Comparison of Clinical Characteristics According to the Existence of Secondary appendicitis in Pediatric Acute Gastroenteritis: A Retrospective Single Center study

Soyoon Choi (✉ dimplech@naver.com)

Research article

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Abstract

Background

In patients with acute gastroenteritis, radiologic findings are sometimes accompanied by secondary inflammation of the appendix. The purpose of this study was to evaluate the clinical features of acute gastroenteritis with secondary inflammation of the appendix.

Methods

Medical records from patients who underwent abdominal ultrasonography or computed tomography among those admitted for acute gastroenteritis at Haeundae Paik Hospital from June 2017 to May 2019 were retrospectively reviewed. Clinical features were compared by distinguishing patients with inflammation of the appendix from those without, based on their symptoms and laboratory findings.

Results

Of the 165 patients, 12 (7.3%) had secondary inflammation of the appendix on ultrasonography and/or computed tomography. Patients with secondary inflammation of the appendix were significantly older than those without (11.7 vs 6.1 years, $p = 0.011$) and more frequently had fever (83.3% vs 49.0%, $p = 0.033$), and high values of C-reactive protein (5.38 vs 0.32 mg/dl, $p < 0.001$). The proportion of viral pathogens was higher in patients without secondary appendicitis (0% vs 40.7%, $p = 0.012$), and the proportion of bacterial pathogens was higher in patients with secondary inflammation of the appendix (60% vs 15.1%, $p = 0.004$).

Conclusions

Patients with acute gastroenteritis accompanied by secondary appendicitis more commonly have fever, higher C-reactive protein levels, higher bacterial pathogen detection rates, and longer hospital stays. Treatment equivalent to that of bacterial infection is required for patients with secondary appendicitis, and that their symptoms should be closely and continuously monitored and followed-up.

Background

Acute gastroenteritis, a disease characterized by inflammation of the small colon and colon, is commonly encountered in pediatrics. Most cases are diagnosed through history assessment and physical examination without special testing needed. Most patients improve with symptomatic treatment, including fluid resuscitation and supplemental nutrition. However, when a patient shows severe or prolonged clinical symptoms, the site of pain is the right lower quadrant, or if there are signs of peritoneal irritation, the condition must be differentiated from others that may show similar clinical symptoms,

particularly acute appendicitis, mesenteric lymphadenitis, appendiceal diverticulitis, and chronic inflammatory bowel disease; this is done using radiologic testing.⁽¹⁾ Radiologic tests (abdominal computed tomography [CT] or abdominal ultrasound [US]) sometimes reveal secondary appendicitis in addition to inflammation in the small and large intestines. Secondary appendicitis refers to inflammation of the appendix resulting from lesions in colonic or periappendiceal sites.

Although acute gastroenteritis is relatively common in children, the clinical features and prognosis of acute gastroenteritis according to the presence of secondary appendicitis have rarely been studied or reported.^(2, 3) Whether the two disease entities should be classified into a single category or should be considered independent categories with distinct treatment approaches remains controversial. Therefore, in the present study, we compared the clinical features and courses of acute gastroenteritis according to the presence of secondary appendicitis.

Methods

Patients and Study Design

Medical records of pediatric patients aged 18 years or younger who received inpatient treatment for acute gastroenteritis at the Inje University Haeundae Paik Hospital between June 2017 and June 2019 were retrospectively analyzed.

Among the patients presenting with inflamed small and large intestines upon radiologic testing (abdominal US or abdominal CT), those with normal appendices were classified as the control group, and those with inflamed appendices were classified as the study group. We recorded the following patient information: sex, age at diagnosis, blood tests (white blood cell [WBC], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], albumin, hemoglobin, amylase, lipase, aspartate aminotransferase [AST], and alanine aminotransferase [ALT]), stool tests (using stool polymerase chain reaction [PCR]), length of hospital stay, duration of nil per oral (NPO) status, use of antibiotics, complications (e.g., acute kidney injury and hemolytic uremic syndrome), and surgery.

The sensitivity and specificity of appendicitis diagnosis were 100% and 68%, respectively, using a maximal outer diameter (MOD) cutoff of 6 mm and 94% and 88%, respectively, using a cutoff value of 7 mm.⁽⁴⁾ The MOD of the appendix was measured in the transverse plane, where the distance from one outer wall to the opposite outer wall of 6 mm or less was considered normal, and a MOD of 7 mm or higher was considered appendicitis. When the MOD was between 6 mm and 7 mm, color Doppler imaging was performed, and appendicitis was diagnosed based on findings indicating hyperemia.⁽⁵⁾ We also measured bowel wall thickness: a thickness of 2 mm or higher was considered thickening. Appendiceal wall thickness was defined as the distance from the inner mucosal layer to the serosal layer, where a distance of 3 mm or higher considered appendicitis.^(6, 7)

Stool samples were tested for five viruses (group A rotavirus, enteric adenovirus, norovirus GI/GII, and astrovirus) and ten bacteria (*Salmonella* spp., *Shigella* spp., *Vibrio* spp., *Campylobacter* spp., *Clostridium difficile* toxin B (CDB), *Clostridium perfringens*, *Yersinia enterocolitica*, *Aeromonas* spp., *Escherichia coli* O157:H7, and verocytotoxin-producing *E. coli* (VTEC)) using Seeplex® Diarrhea ACE detection kits (Seegene, Seoul, Korea), which utilize multiplex PCR. Positive samples were analyzed.

Statistical Analysis

The data were expressed as frequency with percentage for categorical variables and median with range for continuous variables. Differences in study participants' characteristics were compared across subgroups using the chi-square test or Fisher's exact test for categorical variables and the independent t-test or Mann-Whitney's U test for continuous variables as appropriate. To check for normal distribution, we used the Shapiro–Wilk test. All statistical analyses were carried out using SPSS 24.0, and p-values less than 0.05 were considered statistically significant.

Ethics Statement

This study was approved by the Institutional Review Board of Haeundae Paik Hospital and was conducted in accordance with the Declaration of Helsinki (Approval No. 2019-10-068-001). As a retrospective study of patients undergoing stool and blood tests, the IRB approved waiving informed consent from patients.

Results

Age And Sex Distribution (Table 1)

Table 1
Age and sex distribution

	With secondary appendicitis (n = 12)			Without secondary appendicitis (n = 153)			P-value
Sex (male, %)	9 (75%)			80 (52.3%)			0.146 ¹
Age (months)	141 (82–203)			73 (1–215)			0.011 ²
Age (month)	Male	Female	total	Male	Female	total	
< 12	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (10.5%)	9 (5.9%)	25 (16.3%)	
13–72	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (17.6%)	24 (15.7%)	51 (33.3%)	
73–120	3 (25.0%)	1 (8.3%)	4 (33.3%)	14 (9.2%)	8 (5.2%)	22 (14.4%)	
121–	6 (50.0%)	2 (16.7%)	8 (66.7%)	23 (15.0%)	32 (20.9%)	55 (35.9%)	
Total	9 (75.0%)	3 (25.0%)	12 (100.0%)	80 (52.3%)	73 (47.7%)	153 (100%)	
Values are either frequency with percentage in parentheses or median with range							
¹ P-values were derived from the Chi-square test.							
² P-values were derived from the Mann–Whitney’s U test.							
Shapiro–Wilk’s test was employed for test of normality assumption.							

Of the 642 patients admitted to the pediatric ward at Inje University Haeundae Paik Hospital between June 2017 and June 2019 for acute gastroenteritis, 165 patients underwent radiologic testing, particularly abdominal US or abdominal CT, after excluding infants and patients with underlying conditions. One hundred twenty-six (76.4%) underwent abdominal US, and 39 (23.6%) underwent abdominal CT. Twelve of these patients (7.2%) had secondary appendicitis, with a male-to-female sex ratio of 3:1 (nine boys, three girls). Ages ranged from 6–17 years. The mean age of patients with secondary appendicitis was 141 months, which was higher than that of the non-secondary appendicitis group ($p = 0.011$).

Symptoms (Table 2)

Table 2
Comparison of presenting symptom between two groups

Presenting symptom	With secondary appendicitis (n = 12)	Without secondary appendicitis (n = 153)	P-value ¹
Abdominal pain	10 (83.3%)	90 (58.8%)	0.128 ²
Diarrhea	8 (66.7%)	109 (71.2%)	0.747 ²
Vomiting	4 (33.3%)	88 (57.5%)	0.135 ¹
Fever	10 (83.3%)	75 (49.0%)	0.033 ¹
Hematochezia	1 (8.3%)	18 (11.8%)	1.000 ²
Values are frequency with percentage in parentheses.			
¹ P-values were derived from the Chi-square test.			
² P-values were derived from the Fisher's exact test.			

The main symptoms were abdominal pain (n = 10), diarrhea (n = 8), vomiting (n = 4), and fever (n = 10), and patients had tenderness in the right lower quadrant. The percentage of patients with fever was significantly greater among those with secondary appendicitis (p = 0.033).

Blood Tests (Table 3)

Table 3
Comparison of blood test results between two groups

Blood test	With secondary appendicitis (n = 12)	Without secondary appendicitis (n = 153)	P- value
White blood cell count (/mm ³)	10,790 (4,670–20,950)	8,750 (2,930–24,470)	0.088 ²
Hemoglobin (g/dL)	13.4 (11.8–15.4)	12.9 (8.2–18.6)	0.583 ²
Platelet (/mm ³)	240.5 (170–287)	288 (96–727)	0.002 ²
Erythrocyte sedimentation rate (mm/h)	35 (7–60)	14 (2–70)	0.102 ²
C-reactive protein (mg/dL)	5.38 (0.05–20.99)	0.32 (0.01–22.07)	0.001 ²
Albumin (g/dL)	4.25 (3.3–4.6)	4.4 (3.1–5.8)	0.306 ¹
Aspartate aminotransferase (U/L)	27.5 (21–140)	32 (12–266)	0.915 ²
Alanine aminotransferase (U/L)	16 (12–251)	17 (6–195)	0.782 ²
Amylase (U/L)	54 (26–273)	49 (4–159)	0.503 ²
Lipase (U/L)	18 (14–53)	18 (8–110)	0.622 ²
Values are median with range			
¹ P-values were derived from an independent t-test.			
² P-values were derived from the Mann–Whitney’s U test.			
Shapiro–Wilk’s test was employed for test of normality assumption.			

Platelet counts were significantly lower among those in the secondary appendicitis group than in those in the non-secondary appendicitis group ($p = 0.002$). By contrast, CRP levels were significantly higher among those in the secondary appendicitis group than in those in the non-secondary appendicitis group ($p < 0.001$).

Stool Multiplex PCR Tests (Table 4)

Table 4
Comparison of Multiplex Stool PCR results between two groups

Variable	With secondary appendicitis (n = 10)	Without secondary appendicitis (n = 86)	P- value ¹
Pathogen detected by multiplex PCR test	6/10 (60.0%)	51/86 (59.3%)	0.850
Viral pathogens	0/10 (0.0%)	37/86 (43.0%)	0.012
Rotavirus	0 (0.0%)	10 (6.5%)	1.000
Norovirus	0 (0.0%)	12 (7.8%)	0.603
Astrovirus	0 (0.0%)	4 (2.6%)	1.000
Enteric adenovirus	0 (0.0%)	8 (5.2%)	1.000
Sapovirus	0 (0.0%)	3 (2.0%)	1.000
Bacterial pathogens	6/10 (60.0%)	14/86 (16.2%)	0.004
<i>Salmonella</i> spp.	3 (25.0%)	3 (2.0%)	0.005
<i>Shigella</i> spp.	0 (0.0%)	0 (0.0%)	-
<i>Campylobacter</i> spp.	2 (16.7%)	5 (3.3%)	0.083
<i>E. coli</i> O157:H7	0 (0.0%)	0 (0.0%)	-
<i>Clostridium difficile</i> Toxin B	0 (0.0%)	5 (3.3%)	1.000
<i>Clostridium perfringens</i>	1 (8.3%)	0 (0.0%)	0.073
<i>Yersinia enterocolitica</i>	0 (0.0%)	0 (0.0%)	-
Verotoxic E. coli	0 (0.0%)	0 (0.0%)	-
<i>Aeromonas</i> spp.	0 (0.0%)	1 (0.7%)	1.000
Values are frequency with percentage in parentheses.			
P-values were derived from the Fisher's exact test.			

Three cases of non-typhoidal *Salmonella*, two cases of *Campylobacter* spp., and one case of *Clostridium perfringens* were detected in stool samples from patients with secondary appendicitis. All multiplex PCR tests were negative in the remaining patients. The percentage of patients positive for *Salmonella* spp. was significantly higher among patients with secondary appendicitis ($p = 0.005$). The percentages of bacterial pathogens such as *Salmonella* and *Campylobacter* were significantly greater among patients with secondary appendicitis, while the percentages of viral pathogens such as norovirus and rotavirus were significantly higher among those without secondary appendicitis.

Clinical Course

Length of stay and duration of NPO were significantly longer in the secondary appendicitis group (6.5 vs. 4 days, $p = 0.002$). The use of antibiotics was significantly higher in the secondary appendicitis group (91.7% vs. 11.1%, $p < 0.001$). The numbers of total radiologic tests were also significantly higher in the secondary appendicitis group ($p < 0.001$).

Surgical Treatment

One patient with secondary appendicitis showed perforation on day 2 of admission and underwent emergency appendectomy with cecectomy. All other patients recovered without complications and were discharged.

Discussion

The clinical significance of appendicitis secondary to acute gastroenteritis is largely unknown. This study is the first to examine the features of pediatric acute gastroenteritis when accompanied by secondary appendicitis in comparison with those with no secondary appendicitis. The findings will contribute to establishing the direction of clinical treatment.

Most primary appendicitis occurs as a result of a series of events resulting from a blockage in the lining of the appendix caused by feces, proliferation of lymphatic tissues, vegetable or fruit seeds, or parasites, which in turn cause closed loop obstructions with continued mucus secretion into the appendiceal lining, thereby distending it and continuously increasing the intraluminal pressure.⁽⁸⁾ Continuous elevation of intraluminal pressure causes occlusion of the appendiceal veins and damages the mucosal barrier, thereby inducing bacterial entry and progressing inflammation.⁽⁹⁾ By contrast, secondary appendicitis refers to periappendicitis or serositis caused by colonic or periappendiceal lesions spreading inflammation to periappendiceal areas, as opposed to a blockage of the appendiceal lumen, and this results from sympathetic mural edema.⁽¹⁰⁾ Secondary appendicitis is classified as intrinsic or extrinsic, where intrinsic appendicitis is caused by an inflammation of the cecum or large intestine connected to the appendix (e.g., ischemic colitis, infectious colitis, pseudomembranous colitis), and extrinsic appendicitis is caused by inflammation resulting from a spread of lesion in the surrounding organs, such as the gallbladder, liver, bladder, ovaries, kidney, or terminal ileum (e.g., Crohn's disease, cystitis, cholecystitis, sigmoid diverticulosis).^(2, 10) In the present study, many cases of appendicitis secondary to acute gastroenteritis were intrinsic cases caused by acute ileocectitis affecting the ileum and cecum around the appendix. Acute gastroenteritis cases in which the inflammation is confined to the ileum and cecum are called ileocectitis, and most of these cases are caused by infection in these areas by bacteria such as *Yersinia enterocolitica*, *Campylobacter jejuni*, and *Salmonella enteritidis*.^(11, 12) Acute gastroenteritis can be diagnosed based on enlarged ileocecal area and normal appendix,⁽¹³⁾ and some cases may show appendiceal infection as well.⁽¹⁴⁾

One shortcoming of diagnostic US is that the diagnosis rate may vary according to the proficiency of the examiner, although it is widely used as the primary test owing to the benefits of US. This includes its noninvasive simple nature. The examiner can talk to the patient while performing the study in real time, observing peristalsis and blood flow distribution of the digestive tract. The test can be safely repeated frequently, and there is no risk of irradiation.^(15, 16) In the present study, US was generally the modality chosen, and abdominal CT was performed in the presence of poor acoustic windows, abdominal obesity, and difficulty of ultrasonography. Generally, secondary appendicitis is distinguished from primary appendicitis according to the patterns of cecal wall thickening. Whereas cecal wall thickening is local, asymmetrical, and irregular in primary appendicitis, it is symmetrical, and regular in secondary appendicitis.^(3, 17) Appendiceal distention can be observed in both cases; however, appendiceal wall thickening and periappendiceal fat deposition are characteristic findings of primary appendicitis.⁽¹²⁾ Color Doppler imaging shows increased blood flow in the thickened appendiceal wall in primary appendicitis, while hyperemia of terminal ileum is characteristic of secondary appendicitis.^(18, 19) Similarly, we diagnosed cases featuring absence of blockage in appendiceal lumen with the presence of symmetrical and regular cecal and appendiceal wall thickening along with inflamed large and small intestines as secondary appendicitis.

The mean age of patients with secondary appendicitis was 11.75 years, suggesting that appendicitis was more common in older children. The major symptoms upon hospital visit were abdominal pain and fever among those with secondary appendicitis, while diarrhea was the most common symptom among those without secondary appendicitis. A significantly higher percentage of patients with secondary appendicitis had fever. CRP levels were significantly higher among patients with secondary appendicitis compared to those without. These findings suggest that patients with secondary appendicitis may have more severe inflammation and therefore have fever more frequently with higher levels of acute inflammation indicators.

Of patients with secondary appendicitis, *Salmonella* spp., *Campylobacter* spp., and *C. perfringens* were detected in the stool samples of five patients, with no viruses detected. Rotavirus, norovirus, and enteric adenovirus were detected among patients without secondary appendicitis. These findings suggest that patients with secondary appendicitis may be more likely to have been infected with bacteria, and this should be noted when determining treatment approaches.

The lengths of hospital stay were longer, and the use of antibiotics was more common among patients with secondary appendicitis. The use of antibiotics and additional radiologic testing were greater among these patients after initial diagnosis because of the persistence and high severity of symptoms. Most patients showed rapid improvement of symptoms only with symptomatic treatment for acute gastroenteritis, and antibiotics were used for shorter periods in the earlier stages with severe symptoms and unclear diagnoses. Nevertheless, because it was reported that infectious ileoceitis occurred in one out of 11 cases of acute appendicitis,⁽¹⁾ and secondary ileoceitis can develop along with fat inflammation even in progressed acute appendicitis, we believe abdominal CT should be performed in

cases in which US findings are unclear. In the present study, one patient was initially diagnosed with secondary appendicitis with ileocectitis, and CT taken on day 2 of admission indicated by worsening of symptoms revealed intestinal perforation and peritonitis, for which appendectomy and cecectomy were performed. Early diagnosis is often difficult and delayed in children because they usually complain of nonspecific symptoms in the earlier stages and have less ability to express their describe their symptoms than do adults. Because children have more lymphoid tissue in the mucosal layer of the appendiceal wall, proliferation of these lymphoid tissues caused by inflammation can more easily occlude the appendix.^(20–22) Children may show quicker progression of inflammation because of their anatomically thin and sparse fiber tissues in the appendiceal wall. They are also at elevated risk for peritonitis because of weak defense systems that might otherwise minimize inflammation in the abdominal cavity; finally, children also have incomplete epiploic development.⁽²³⁾ As shown in the present study, even if appendicitis secondary to acute gastroenteritis had been initially diagnosed, it is possible to have mistaken ileocectitis secondary to progressed primary appendicitis. Even if the diagnosis is correct, it may progress severely and cause peritonitis. Therefore, it is important to continuously and closely monitor symptoms and to perform additional radiologic testing as necessary.

This study has a few limitations. First, the small sample size limits the generalizability of the clinical presentations. Second, bacterial and viral detection rates using stool PCR were low, at 59.4%. Subsequent studies are required to examine larger sample sizes and to strive to enhance bacterial identification and virus detection using various media in order to illuminate the etiology and clinical course of this disease.

Conclusions

In conclusion, we found that patients with acute gastroenteritis accompanied by secondary appendicitis more commonly had fever, higher CRP, higher bacterial pathogen detection rates, and longer hospital stays. These findings suggest that treatment equivalent to that of bacterial infection is required for patients with secondary appendicitis, and that their symptoms should be closely and continuously monitored and followed-up.

Abbreviations

CT
Computed tomography
US
Ultrasound
WBC
White blood cell
CRP
C-reactive protein
ESR
Erythrocyte sedimentation rate

AST
Aspartate aminotransferase
ALT
Alanine aminotransferase
PCR
Polymerase chain reaction
NPO
Nil per oral [NPO]
MOD
Maximal outer diameter

Declarations

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Author information

Affiliations

Department of Pediatrics, Division of Pediatric Gastroenterology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Contributions

SYC conceived of the study and was involved in the design of the study, and reviewed the article, analysis, report writing, and preparation of the manuscript, read and approved the final manuscript.

Authors' information

SYC is a pediatrician and an assistant professor of pediatrics at Inje University College of Medicine.

Corresponding author

Correspondence to So Yoon Choi.

Ethics declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Haeundae Paik Hospital and was conducted in accordance with the Declaration of Helsinki (Approval No. 2019-10-068-001). As a retrospective medical record study, informed consent was waived from the patient.

Consent for publication

Not applicable.

Competing interests

No potential conflict of interests with respect to the research, authorship and/or publication of this article.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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