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Clinical characteristics and prognosis of 69 cases of neonatal appendicitis

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ABSTRACT

Importance: Neonatal appendicitis (NA) is a rare and potentially fatal neonatal disease. However, misdiagnosis is common owing to atypical clinical manifestations and non-specific laboratory tests.

Objective: The aim of this study was to summarize the clinical characteristics, treatments, and prognoses of infants with NA.

Methods: This retrospective analysis included 69 patients diagnosed with NA admitted to Beijing Children's Hospital between 1980 and 2019. The patients were divided into surgical and non-surgical groups based on whether surgery was performed. Their clinical characteristics were analyzed using the chi-square test, *t*-test, or the Mann-Whitney *U* test.

Results: The study included 47 males and 22 females with NA. The primary symptoms were abdominal distension ($n = 36$, 52.2%), fever ($n = 19$, 27.5%), refusal to feed or decreased feeding ($n = 16$, 23.2%), and vomiting ($n = 15$, 21.7%). Sixty-five patients underwent abdominal ultrasound examinations; 43 had definite appendiceal abnormalities, 10 had right lower abdominal adhesive masses, and 14 had neonatal enterocolitis manifestations. Twenty-nine and 40 patients were in the surgical and non-surgical groups, respectively. No statistically significant differences were observed between the groups regarding sex, age at onset, birth weight, admission weight, or hospitalization time. However, parenteral nutrition was prolonged in the surgical group ($P = 0.001$). Additionally, two patients (2.9%) died.

Interpretation: NA is a rare neonatal disease with atypical clinical manifestations. Abdominal ultrasonography may aid in the diagnosis. Similarly, appropriate treatment can improve the prognosis.

KEYWORDS

Acute appendicitis, Diagnosis, Neonatal, Therapy

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INTRODUCTION

Acute appendicitis is a common condition in children; nonetheless, its incidence decreases considerably to <2% in infants aged <2 years.[1] Neonatal appendicitis (NA) is a rare disease with an incidence of 0.04%–0.2%, and the male-to-female ratio is approximately 3:1.[2] The incidence of NA is challenging to ascertain because NA frequently mimics other common abdominal conditions, such as necrotizing enterocolitis (NEC), obstruction, and gastroenteritis.[1] In addition, atypical and, in many cases, non-expressive clinical presentations contribute to a significant rate of diagnostic errors.

Considering the long-term radiation exposure risk, diagnosing pediatric acute appendicitis (PAA) is primarily based on clinical history, physical examination, basic laboratory tests (complete blood counts and biochemistry), and abdominal ultrasonography. Several diagnostic tools have been recently developed to improve the accuracy of PAA diagnosis. Blood parameters such as the neutrophil-to-lymphocyte ratio and lymphocyte-to-monocyte ratio and clinical scores combining symptoms, signs, and laboratory test results partially improve the diagnostic accuracy of PAA.[3–6] Prospective studies and systematic evaluations have assessed blood biomarkers, such as interleukin-6, pentraxin-3, neutrophil gelatinase-associated lipocalin, total serum bilirubin, calprotectin, and APPY-1 tests, as potential diagnostic tools for PAA; however, the diagnostic ability of these biomarkers seems to be moderate.[7–11] Moreover, these studies included the general pediatric population, and no novel diagnostic tool exists for NA.

NA progresses rapidly and may induce appendiceal perforation and peritonitis, endangering the patient's life. A recent literature review indicated a perforation rate of approximately 85% in patients diagnosed with NA during laparotomy.[12] The mortality rate of NA remains high at 23%, although it has gradually declined over the last century.[12] An early diagnosis and taking reasonable and effective treatment measures are key to treating the disease and preventing severe complications. In this study, we aimed to retrospectively analyze the clinical characteristics, treatments, and prognoses of patients with NA admitted to our hospital to improve the clinical knowledge regarding the diagnosis and treatment of the disease.

METHODS

Ethical approval

The study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (number: 2023-E-005-R). Furthermore, the requirement for informed consent from the patients' guardians was waived because this was a retrospective study and the data were analyzed anonymously.

Patients

Data of patients with NA admitted to the Beijing Children's Hospital, Capital Medical University, between 1980 and 2019 were collected.

Diagnostic criteria for NA: Appendicitis was diagnosed using abdominal ultrasound and/or operation.

Inclusion criteria were: (1) age ≤28 days; (2) diagnosis of appendicitis using abdominal ultrasound or operation.

The exclusion criterion was incomplete case records.

Data collection

Clinical data were retrospectively collected, including patient gender, gestational age, birth weight, age at onset, weight at onset, C-reactive protein (CRP) level, white blood cell count, neutrophil percentage, abdominal ultrasound, and radiography data, time from symptom onset to a definitive diagnosis, treatment, comorbidities, parenteral nutrition time, hospitalization time, and patient outcome.

Statistical analysis

SPSS 20.0 was used for data analyses. Categorical data were expressed as percentages, and the comparison between groups was performed using the chi-square test. Continuous data were expressed as mean ± standard deviation for normally distributed data or median (interquartile range) for non-parametric data and analyzed using a *t*-test or the Mann-Whitney *U* test, as appropriate. Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

This study included 69 patients with NA, consisting of 47 males (68.1%) and 22 females (31.9%), with a male-to-female ratio of 2.14:1. Three cases involved twins, each with the onset of NA in one of the twins. Twenty infants (29.0%) were preterm, and 49 (71.0%) were full-term. The admission weights were 860–4400 g, and the mean weight was 3130 ± 730 g. Seventeen patients (24.6%) had low birth weights, 42 (60.9%) had normal birth weights, and 10 (14.5%) had macrosomia. The time from symptom onset to definitive diagnosis was 1–22 days. Forty cases (58%) were in the non-surgical group, and 29 (42%) were in the surgical group, including 22 of simple appendectomy, three of appendectomy and enterostomy, two of appendectomy and high ligation of the hernia sac, and two of abdominal drainage tube placement.

TABLE 1 Clinical manifestations of patients with neonatal appendicitis

Items	Number of patients, *n* (%)
Main symptoms and signs	
Abdominal distention	36 (52.2)
Fever	19 (27.5)
Refusal or decreased feeding	16 (23.2)
Vomiting	15 (21.7)
Lethargy	13 (18.8)
Bloody stool	7 (10.1)
Irritability	6 (8.7)
Abdominal tenderness	6 (8.7)
Abdominal muscle tension	4 (5.8)
Abdominal wall cellulitis	3 (4.3)
Abdominal mass	2 (2.9)
Comorbidities	
Necrotizing enterocolitis	14 (20.3)
Hirschsprung's disease[†]	3 (4.3)
Pneumonia	3 (4.3)
Right inguinal incarcerated hernia	2 (2.9)
Jaundice	2 (2.9)
Wet lung	1 (1.4)
Sepsis	1 (1.4)
Sigmoid atresia (type II)	1 (1.4)
Refractory cardiac arrhythmia	1 (1.4)

[†]Including one case of total colonic Hirschsprung's disease.

Clinical manifestations

The clinical manifestation of patients with NA is presented in Table 1. The most common symptoms were abdominal distension (36, 52.2%), fever (19, 27.5%), refusal of or decreased feeding (16, 23.2%), and vomiting (15, 21.7%). Physical examinations revealed abdominal tenderness (6, 8.7%), abdominal muscle tension (4, 5.8%), and abdominal wall cellulitis (3, 4.3%). The main comorbidities were NEC (14, 20.3%), Hirschsprung disease (3, 4.3%), and pneumonia (3, 4.3%).

Laboratory and imaging findings

All patients underwent complete blood counts and CRP tests. CRP levels increased in 58 (85.5%) patients (16–160) mg/L. White blood cell (WBC) counts were normal in 12 (17.4%), increased ([10.65–35.31]$\times 10^9$/L) in 52 (75.4%), and decreased ([2.08–5.88]$\times 10^9$/L) in 5 (7.2%) cases. The neutrophil percentage increased in 56 (81.2%) and was normal or decreased in 13 (18.8%) cases. Sixty-six patients underwent abdominal X-ray examination; six had gas shadows below the diaphragm; 41 had abdominal distention, intestinal gap thickening, and intestinal stasis; nine had an incomplete intestinal obstruction. Sixty-five patients underwent abdominal ultrasound examination; 43 had acute appendicitis, appendiceal perforation, or periappendiceal abscess; 10 had an adhesive mass in the right lower abdomen; 14 patients had NEC with terminal ileum, ileocecal, and ascending colon involvement.

Treatments and outcomes

As indicated in Table 2, 40 and 29 patients were in the non-surgical and surgical groups, respectively. Significant differences were observed in the parenteral nutrition time (non-surgical group: 5.5 ± 2.2 days *vs.* surgical group: 8.6 ± 4.5 days, $P = 0.001$). No significant differences existed between both groups regarding gender, age at onset, birth weight, weight at admission, or hospitalization time.

Forty patients in the non-surgical group underwent fasting, intravenous nutritional support, and anti-infection treatment. A combination of third-generation cephalosporins and metronidazole was administered empirically and subsequently adjusted based on the drug effectiveness and sensitivity test results.

The condition of three patients with scrotal swelling and tenderness as their initial symptoms gradually improved after treatment. Their blood supply to the testes was normal according to the follow-up ultrasonography. The two patients with delayed meconium excretion recovered well after adjuvant treatment with colonic irrigation. A full-term female infant received conservative treatment, and ultrasonography revealed blurred images of the right ovary; however, the test could not define the follicular structure and blood supply. One preterm female infant had recurrent appendicitis five months after the conservative treatment and underwent laparoscopic appendectomy without significant adhesions in the right lower abdomen perioperatively.

Among the 29 patients who underwent surgical treatment, 22 underwent simple appendectomy. Postoperative histopathology revealed 6 cases of simple acute appendicitis, 12 of acute purulent appendicitis, and 4 of gangrenous appendicitis. Two patients underwent only flushing of the abdominal cavity and indwelling abdominal drainage tube placement because the appendix could not be resected owing to severe adhesions in the right lower abdomen. One patient had three postoperative intestinal obstructions, which were cured after one surgical and two conservative treatments. Three patients with Hirschsprung disease recovered after first-stage appendectomy and enterostomy and second-stage radical surgery. Two patients with Amyand's hernia underwent appendectomy concurrently with high ligation of the hernial sac, with no postoperative abnormal testicular blood supply or recurrence of the

TABLE 2 Characteristics for patients undergoing surgical and non-surgical treatment

Variables	Non-surgical group ($n = 40$)	Surgical group ($n = 29$)	*P*-value
Gender			0.359†
Male	29 (72.5)	18 (62.1)	
Female	11 (27.5)	11 (37.9)	
Gestation (weeks)			0.749†
≤ 37	29 (72.5)	20 (69.0)	
> 37	11 (27.5)	9 (31.0)	
Age of onset (days)	8 (9)	11 (14)	0.394‡
Age of admission (days)	11 (8)	13 (14)	0.327‡
Admission weight (g)	3172.0 ± 674.2	3075.0 ± 807.0	0.589§
Birth weight (g)	3048.8 ± 569.9	2775.0 ± 698.0	0.078§
Hospitalization time (days)	16 (10)	15 (27)	0.268‡
Parenteral nutrition time (days)	5.5 ± 2.2	8.6 ± 4.5	0.001§

Data are shown as *n* (%) or mean ± standard deviation or median (interquartile range).
†chi-square test;
‡Mann Whitney *U* test;
§*t*-test.

inguinal hernia. Additionally, the condition of one full-term male infant with refractory cardiac arrhythmia gradually improved and was cured after appendectomy.

In this study, all the patients were discharged except for two who died. One who underwent conservative treatment died after being abandoned by the parents for financial reasons, and one with postoperative Hirschsprung disease complicated by enterocolitis and appendicitis died after enterostomy.

DISCUSSION

Acute appendicitis is common in children; however, it is rare in neonates. The possible reasons for the low incidence of NA in infants include (1) funnel-shaped appendix with a wide base in neonates, (2) liquid diet, (3) constant supine position, and (4) low incidence of gastrointestinal and respiratory infections during the neonatal period.[13] However, NA occurs most often in preterm infants, accounting for approximately 25%–50% of cases.[14] Consistent with the literature, our data revealed that 29.0% of infants with NA were preterm.

The clinical symptoms of NA are atypical, with rapid progression, a high incidence of perforation, and an easily endangered life. For instance, Schwartz et al.[15] summarized and analyzed 32 NA cases, in which abdominal distention, vomiting, refusal of feeding, and temperature instability were the most common clinical manifestations, with abdominal distention accounting for approximately 75% of the cases. Similarly, Karaman et al.[13] summarized the clinical presentations of 17 NA cases and reported that abdominal distension and bilious vomiting were the most common symptoms, with incidence of 11 (64.7%) and eight (47.1%) cases, respectively. Additionally, abdominal wall edema and right lower abdominal masses were commonly observed. In our study, the main symptoms were abdominal distension, fever, refusal to feed or decreased feeding, and vomiting, accounting for 52.2%, 27.5%, 23.2%, and 21.7% of cases, respectively, consistent with the literature. Owing to poor neonatal mental development, abdominal inflammation is not easily confined by wrapping when appendicitis and perforation occur. No visible right lower abdominal mass or signs of peritoneal irritation, such as pressure and rebound pain, were observed. Moreover, abdominal distention was the most common symptom. Additionally, abdominal wall cellulitis was observed in some patients with perforated appendices; however, it remained non-specific. Few patients had a swollen scrotum with tenderness, mostly right-sided and associated with a combined inguinal hernia or syringomyelia.

The clinical symptoms of NA are inconsistent with those typical of acute appendicitis in childhood,[16] which may be related to the pathogenesis of NA. The pathogenesis of NA is controversial, and various hypotheses have been proposed, three of which are prominent. The first is related to immune deficiency, frequently exacerbated by premature birth, chorioamnionitis, neonatal sepsis, and NEC, which increase susceptibility to infection.[14,17,18] Second, hypoxia or hypoperfusion (perinatal asphyxia and congenital heart disease) leads to vascular insufficiency, causing a perforated appendix.[14] Third, NA is caused by an underlying disease, such as Hirschsprung disease or meconium intestinal obstruction, causing cecum volvulus with bacterial overgrowth and proliferation, further increasing

intraluminal pressure, leading to perforation.[17,19] In this study, 20 patients were preterm, and 14 had combined NEC, supporting the first hypothesis. We had three cases of Hirschsprung disease (one case of total colonic megacolon), two of delayed meconium excretion, and one of sigmoid atresia (type II), supporting the third hypothesis.

The clinical presentation of NA is non-specific and overlaps with that of other common surgical neonatal diseases, particularly NEC, leading to misdiagnoses. In some cases, NEC occurs before appendicitis or perforation onset or is associated with the perforation.[20] Bax et al.[18] suggested that localized total necrosis of the appendix, a specific form of NEC, is characteristic of NA. Cui et al.[21] analyzed 48 NA cases and reported that abdominal distention was the most common singular NA symptom. Additionally, bloody stools were the most common symptom of NA combined with NEC, followed by abdominal distention. Notably, no patient treated for NA alone had bloody stools. In our study, 14 patients had NEC, and three had NEC-related symptoms as their first presentations. Thus, making an early differential diagnosis between NA and NEC is challenging.

Amyand's hernia is a rare condition that occurs when the appendix is included in the hernia sac. The condition can be treated early and effectively and has a good prognosis owing to its typical presentation, such as testicular torsion or incarcerated hernia. If the appendix is severely adherent to the inguinal region, forcefully returning the appendix may rupture it, contaminating the abdominal cavity and aggravating the infection. Therefore, traditional surgical intervention may be required to separate the adhesions, remove pus, resect the appendix, and ligate the hernia sac at a high level.[22] Laparoscopy is recommended for the following reasons: (1) observation of the abdominal cavity for pus accumulation or inflammatory exudates, (2) clear diagnosis and identification of the inflamed appendix, and (3) examination of the contralateral internal ring. In this study, two patients with Amyand's hernia were born prematurely and had low birth weights; they underwent traditional inguinal surgery rather than laparoscopic exploration.

Laboratory examination of acute appendicitis in children is primarily characterized by elevated non-specific inflammatory markers, such as white blood cell count, neutrophil percentage, and CRP level.[23] However, 17 and 13 patients in this study had normal and decreased WBC counts and neutrophil percentages, respectively, possibly related to their weak resistance and severe infections. Diagnosing NA using abdominal radiography is challenging; however, the analysis may reveal findings consistent with those indicating other intra-abdominal lesions or complications. A gas shadow below the diaphragm indicates a surgical requirement and can effectively guide clinical management. The American College of Radiology recommends ultrasonography as the first test for diagnosing acute appendicitis, currently used mainly in children aged 5–12 years.[24] Direct signs of ultrasound diagnosis of NA include the outer diameter of the appendix, thickness of the outer wall of the appendix, blood flow, continuity, and fluid in the appendix lumen. When typical direct signs of the appendix are lacking in neonates owing to its anatomical features, attention should be paid to the indirect signs,[25] including fluid accumulation in the right lower abdomen, thickened echogenic enhancement of the greater omentum in the right lower abdomen, and enlarged mesenteric lymph nodes in the right lower abdomen.[26] Additionally, observing the morphologies of the intestine and colon to differentiate NA from NEC is essential. Among the 65 patients who underwent abdominal ultrasonography in this study, 43 (66.2%) had definite appendiceal abnormalities, and 10 (15.4%) had right lower abdominal adhesive masses. Laboratory tests and imaging examinations for NA lack specificity. Hence, a diagnosis should be considered with clinical manifestations.

Most scholars recommend immediate appendectomy for NA and that dissection or laparoscopic exploration is feasible when appendicitis is suspected early.[13,21,27] Owing to the complexity of early diagnosis and rapid NA progression, most cases involve perforation at diagnosis, with heavy peri-appendiceal adhesions and appendiceal abscesses, making surgical resection challenging.[28] No significant differences existed in sex, age at onset, admission weight, birth weight, preterm delivery rate, or hospitalization time between both groups of patients in this study. However, a significant difference was observed in the parenteral administration duration.

Furthermore, the clinical diagnosis and treatment plan for NA are based on a comprehensive assessment of symptoms, abdominal signs, infection indicators, and abdominal ultrasound findings. Infection indicators and abdominal ultrasound findings should be monitored during conservative treatment, and surgery should be promptly performed if they worsen. If excessive abdominal pus is observed, ultrasound-guided laparotomy can help patients recover faster. The same therapeutic results can be obtained with conservative treatment if the patient's condition is stable.

The causative agents of NA are mostly gram-negative bacteria, primarily *Klebsiella pneumoniae* and *Escherichia coli*.[29] When NA is clinically suspected, broad-spectrum antibiotic therapy should be administered early. Our medication experience suggests administering third-generation cephalosporins or meropenem and metronidazole before obtaining drug sensitivity results and adjusting based on the results. In our grouping, 25 patients had blood cultures, and 12 had pus cultures; however, only 5 tested positive. The

low positivity rate was related to the early administration of broad-spectrum antibiotics.

Karaman et al.[13] summarized the prognosis of NA in the last century, dividing it into three periods: 1901–1975, 1976–1984, and 1985–2000. The perforation rates (73%, 70%, and 82%) were similar during the three periods, while the mortality rates (78%, 33%, and 28%) decreased. Only two deaths occurred in this study, possibly attributed to rapid advances in antibiotics and surgical treatment.

This study has some limitations. First, we included cases confirmed via surgery and/or ultrasound because pathological specimens were unavailable preoperatively for patients who received non-surgical treatments. However, a pathological examination is considered the gold standard method for diagnosing appendicitis. Additionally, some studies have reported a moderate agreement between intraoperative and histopathological examinations to diagnose appendicitis in children.[30–32] Second, this study spanned a long period, and the timing of surgery and the surgeon's skill level affected the postoperative outcomes. Additionally, some patients with combined Hirschsprung disease underwent enterostomy simultaneously with appendectomy, which could be confounding for the parenteral nutrition time variable. Third, this was a retrospective study where information was extracted from medical records. The long-term follow-up information was insufficient to explore further the sequelae and esthetic results of the intervention. Therefore, further studies are anticipated.

In conclusion, NA is a rare neonatal disease easily misdiagnosed and missed because of its atypical clinical symptoms and signs. Abdominal ultrasonography may aid in the diagnosis. In addition, correct and reasonable treatment plans can improve the prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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