attention deficit hyperactivity disorder, GDD: Global developmental delay, PDA: Patent ductus arteriosus

Statistically significant differences were observed in those patients with CAA, compared to the others (NCAA) in terms of their preoperative sodium levels, along with intra-operative findings of perforated appendicitis. A statistically significant difference between CAA, and NCAA was found with regard to the laboratory investigations, namely sodium levels with a p value of 0.011 which is below the 5% level of significance (Table IV). Other laboratory investigations showed differences as well, including: WBC pre-Op 16 10^9/L vs. 13.5 10^9/L, p value of 0.009, and neutrophil absolute count pre-op 14.3 10^9/L vs. 10 10^9/L, p value of 0.009. Interestingly, substantially reduced mean serum sodium levels were observed in CAA, compared to NCAA when comparing the two groups with the presence of hyponatremia (Tables V, VI) (Figure 2**)** with a p value of 0.001, OR 4.60, and 95% confidence interval of 1.83-11.55.

Regarding radiological investigations, ultrasound (US) was diagnostic in 60.5%, and not in 33.3%, while computed tomography (CT) was diagnostic in 17.9%, and ruled out in 27.2%. It is important to mention here that, in our practice, it is unusual to apply CT except in cases of borderline presentation, along with physician suspicion of either ruling in or ruling out the diagnosis of acute appendicitis. Moreover, radiological diagnoses of NCAA were 82%, and of CAA, it was (10.5%). Other cases that did not undergo imaging investigations, either clinically diagnosed or US could not visualize the appendix, which is why they were subtracted from the percentage group (10 cases were not performed, while two cases were not performed, but were not diagnostic) (Table VII). Table VIII demonstrates the intra-operative findings, along with any complications.

Table III. Clinical presentations in both groups (complicated acute appendicitis) versus (non-complicated acute appendicitis)

Symptom	Group I complicated acute appendicitis (n=31) n (%)	Group II non-complicated acute appendicitis (n=131) n (%)	p value
Abdominal pain (n=162)	31 (100)	131 (100)	0.998
Nausea/Vomiting (n=144)	31 (100)	113 (86.3)	0.029*
Anorexia (n=141)	30 (96.8)	111 (84.7)	0.072
Fever (n=62)	17 (54.8)	45 (34.4)	0.036*
Constipation (n=21)	7 (22.6)	14 (10.4)	0.068
Diarrhea (n=29)	6 (19.4)	23 (17.6)	0.815
Dysuria (n=7)	3 (9.7)	4 (3.1)	0.107
History of recent (URTI)** (n=20)	5 (16.1)	15 (11.5)	0.486
Incidental finding (n=1)***	0 (0.0)	1 (0.8)	0.918

*Statistically significant at the 5% level of significance
**Upper Respiratory Tract Infections (URTI)
***The reason for the other diagnostic workup (n=1): Enlarged right kidney with grade 4 hydronephrosis and features of PUJ obstruction. Left grade 1 hydronephrosis

Table IV. Laboratory values

	Group I complicated acute appendicitis (n=31) median (IQR)	Group II non-complicated acute appendicitis (n=131) median (IQR)	p value
Na level pre-op (normal 135-145 mmol/L)	137 (133-138)	137 (136-139)	0.011*
Na level post op (n=3)	135 (135-135)	139.5	0.221
WBC pre-op (normal 4.00-11.00 *10^9/L)	16 (12.8-20)	13.5 (9.3-16.9)	0.009*
WBC post-op (n=3)	8.4 (8.4-8.4)	7.2	0.221
Neutrophils absolute count pre-op (normal 2.8-6.30 10^9/L)	14.3 (9.2-16.9)	10 (6.5-13.5)	0.009*
Neutrophils post-op (n=3)	2.4 (2.4-2.4)	5.6	0.221
Chloride level at presentation (normal 95-110 mmol/L)	98.5 (96.8-102)	101 (100-103)	0.003*
Potassium level at presentation (normal 3.5-5.1 mmol/L)	4 (3.8-4.3)	4 (3.8-4.2)	0.416

Table IV. Continued

	Group I complicated acute appendicitis (n=31) median (IQR)	Group II non-complicated acute appendicitis (n=131) median (IQR)	p value
Creatinine level at presentation (normal 39-60 mcmol/L)	45 (32-50)	40 (35-46)	0.568
BUN level at presentation (normal 1.8-6.4 mmol/L)	3.4 (2.7-3.9)	3.6 (2.9-4.2)	0.267
The glucose level at presentation (3.3-5.6 mmol/L)	6.3 (4.8-7.2)	5.6 (5-6.4)	0.286

*Statistically significant at a 5% level of significance the medians are equal but with different distributions (the means are 135.5 and 137.5)
IQR: Interquartile range, WBC: White blood cell, BUN: Blood urea nitrogen

Table V. Sodium level correlation with the severity of acute appendicitis

	Na level pre-op median (IQR)	p value
Group I complicated acute appendicitis (n=31)	137 (133-138)	0.011*
Group II non-complicated acute appendicitis (n=131)	137 (136-139)	

*Statistically significant at the 5% level of significance
IQR: Interquartile range

Table VI. Hyponatremia correlation with the severity of acute appendicitis

	Hyponatremia				
	Yes (n=25) n (%)	No (n=137) n (%)	p value	OR	[95% CI]
Group I complicated acute appendicitis (n=31)	11 (35.5)	20 (64.5)	0.001*	4.60	[1.83-11.55]
Group II non-complicated acute appendicitis (n=131)	14 (10.7)	117 (89.3)			

*Statistically significant at the 5% level of significance
OR: Odds ratio, CI: Confidence interval

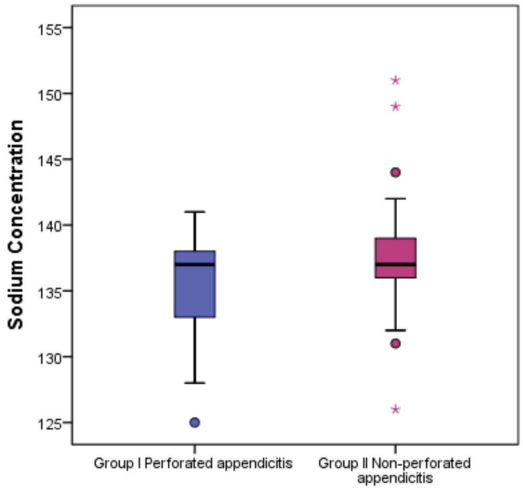

Figure 2. Box and Whisker Plot Diagram, Representing Sodium Concentration by Grouping of Acute Appendicitis

Table VII. Radiological diagnostic modalities

	n (%)
US	
Performed and diagnostic	98 (60.5)
Performed but non-diagnostic	54 (33.3)
Not performed	10 (6.2)
CT	
Performed and diagnostic	29 (17.9)
Performed but non-diagnostic	44 (27.2)
Not performed	89 (54.9)
Non-complicated acute appendicitis (radiologically)*	133 (82.1)
Complicated acute appendicitis (radiologically)*	17 (10.5)

*Diagnostic radiological findings (n=150); other patients were either clinically diagnosed or the US could not visualize the appendix and diagnosis was based on our clinical findings (n=12)
US: Ultrasound, CT: Computed tomography

Table VIII. Intra-operative findings+complications	
n (stand for number)	**n (%)**
Non-perforated	134 (82.7)
Perforated	28 (17.3)
Appendiceal mass	4 (2.5)
Adjacent bowel injury	0 (0.0)
Bleeding	3 (1.9)

Discussion

Patients diagnosed with CAA throughout the study period were the focus of this study. Individuals with low serum sodium levels were the primary focus of this study. Urgent medical attention is required in cases of acute appendicitis, the leading cause of abdominal pain (7). There is a peak occurrence between the ages of 10 and 30, and the lifetime chance of suffering acute appendicitis is 7% according to studies (8,9). Recent studies have shown that complex appendicitis is associated with low blood-salt levels. Nevertheless, it is still not known what causes hyponatremia in people with CAA (3,4,10).

Acute appendicitis is a common surgical emergency associated with several complications if left untreated. According to recent research examining this possibility, hyponatremia may serve as a diagnostic indicator of CAA, according to recent research which has looked at this possibility (11). Patients with preoperative hyponatremia have an increased risk of CAA (12). Additionally, another study showed that individuals with CAA had lower blood sodium levels (13). Therefore, monitoring sodium levels can help determine the probability of complications in those individuals with acute appendicitis. It is vital to remember that hyponatremia can also result from several other illnesses such as primary bacterial peritonitis (14). In order to choose the best course of action, it is necessary to determine the underlying cause of the low serum sodium levels. The diagnosis of acute appendicitis using CT scan was shown to have a sensitivity of 98.6% and a specificity of 3.4%, while US had a sensitivity of 70.5% and a specificity of 36.8% (15).

A review of the literature revealed strong evidence linking blood sodium levels to the development of CAA (1). Hyponatremia may be worsened by additional risk factors in adulthood, such as certain medications and comorbidities, which can increase the effect of complex appendicitis on blood sodium levels (16). Hyponatremia in appendicitis has no recognized etiology; however, interleukin-6 has been suggested to play a role (17). An extensive literature review revealed that most studies examining the link between hyponatremia and intricate appendicitis have concentrated on adults or children, implying that this specific occurrence has not been thoroughly investigated in previous studies (18,19). Our investigation revealed that those individuals with histologically proven CAA were more likely to have hyponatremia, with a cut-off value of 135 meq/L. Another study found a clear link between the two (2).

Our study may help evaluate the risks of delaying surgical intervention, recognizing the burden of CAA, and using hyponatremia as a diagnostic indicator for complex situations in children. Acute appendicitis is a common and challenging condition to manage owing to its complicated nature. Identifying more markers to help in diagnosis would be advantageous because a more complicated condition may significantly harm the patient.

Study Limitations

It is important to acknowledge the limitations of this study, such as its retrospective design, which depended on pre-existing medical information, and its small sample size. Further prospective, well-designed studies are required in order to evaluate and enhance the accuracy of hyponatremia in predicting CAA.

Conclusion

The findings of the current study add to what is already known regarding the identification and treatment of acute appendicitis. According to this study, hyponatremia may be a useful physiological biochemical indicator of CAA. These findings are in line with a recent systematic review which examined the same issue; thus, it seems that this topic deserves further research. In addition, a correlation between hyponatremia and CAA was shown in this study. Medical and surgical professionals may help improve patient outcomes in CAA by identifying hyponatremia early and responding appropriately, leading to more focused and successful treatment approaches.

Ethics

Ethics Committee Approval: Ethical permission was obtained from The Prince Sultan Military Medical City (Ethical Board Committee) accepted our study (IRB approval no.: E-2130).

Informed Consent: Informed consent not applicable in this study as such study is not requiring patients consent.

Authorship Contributions

Surgical and Medical Practices: A.A.A., J.A.-H., A.M.Z., Concept: A.A.A., J.A.-H., Design: A.A.A., J.A.-H., Data

Collection and/or Processing: A.A.A., A.M.Z., N.M.A.-H., S.A.A., M.A.H., O.K.A.-H., N.A.A., Literature Search: A.A.A., J.A.-H., A.M.Z., N.M.A.-H., S.A.A., M.A.H., O.K.A.-H., N.A.A., Writing: A.A.A., J.A.-H., A.M.Z.

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