Intraluminal appendiceal fluid is a predictive factor for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis in pediatric patients

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A B S T R A C T

Background: The risk factors for recurrent appendicitis in pediatric patients are unclear. This study aimed to identify the predictive factors for recurrent appendicitis in pediatric patients who initially underwent successful non-operative management of uncomplicated appendicitis.

Methods: Potential predictive factors for recurrent appendicitis in terms of clinical characteristics, laboratory data, and abdominal ultrasonography and computed tomography findings, were evaluated.

Results: This study included 125 patients who underwent initial successful non-operative management of uncomplicated appendicitis. The rate of recurrent appendicitis was 19.2%, and the mean time to recurrence was 12.6 months. Univariate analyses found that rebound tenderness, muscle guarding, appendicoliths, appendiceal diameter > 9 mm, and intraluminal appendiceal fluid were associated with recurrent appendicitis. Multivariate analysis identified only intraluminal appendiceal fluid as an independent predictor of recurrent appendicitis.

Conclusions: Intraluminal appendiceal fluid is a predictive factor for recurrent appendicitis after initial non-operative management. The results of this study provide valuable information that may help to determine the appropriate management during the first episode of appendicitis.

The risk factors for recurrent appendicitis after initial non-operative management in pediatric patients remain unclear. The aim of this study was to identify the predictive factors for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis in pediatric patients.

1. Methods

1.1. Patients

A total of 302 pediatric patients aged 12 months to 15 years were clinically diagnosed with acute appendicitis and managed at the National Mie Hospital between January 2004 and December 2010. The flow of diagnosis and management of these patients is shown in Fig. 1. Patients admitted to the emergency department were suspected of acute appendicitis if they had the following findings: right lower quadrant abdominal pain and elevated white blood cell count (&gt;9000/μl) or C-reactive protein (&gt;0.3 mg/dl). All patients with suspected acute appendicitis underwent ultrasonography (US). When the diagnosis of acute appendicitis by US was uncertain, additional non-contrast computed tomography (CT) was performed. Appendicitis was suspected if imaging examinations showed an appendiceal diameter (&gt;6 mm), noncompressible appendix, pericecal inflammatory changes, appendicolith, or pericecal abscess. If none of these findings were observed on US or CT, appendicitis was not diagnosed, and other causes of abdominal pain were considered. Patients were excluded from this study if the appendix was not detected on US or CT. The pediatric appendicitis score reported by Samuel [1] was assessed in all patients. This score assigns 2 points for cough/percussion/hopping tenderness in the right lower quadrant of the abdomen, 2 points for tenderness over the right iliac fossa, and 1 point for each of: anorexia, pyrexia, nausea/emesis, leukocytosis, polymorphonuclear neutrophilia, and migration of pain. The maximum total score is 10, and a score of ≥7 is strongly suspicious of acute appendicitis. All the patients included in this study had a score of ≥7. Recurrent appendicitis was diagnosed using the same criteria as for the initial episode. All patients who met the diagnostic criteria and underwent non-operative management with antibiotic therapy or operative management for appendicitis during the study period were included in this study. Appendicitis was classified as complicated or uncomplicated based on the clinical and
imaging examination findings. Appendicitis was classified as uncomplicated when a large external appendiceal diameter (≥6 mm) without abscess formation was observed. Appendicitis was classified as complicated if a periappendiceal or pericecal abscess, or a gangrenous appendix, was observed. In cases of uncomplicated appendicitis, patients and their parents were informed of the potential advantages and disadvantages of both operative and non-operative management, including discussion of the current uncertainty regarding the optimal management of such cases. In cases of uncomplicated appendicitis, after these explanations, we left the final decision to the patient’s parents. In cases of complicated appendicitis, emergent appendectomy or interval appendectomy was advised.

Consent for inclusion in the study, which comprised a retrospective chart review, was obtained from the parents of patients with uncomplicated appendicitis who selected initial non-operative management.

### 1.2. Interventions and data collection

A total of 134 patients with uncomplicated appendicitis underwent initial non-operative management and received intravenous antibiotic therapy (cefoperazone, 60 mg/kg/day divided into 8-hourly doses) for at least 48 hours. As no appropriate protocols for the non-operative management of uncomplicated appendicitis in pediatric patients were identified in previously reported studies, we developed our own protocol, as follows. On the first day of admission, antibiotic therapy was initiated, and patients were fasted and received intravenous fluid therapy. Eating was allowed from the second day of admission. Patients were discharged when they had no abdominal pain, body temperature <37.0 °C, and no increase in the levels of inflammatory markers compared with admission or the time of resumption of oral intake. If the C-reactive protein level was >1.0 mg/dL at discharge, oral antibiotic therapy (cefcapene pivoxil) was prescribed for 3 days.

Fig. 1. Patient enrollment. A total of 125 patients who underwent successful initial non-operative management were analyzed in this study.
All patients who underwent non-operative management of uncomplicated appendicitis were followed up for at least 1.5 years. Our region (Mie prefecture) has only two hospitals with pediatric surgeons (Mie University Hospital and National Mie Hospital). All patients were instructed to return to our hospital if they developed recurrent abdominal pain. Patients who returned with a presentation suspicious of recurrent appendicitis underwent abdominal US but not CT, to avoid additional radiation exposure. The follow-up period of patients without recurrence was determined by examination of the medical records. If there was no follow-up information in the records, follow-up was performed by telephone. The mean follow-up period was 30.6 months. Successful initial non-operative management was defined as no recurrence during the initial non-operative management.

Data from the initial admission were retrospectively collected, including clinical characteristics (age, sex, historical findings), physical examination findings, laboratory data (levels of inflammatory markers at admission and discharge), clinical course (duration of fever, duration of abdominal pain), and imaging examination findings (abdominal US and CT). The initial non-operative management period was defined as the time from admission to our hospital for appendicitis until discharge. Intraluminal appendiceal fluid was diagnosed based on abdominal US or CT findings [2–4]. All US examinations were performed using the graded compression technique described by Puylaert [5,6], using a Xario SSA-660A system (Toshiba Medical Systems Corp, Tochigi prefecture, JAPAN) with a 7.5–12 MHz linear transducer. If clear images or findings of appendicitis were not obtained, patients underwent abdominal non-contrast CT. All CT examinations were performed using a 16 multi-detector row scanner (Bright Speed Elite GE Healthcare, Fairfield, CT, USA) with detector width 0.8–1.5 mm, 120 kVp, and 40–250 effective mAs. Multiplanar reconstruction was performed if necessary. Typical images showing intraluminal appendiceal fluid are shown in Fig. 2. All scans were evaluated for intraluminal appendiceal fluid by the pediatric surgeon at the time of admission, and the findings were therefore recorded before outcome information was available.

To check the risk and cost of non-operative management, we collected additional data regarding the total length of stay (LOS) and the total cost of the hospital stay (including the costs of medications, laboratory tests, imaging examinations, and procedures) from the chart review, and additional data analyses were performed to determine the pros and cons of both appendectomy and non-operative management in the uncomplicated appendicitis.

1.3. Statistical analysis

All data were analyzed using JMP software version 6.0 (SAS Institute, Cary, NC, USA). The Mann-Whitney U test, chi-square test, and Student’s t test were used to analyze differences between patients with and without recurrent appendicitis after initial non-operative management. The factors found to be significantly associated with recurrent appendicitis on univariate analyses (P < 0.05) were included in a multivariate logistic regression analysis. The cumulative rate of recurrence after the initial hospitalization was calculated by the Kaplan–Meier method and was compared between patients with and without intraluminal appendiceal fluid using the log-rank test.

2. Results

The flow of diagnosis and management of patients who were treated for appendicitis during the study period is shown in Fig. 1. A total of 302 patients were treated, of which 248 (82.1%) were initially diagnosed with uncomplicated appendicitis, including 114 (114/248, 46.0%) who underwent initial operative management and 134 (134/248, 54.0%) who underwent initial non-operative management. Nine of the 134 patients with uncomplicated appendicitis who underwent initial non-operative management were excluded from the study because the US findings could not be located at the time of review (n = 2), they had a past history of suspected appendicitis (n = 2), or non-operative management failed (n = 5). In all cases of failed non-operative management, the parents decided to change to operative management within 1 day of hospitalization even though there was no worsening of symptoms. The remaining 125 patients who underwent successful non-operative management of uncomplicated appendicitis were included in this study. None of these study patients received additional treatments, such as abscess drainage, during the initial non-operative therapy period.

The characteristics of the patients included in the study are shown in Table 1. Intraluminal appendiceal fluid was the most common abnormal imaging finding (37/125, 29.6%), followed by appendicoliths (9.6%). CT was performed in 109 patients. In the 16 patients who underwent US but not CT, intraluminal appendiceal fluid was the most common abnormal imaging finding (9/16, 52.5%), followed by appendicoliths (3/16, 18.7%). Recurrent appendicitis occurred in 24 patients (19.2%) during the study period, with a mean time to recurrence of 12.6 months (range, 2–36 months). Fourteen of these patients (14/24, 58.3%) underwent appendectomy.

Fig. 2. Imaging results. (A) The US findings of the intraluminal appendiceal fluid. The white arrowhead shows slightly opacified fluid in the intraluminal appendiceal space. (B) The CT findings of the intraluminal appendiceal fluid. The appendix just below the abdominal wall was swollen, and thickness of its wall was observed (white arrow). There was also slightly opacified fluid in the intraluminal appendiceal space.
at the time of readmission. All cases of recurrence were uncomplicated based on US findings.

Comparisons of other imaging findings (appendiceal diameter >9 mm and appendicolith) between patients with and without intraluminal appendiceal fluid are shown in Table 2. Receiver operating curve analysis showed that appendiceal diameter >9 mm was the best cut-off value for predicting recurrent appendicitis. Intraluminal appendiceal fluid was significantly associated with other abnormal imaging findings (P < 0.05).

The results of univariate analyses of potential predictive factors for recurrent appendicitis are shown in Table 3. Rebound tenderness, muscle guarding, appendiceal diameter >9 mm, intraluminal appendiceal fluid, and appendicoliths were significantly associated with recurrence. The pediatric appendicitis score at the initial presentation was also significantly associated with recurrence (P = 0.0096). There were no significant differences between the success and recurrence groups in terms of clinical course (duration of fever, duration of abdominal pain) or levels of inflammatory markers during the initial admission. Multivariate analysis including the factors found to be significantly associated with recurrence on univariate analyses identified only intraluminal appendiceal fluid as an independent predictor of recurrent appendicitis (P = 0.0019) (Table 4).

The 3-year cumulative rates of recurrent appendicitis in patients with and without intraluminal appendiceal fluid are shown in Fig. 3. Patients with intraluminal appendiceal fluid had a significantly higher 3-year rate of recurrent appendicitis than patients without intraluminal appendiceal fluid (45.9% vs. 7.95%, P < 0.0001). Moreover, patients with intraluminal appendiceal fluid were more likely to develop recurrence within 1 year than patients without intraluminal appendiceal fluid (32.4% vs. 5.68%, P < 0.0001). Almost all patients with recurrent appendicitis who had intraluminal appendiceal fluid at the time of the initial presentation also had intraluminal appendiceal fluid at the time of recurrence (15/17, 88.2%).

The total length of stay in the 125 patients who underwent non-operative management was similar to that of the 114 patients who underwent operative management of uncomplicated appendicitis (4.4 ± 2.8 days vs. 6.7 ± 2.7 days). The total cost of the hospital stay (including the costs of medications, laboratory tests, imaging examinations, and procedures) was significantly lower in patients who underwent non-operative management than in patients who underwent operative management (81,000 ± 5,700 yen vs. 126,364 ± 16,991 yen, P = 0.041).

3. Discussion

Emergent surgical removal of the appendix has been the gold standard treatment for acute appendicitis since Groves performed the first appendectomy in 1883 [7,8]. Non-operative management of
acute appendicitis was first reported in 1945 [9]. In recent years, there has been increasing interest in non-operative management with antibiotic therapy for the primary treatment of uncomplicated appendicitis [10–12]. Although some studies reported that non-operative management was inferior to emergency appendectomy, a recent meta-analysis found that primary antibiotic therapy was effective and safe in patients with uncomplicated acute appendicitis [13,14]. However, these studies did not include pediatric patients, who have a higher risk of perforation than adult patients. A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy for the treatment of uncomplicated acute appendicitis (APPAC trial) is currently underway [15].

Non-operative management of uncomplicated appendicitis may eliminate the need for appendectomy in some patients. However, the reported rates of recurrent appendicitis after initial non-operative management of uncomplicated appendicitis range from 14% to 26% [10,11]. It is currently still unclear which children benefit from an initial non-operative approach. This study was not randomized, but it is the first reported study that analyzed predictive factors for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis in pediatric patients. This study has the advantage of a longer follow-up period than previously reported studies [10].

Historically, diagnosis of acute appendicitis has been more difficult in children than in adults because of the lack of classic symptoms and delay in presentation, resulting in a higher perforation rate [16–20]. In this study, fortunately, no complications were observed among patients who underwent initial non-operative management of uncomplicated appendicitis. One of the reasons for this may be that only 15 (15/248, 6%) of the patients diagnosed with uncomplicated appendicitis were less than 5 years old. Therefore, recommendations regarding non-operative management of uncomplicated appendicitis in less than 5 years old are still unclear.

As for the total length of stay and the total cost of the hospital stay, there is substantial national bias in this analysis because the Japanese medical insurance system differs significantly from systems in Western countries, and the daily cost of hospitalization is lower in Japan than in Western countries. This low hospitalization cost results in much longer periods of hospitalization in Japan than in Western countries. Conducting additional data analyses, patients with recurrent appendicitis had a longer total LOS because their re-admission was included in the calculation, resulting in higher total costs than in patients without recurrence. The increased total LOS and hospital costs are a potential disadvantage of non-operative management of uncomplicated appendicitis.

Rollins et al and Alfeer et al. [21,22] recently reported that appendicoliths are associated with a low risk of appendicitis and are often transient. As for the complicated appendicitis, Ein et al [23] showed that the presence of an appendicolith predicts recurrent appendicitis in case of non-operative management for pediatric ruptured appendicitis. For the case of uncomplicated appendicitis, in our experience, appendicoliths observed at the time of initial non-operative management sometimes disappear during follow-up. Motoke et al. [2–4] reported that intraluminal appendiceal fluid could be a new diagnostic criterion for acute appendicitis. They reported that a maximum depth of intraluminal appendiceal fluid of >2.6 mm had a sensitivity and specificity of 90% for diagnosing acute appendicitis, and that intraluminal appendicular fluid was detected in 86.6% of all patients with appendicitis [2–4,24]. We have evaluated intraluminal appendiceal fluid in pediatric patients with suspected appendicitis using both US and CT since 2004, and found that intraluminal appendiceal fluid was frequently associated with acute appendicitis. Moreover, this finding had a higher detection rate than appendicolith although appendicolith was reported to predict the negative outcome in non-operative management for suspected appendicitis [25]. In this study, intraluminal appendiceal fluid was strongly associated with both appendicolith and increased appendiceal diameter (Table 2). Intraluminal appendiceal fluid was the most common abnormal finding, even in patients who only underwent US examination. This suggests that intraluminal appendiceal fluid is relatively easy to detect in pediatric patients with acute appendicitis.

In this study, intraluminal appendiceal fluid was observed at the initial presentation in 70% of patients who developed recurrent appendicitis. Furthermore, recurrent appendicitis occurred in 45.9% (17/37) of patients with intraluminal appendiceal fluid at the initial presentation. Therefore, if all patients with intraluminal appendiceal fluid at the initial presentation had undergone operative management, the rate of recurrent appendicitis in patients who underwent non-operative management would have decreased from 19.2% to 7.5%, although there is a possibility of historical bias because of the long timeframe of this study. Patients with intraluminal appendiceal fluid at the initial presentation had a higher risk of recurrence than patients without intraluminal appendiceal fluid. These results may be useful for determining which patients with uncomplicated
appendicitis require close follow-up after initial non-operative management because they have a high risk of recurrence.

This study has the following limitations. First, non-contrast CT may have a lower sensitivity for the diagnosis of appendicitis than contrast-enhanced CT, and may miss 10–16% of cases [26,27]. Second, some patients with appendicitis may have been excluded from the study, because some patients do not have elevated levels of inflammatory markers [28]. Finally, this study classified gangrenous appendicitis as complicated, although not all pediatric surgeons would consider a gangrenous appendix to indicate complicated appendicitis [29]. However, only one patient in this study had a gangrenous appendix.

In conclusion, intraluminal appendiceal fluid is a predictive factor for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis, and may therefore be suitable for elective interval appendectomy.

References

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