



Acute Appendicitis and Enterobiasis: More Than A Coincidence?

Akut Apandisit ve Enterobiasis: Bir Tesadüften Fazlası mı?

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Abstract

Objective: Acute appendicitis (AA) and enterobiasis are common problems of the childhood. The relationship between two incidents have been controversial. The purpose of this study was to document the rate and features of enterobiasis in paediatric appendicitis cases of our hospital.

Material and Methods: This study was conducted in a tertiary healthcare center. Data of 15 years were presented. The study and control groups consisted of AA cases associated with and without enterobiasis were matched according to age. The information on socio-demographic, clinical, laboratory, histopathological, and radiological results were collected from on call surveys and hospital record system. The statistical analyses were performed by statistical package program software.

Results: The rate of enterobiasis was 1.6% (n= 53). Lower ultrasonographic appendiceal diameter, acute phase response and higher eosinophil levels were the features of the study group. Lymphoid hyperplasia was the most frequent histopathological diagnose.

Conclusion: AA is one of the most common surgical problems in paediatric emergency, but it is rarely associated with enterobiasis. History of pruritus ani, lower signs of systemic inflammation, ultrasonographic diameter of the appendix and eosinophilia can warn the surgeon about the parasite. Anthelmintic drugs are necessary to complete the therapeutic process.

Keywords: Enterobiasis, acute appendicitis, reactive lymphoid hyperplasia, children

Öz

Giriş: Akut apandisit (AA) ve enterobiasis çocukluk çağının sık görülen sorunlarıdır. İki olay arasındaki ilişki açıklığa kavuşmamıştır. Bu çalışmanın amacı hastanemizdeki pediyatrik apandisit olgularında enterobiasis oranını ve özelliklerini ortaya koymaktır.

Gereç ve Yöntemler: Bu çalışma üçüncü basamak bir sağlık kuruluşunda gerçekleştirildi. On beş yılın verileri sunuldu. Çalışma ve kontrol grupları yaşa göre eşleştirilmiş enterobiasis ile ilişkili ve enterobiasis olmayan AA olgularından oluşturuldu. Sosyo-demografik, klinik, laboratuvar, histopatolojik, radyolojik sonuçlara ilişkin bilgiler anketlerden ve hastane kayıt sisteminden toplandı. İstatistiksel analizler istatistiksel paket program yazılımı kullanılarak yapıldı.

Bulgular: Enterobiasis oranı %1.6 (n= 53) olarak bulundu. Ultrasonografik apendiks çapının düşük olması, akut faz yanıtının düşük ve eozinofil düzeylerinin yüksek olması çalışma grubunun özellikleriydi. Lenfoid hiperplazi en sık görülen histopatolojik tanı olarak saptandı.

Sonuç: Akut apandisit, pediyatrik acillerde en sık görülen cerrahi problemlerden biridir; ancak nadiren de olsa enterobiasis ile ilişkilidir. Perianal kaşıntı öyküsü, düşük sistemik enflamasyonun belirteçleri, apendiksin ultrasonografik çapı ve eozinofili, cerrahi parazit konusunda uyarabilir. Terapötik süreci tamamlamak için antihelmintik ilaçlar gereklidir.

Anahtar Kelimeler: Enterobiasis, akut apandisit, reaktif lenfoid hiperplazi, çocuklar

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Introduction

Acute appendicitis (AA), inflammation of the appendix due to luminal obstruction, is one of the most common problems of emergency services, requiring surgical intervention worldwide (1,2). The incidence rate peaks in adolescence and females (3). It is presented with sudden, unremitting abdominal pain, nausea, vomiting, poor general condition, dehydration, tenderness in the right iliac fossa, defence, and rebound (1). Although there are many laboratory and radiological diagnostic facilities for evaluation, all should be supported by repeating physical examination and confirmed by histopathology (4). Luminal obstruction is the pathophysiological reason for AA. Thus, lymphatic drainage fails, and edema and mucosal ulceration disrupt venous circulation. Ischemic necrosis occurs at the wall of the appendix (5,6). Fecal stasis, fecaloids, tumors, bacterial, parasitic, or protozoa infections may trigger this process. Enterobiasis is one of the most popular unusual findings of appendectomy specimens (7).

Enterobius vermicularis (*E. vermicularis*; pinworm, tapeworm, threadworm, seatworm, oxyuriasis) is an obligatory nematode and responsible for the most frequent gastrointestinal parasitic infection in humans (8,9). It has a worldwide distribution affecting all population groups and geographic areas with higher incidence in low socioeconomic classes and warm climate belts. It is more common in children and people who live in close quarters with poor hygienic conditions (8-10). Examining the *Enterobius* ova under the microscope via cellophane tape or paddle test techniques are the ways of the microbiological analyses, but clinical diagnosis is more important (11). Enterobiasis infection may be asymptomatic, or present with perianal pruritus, abdominal pain, poor appetite, nausea and sleep disturbances. The parasite may be related with colitis, perianal infections, abscesses, granulomas, pelvic inflammatory disease, chronic pelvic pain or gynaecologic infections (12). During the migration through the gastrointestinal tract, it may stay in the appendix. One of the complex manifestations of *E. vermicularis* is "appendiceal colic", which is defined as the situation mimicking the clinical features of AA without histopathological findings of acute inflammation (12-15). Appendiceal colic may result in unnecessary surgical processes and rarely intra-abdominal dissemination of the parasite during surgery. In addition, antihelminthic therapy may be overlooked (16).

The role of enterobiasis in the pathogenesis of AA has been in debate since the late nineteenth century (17). The agent itself may be the trigger of luminal obstruction or the inflammatory response. Reactive lymphoid hyperplasia (LH) or mucosal invasion with inflammation of the appendix by the parasite has been reported (15,18). Authors thought that it was an incidental finding and reported that the invasion of

the agent into the appendix wall because of hypoxia occurred during appendectomy (19,20).

This study aims to document the rate of enterobiasis associated acute appendicitis (EAAA) in our hospital and analyse the clinical, laboratory, and histopathological features of these patients to compare their results with non-enterobiasis associated acute appendicitis (NEAAA) cases.

Materials and Methods

This study was conducted in a tertiary healthcare centre between January 1, 2008 and June 30, 2023. All paediatric patients aged between 0-18 years old who underwent appendectomy with a preliminary diagnosis of AA were queried through the hospital record system retrospectively. The patients' histopathological reports were reviewed for *E. vermicularis*. The study group consisted of the patients having appendectomy specimens containing the parasite whereas the members of the control group had AA without enterobiasis and operated during the same period. Two groups were matched according to age randomly. The information about socio-demographic and clinical features at the time of operation (age, sex, place of residence, number of siblings, number of household members, water supply, private room for children in the house, maternal and paternal education levels; existence of the pruritus ani, abdominal pain, nausea, vomiting, difficulty in defecation, fever at the time of hospital admission) were obtained by the structured questionnaire prepared by the researchers and filled on phone calls. The patients whose questionnaires were not fully filled were excluded. The total number of pediatric appendectomies performed during the study period based on clinical and radiologic diagnosis of AA was 3300, and the rate of enterobiasis was 1.6% (n= 53). After exclusion, 46 patients with EAAA and a control group matched according to age with NEAAA were determined. The data of 92 cases were evaluated.

Body mass indexes were calculated through hospital records and grouped according to the growth charts based on age and sex for Turkish children (Thin: < 5%; Average: 5-95%; Obese: >95%) (21). Laboratory data [initial complete blood count (CBC), C-reactive protein (CRP), serum sodium, blood urea nitrogen/ creatinine ratio (BUN/Cr)], urine density, and radiologic reports were documented and recorded through hospital's electronic data system. White blood cells (WBC), neutrophils and CRP were defined as "acute phase reactants" and analysed to identify systemic inflammatory response. Serum sodium, BUN/Cr and urine density were taken into consideration as the premonitory markers of dehydration. Serum bilirubin level was evaluated to be a follow up marker of complicated appendicitis (4,22). Ultrasonography diagnosis of AA was confirmed when the appendix was enlarged (appendiceal diameter measured ≥ 6 mm) and/or non-compressible.

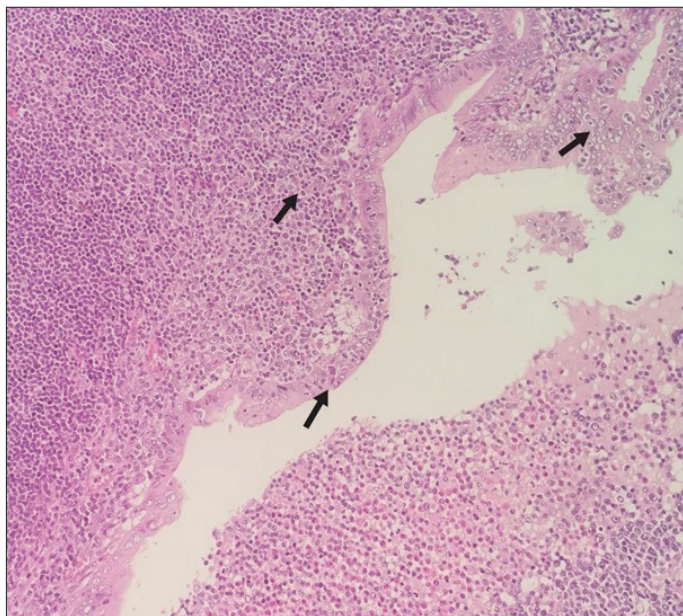


Figure 1. Hematoxylin Eosin staining, x200. Acute appendicitis: Inflammation accompanied by polymorphous nucleated leukocytes and lymphocytes progressing towards the muscularis propria layer.

All appendectomy materials were examined histologically in our hospital within a routine procedure: The specimens were fixed in 10% formalin for 24 hours and four samples of five microns thickness were dissected for evaluation. After macroscopic evaluation, Hematoxylin-eosin stained slides were examined under a microscope. Clinical diagnoses and microscopic examination results were recorded. The cases in which neutrophil infiltration was observed in the muscularis propria of the appendix were defined as "AA" histopathologically (Figure 1). The specimens of the two

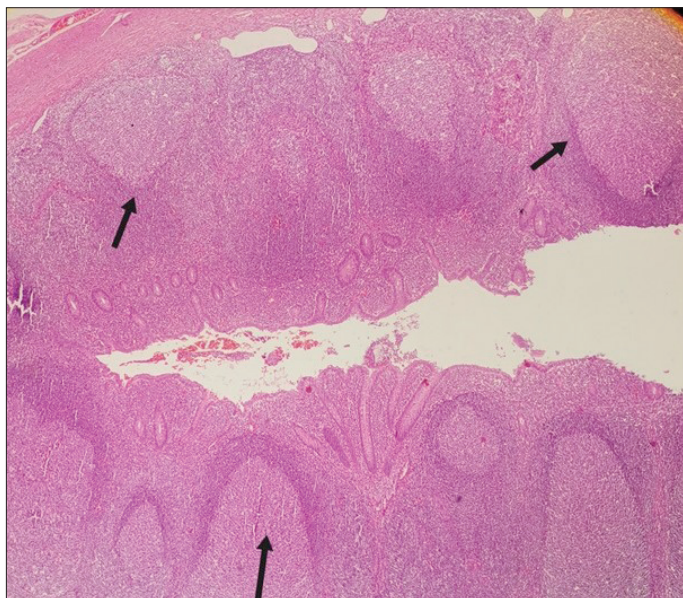


Figure 2. Hematoxylin Eosin staining, x50. Reactive lymphoid hyperplasia: Lymphoid follicles with prominent germinal centers in the muscularis propria layer (black arrow).

groups were re-evaluated and reported as LH (Figure 2), congestion, periappendicitis, hemorrhagic appendicitis, perforated appendicitis, abscess, phlegmonous appendicitis, gangrenous appendicitis, necrotizing appendicitis and *E. vermicularis* with or without peritonitis (Figure 3). The samples having hemorrhage, perforation, abscess, necrotizing, phlegmonous and/or gangrenous features were defined to be "complicated appendicitis." *E. vermicularis* cases underwent additional procedures: Histochemical staining was performed with Periodic acid- Schiff (PAS) dye to evaluate the cuticular membrane consisting of a two-layered chitin layer, thick muscle-layered esophagus, cervical alae, intestinal walls, uterus and testicular tissue of the nematode, which were pathognomonic in histopathological diagnosis of enterobiasis (Figure 4, 5).

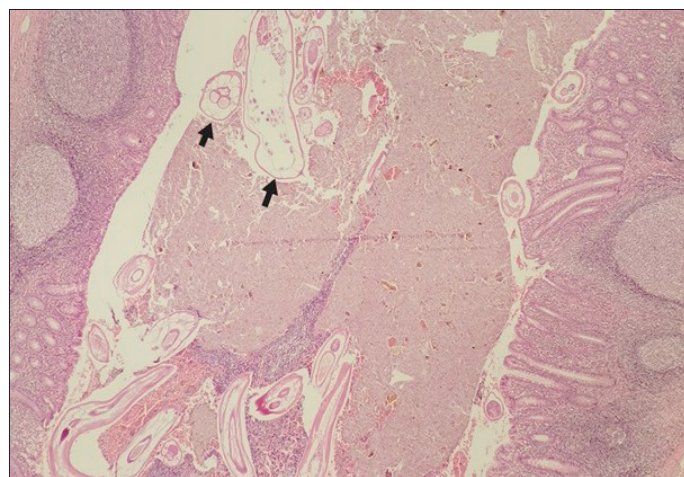


Figure 3. Hematoxylin Eosin staining, x50. Reactive lymphoid hyperplasia: Lymphoid follicles with prominent germinal centers in the muscularis propria layer. Longitudinal and horizontal section of *E. vermicularis* with the cuticular membrane consisting of two-layered chitin layer in the lumen (black arrow).



Figure 4. Hematoxylin Eosin staining, x200. Adult, male *E. vermicularis* with the cuticular membrane consisting of two-layered chitin layer (pink arrow), horizontal section, cervical alae on both sides (yellow arrow), thick muscle-layered esophagus (black arrow), testis (blue arrow) and longitudinal section of the muscular layer of the intestines.

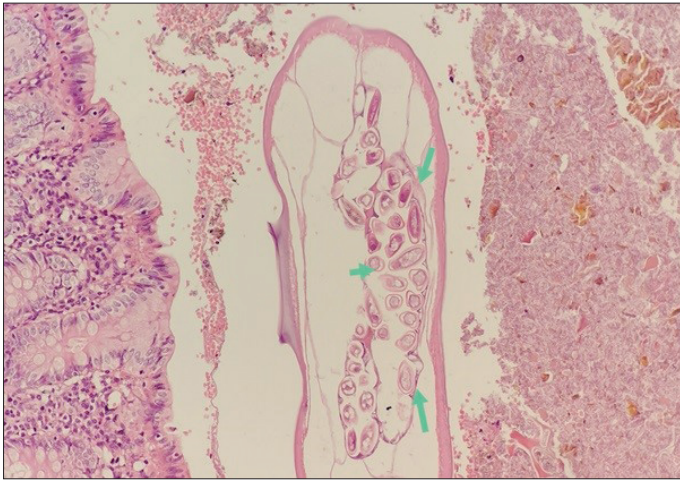


Figure 5. Hematoxylin eosin, x200. Adult, female, pregnant, *E. vermicularis* with thick hyaline outer cuticle layer, longitudinal section and numerous eggs in the uterus (green arrow).

Statistical Analysis

The analyses were performed by statistical package program software. The data were presented as percentages, frequencies, medians and minimum-maximum ranges or mean and standard deviation (SD) by descriptive statistics. Independent samples t-test was applied for the analyses of normally distributed continuous variables; whereas Mann-Whitney U or Kruskal Wallis tests were applied for the evaluation of abnormally distributed variables with Bonferroni correction when indicated. Cross-tables with chi-square test (χ^2) and Fisher's exact test were performed for the evaluation of categorical variables. Probability factor (p) less than 0.05 was regarded to be statistically significant.

The study was approved by the Ethics Committee of Non-Invasive Clinical Research of Amasya University (registration no: E-76988455-050.01.04-135458).

Results

Mean age of the whole study population was 10.15 ± 3.54 years. The sex ratio of the study and control groups was man/female: 0.84/ 0.70. The difference in sex was not statistically significant ($p= 0.84$). Most of the study group members lived in rural areas ($n= 33$; 71.7%), and 31 (67.4%) members of the control group lived in urban areas, which was statistically significant ($p< 0.0001$). The rate of high-income level was higher in the control group ($p= 0.001$). Most of the population in both groups had crowded families (number of household members ≥ 6). The frequency of children having their own room was significantly higher in the control group ($p< 0.0001$). Statistical difference was found in the water supply item ($p= 0.026$); the source of water supply was mains water in 84.8% ($n= 39$) of the control group whereas 34.8% ($n= 16$) of the study group had spring water. The frequency of enterobiasis

decreased significantly while the education levels of the parents increased ($p< 0.0001$).

The data on symptoms before appendectomy were obtained from the parental on call surveys. Abdominal pain and nausea were the most common symptoms in both groups without a statistical difference ($p= 0.39$, $p= 0.38$; respectively). Pruritus ani presence was significantly higher in the study group ($p< 0.0001$). Vomiting, difficulty in defecation and fever were more frequent in the control group ($p< 0.0001$; $p< 0.0001$; $p< 0.0001$, respectively). Prevalence of growth retardation (Body mass index $< 5\%$) was significantly higher in the study group [39.1% ($n= 18$) vs. 10.9% ($n= 5$); $p< 0.0001$].

Approximately half of the patients ($n= 50$; 53.4%) had radiological evaluation while the rest went through surgery on clinical diagnosis. The rate of AA was higher in the study group (32.6%; $n= 15$ vs. 19.6%; $n= 9$), which was statistically significant ($p= 0.001$). In addition, only one patient (2.2%) was diagnosed as "normal" in the control group; but the report of 10.9% ($n= 5$) of the study group was "normal", which was a significant result ($p< 0.0001$). The appendiceal diameter was higher and statistically confirmed in the control group (9.05 ± 2.60 vs. 6.50 ± 1.12 ; $p= 0.002$).

The average of WBC and neutrophils in CBC were higher in the control group [$14530 \pm 5900/\text{mm}^3$; $10500/\text{mm}^3$ (1500-29300), respectively]. In addition, median of CRP levels was 1.67 mg/dL (0.5-89.9) in the study group and 12.5 mg/dL (0.25-172.8) in the control group. Elevation of acute phase reactants (WBC, neutrophils, CRP) was significantly lower in the enterobiasis group ($p= 0.002$; $p= 0.005$; $p< 0.0001$, respectively) whereas the median of eosinophils was higher ($100/\text{mm}^3$ vs. $50/\text{mm}^3$; $p= 0.004$). There was no statistical significance in serum BUN/Cr, bilirubin, sodium and urine density levels between the groups.

LH, which is thought to be reactive, was the most frequent histopathological diagnosis in the appendectomy specimens containing *E. vermicularis* ($n= 27$; 58.7%). The rate of complicated appendicitis was 73.9% ($n= 34$) in the control group and LH was not detected. The rates of LH, AA and complicated appendicitis were different statistically between the groups ($p< 0.0001$). Socio-demographic, laboratory, radiologic and histopathological features of the groups are summarized in Table 1.

Discussion

E. vermicularis is a nematode requiring a human host and completing its life cycle usually in the different parts of the gastrointestinal tract. During its migration, when it visits the appendix, it may cause "appendiceal colic" and the story ends with appendectomy.

Table 1. Clinical, socio-demographic, laboratory, radiological and histopathological features of the patients

	Study Group (Enterobiasis)	Control Group (Non-enterobiasis)	p
Sex	Male/Female (n= 21; 45.7% / n= 25; 54.3%)	Male/Female (n= 19; 41.3% / n= 27; 58.7%)	0.84
Number of siblings	2 (1-5)	2 (1-4)	0.55
Residence			<0.0001
Urban area	19.6% (n= 9)	67.4% (n= 31)	
Rural area	71.7% (n= 33)	32.6% (n= 15)	
Income level			0.001
Low	26% (n= 12)	17.4% (n= 8)	
Intermediate	58.7% (n= 27)	50.0% (n= 23)	
High	4.3% (n= 2)	32.6% (n= 15)	
Household members			0.310
<6	19.6% (n= 9)	26.1% (n= 12)	
≥6	80.4% (n= 37)	73.9% (n= 34)	
Water supply			0.026
Mains water	65.2% (n= 30)	84.8% (n= 39)	
Spring water	34.8% (n= 16)	15.2% (n= 7)	
A private room for children			<0.0001
Yes	36.1% (n= 22)	84.8% (n= 39)	
No	63.9% (n= 24)	15.2% (n= 7)	
Maternal education			<0.0001
Primary education	45.7% (n= 21)	13% (n= 6)	
Secondary education	43.5% (n= 20)	41.3% (n= 19)	
High education	10.9% (n= 5)	45.7% (n= 21)	
Paternal education			<0.0001
Primary education	50.0% (n= 23)	13% (n= 6)	
Secondary education	37.0% (n= 17)	39.1% (n= 18)	
Higher education	13.0% (n= 6)	47.8% (n= 22)	
Body mass index			<0.0001
<5%	39.1% (n= 18)	10.9% (n= 5)	
5-95%	52.2% (n= 24)	52.2% (n= 24)	
>95%	8.7% (n= 4)	37% (n= 17)	
Pruritus ani			<0.0001
Yes	78.3% (n= 36)	10.9% (n= 5)	
No	21.7% (n= 10)	89.1% (n= 41)	
Abdominal pain			0.39
Yes	80.4% (n= 37)	84.8% (n= 39)	
No	19.6% (n= 9)	15.2% (n= 7)	
Nausea			0.38
Yes	82.6% (n= 38)	87.0% (n= 40)	
No	17.4% (n= 8)	13.0% (n= 6)	
Vomiting			<0.0001
Yes	21.7% (n= 10)	80.4% (n= 37)	
No	78.3% (n= 36)	19.6% (n= 9)	
Difficulty in defecation			<0.0001
Yes	21.7% (n= 10)	89.1% (n= 41)	
No	78.3% (n= 36)	10.9% (n= 5)	
Fever (≥38 °C)			<0.0001
Yes	17.4% (n= 8)	76.1% (n= 35)	
No	77.6% (n= 38)	22.4% (n= 11)	
WBC (/mm ³) (mean ± SD)	11240 ± 4030	14530 ± 5900	0.002
Neutrophils (min-max)	8590 (1790-17840)	10500 (1500-29300)	0.005
Lymphocytes (/mm ³)	2100 ± 980	2200 ± 1110	0.655

Table 1. Clinical, socio-demographic, laboratory, radiological and histopathological features of the patients (continue)

	Study Group (Enterobiasis)	Control Group (Non-enterobiasis)	p
Eosinophils (/mm ³)	100 (0-800)	50 (0-410)	0.004
Neutrophils (%)	71.3 (4.67-94.5)	78.1 (32.8-92.3)	0.256
Lymphocytes (%)	20 (5-50)	13.1 (4.4-55.5)	0.064
Eosinophils (%)	1 (0-9.2)	0.15 (0-3.6)	<0.0001
CRP (mg/dL)	1.67 (0.5-89.9)	12.5 (0.25-172.8)	<0.0001
Bilirubin (mg/dL)	0.38 (0-1.21)	0.15 (0.15-1.6)	0.30
BUN/Creatinine	40.24 ± 20.91	48.04 ± 17.69	0.06
Sodium (mEq/mL)	137 (121-144)	137 (131-145)	0.584
Urine density	1020 (1010-1030)	1018 (1001-1065)	0.819
Ultrasonographic appendix diameter	6.5 ± 1.12	9.05 ± 2.60	0.002
Ultrasonographic diagnosis			
AA	19.6%; n= 9	32.6%; n= 15	0.001
Normal	10.9%; n= 5	2.2%; n= 1	<0.0001
Histopathological evaluation			
AA	37.9%; n= 17	26.1%; n= 12	
Complicated appendicitis	4.3% n= 2	73.9%; n= 34	
Reactive lymphoid hyperplasia	58.7%; n= 27	0%; n= 0	<0.0001

SD: Standard deviation, WBC: White blood cell, CRP: C-reactive protein, BUN: Blood urea nitrogen.

The rate of appendiceal enterobiasis in children of our hospital during the study period was 1.6%, which was compatible with the literature. Most of the study group members were from rural areas and low or intermediate socioeconomic levels having unsanitary water supply. The education levels of the parents were lower in the study group. Vomiting, difficulty in defecation, and fever, which are symptoms pointing to a salient surgical problem, were more common in the control group; whereas pruritus ani and growth retardation prevalences were higher in the study group, as expected. Lower ultrasonographic appendiceal diameter, WBC, neutrophil, CRP and higher eosinophil levels were the features of the study group. The rate of complicated appendicitis was lower in the study group and LH was the most frequent histopathological diagnosis.

In a systematic review, a total of 103195 appendicitis cases were evaluated for *E. vermicularis* infestation, of which 2983 (2.89%) patients were positive (23). The rate of *E. vermicularis* was reported to be 1.5-3% in Türkiye in the same study (23). Enterobiasis in appendicitis was declared to be 7.69%-80% in some other reports focusing on the role of parasitic infections in AA (12,15,24-26). The rate of enterobiasis was inversely proportional with income levels, which was also compatible with our results (23). The results on the statistical significance of sex varied in the literature; the rate of enterobiasis was higher in girls and boys in different reports (12,19,27). The prevalence of infestation was higher in rural area residents, compatible with some reports (27). Low education levels, crowded household members, and water supply with poor

sanitation conditions are known risk factors in parasitic infestations as reported in our study (28). The parasite has a worldwide distribution affecting all population groups and geographic areas, therefore the results of studies about socio-demographic features may vary (23).

AA is a surgical diagnosis based on clinical suspicion (1). Pruritus ani is an expected symptom in enterobiasis, as in our results; however, reports on other gastrointestinal symptoms such as vomiting, fever, difficulty in defecation have different conclusions (19,25). This may be because of the evaluation of different populations. In fact, it is impossible to predict EAAA just by considering clinical complaints.

Radiological evaluation usually provides confirmation of AA. Ultrasonography is reported to be more reliable than other laboratory tests for confirmation or exclusion (29). However, ultrasonography or other imaging diagnostic techniques are not reliable to diagnose EAAA (25). In our population, the rate of AA diagnosis and appendicular diameter were lower in the EAAA group, compatible with the literature (25).

Elevated WBC, neutrophil and CRP levels establish positive acute phase response pointing to systemic inflammation. In our study, compatible with the literature, NEAAA cases had higher acute phase responses (19,25). Eosinophilia is expected to be related to parasitic infections, and eosinophil counts were higher in the EAAA group in our study (19). However, results of some reports were different, pointing no relationship with eosinophilia and enterobiasis (25,30). Serum sodium, BUN/Cr and urine density were analysed to confirm dehydration, no statistical difference between the groups

was found. There was no study focusing on these parameters in the literature. Serum bilirubin level has been reported to be a follow up marker of complicated appendicitis in the literature (4,22). In our study, the results were analysed and no difference between the groups was detected although the rate of complicated cases was higher in the control group (31,32).

The appendix is a lymphoid organ that ends with a blind space, and therefore, LH is a common finding in appendectomy specimens, as in this study. Pehlivanoglu et al. reported LH in all EAAA cases of their study and concluded that *E. vermicularis* was not a reason of AA (33). There are reports pointing to enterobiasis as the etiologic agent of acute inflammation or incidental finding, but determining its role in AA is impossible because of low number of cases and non-homogeneous study groups and designs (19,34). In this study group, the rate of AA was 37.9%, so it is also difficult to define the role of *E. vermicularis* in AA due to our results. However, increased intraluminal pressure of appendix may result in appendicitis by any reason, and enterobiasis may be one of the reasons of this pathological process.

This study has several limitations: it has a retrospective nature and small sample size that may not let us come to definite conclusion. Although our results note the differences and similarities between EAAA and NEAAA, the data are based on hospital records and questionnaire answers of the parents which may have memory bias. Data from physical examinations were not detailed properly. The surgical procedures were not mentioned. The sample size is small, but it is still one of the large paediatric series in the literature mentioning clinical, hematologic, biochemical, radiologic, and histopathological data from a holistic point of paediatric view. Preoperative diagnosis is challenging because AA is one of the most common surgical problems, but EAAA in these cases is rare. The history of pruritus ani, lower markers of systemic inflammation, appendiceal diameter and higher eosinophilia can be alarming for the surgeon about the parasite. At this point, medical therapy by anthelmintic drugs and whole family therapy must be taken in consideration to complete the therapeutic process.

Ethics Committee Approval: This study has been approved by the Non-Interventional Clinical Research Ethics Committee of Amasya University Rectorate (Decision no: 2023/89, Date: 13.06.2023).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - All of authors; Design - All of authors; Supervision - All of authors; Resource - All of authors; Data Collection and/or processing - FZÖ; Analysis and/or interpretation - GC; Literature search - All of authors; Writing - GC; Critical review - All of authors.

Conflict of Interest: All authors declare that they have no conflict of interest.

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