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Original Article

What are the Risk Factors Responsible for the Delay in Diagnosis of Acute Appendicitis in Children? Eleven-year Research from a Single Institution

Katerina Kambouri[1], Maria Aggelidou[1], Savvas Deftereos[2], Aggelos Tsalkidis[3], George Vaos[4], Michail Pitiakoudis[5]

[1] *Department of Paediatric Surgery, Faculty of Medicine, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Greece*
[2] *Department of Radiology, Faculty of Medicine, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Greece*
[3] *Department of Paediatrics, Faculty of Medicine, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Greece*
[4] *Department of Paediatric Surgery, Attikon University Hospital, Athens University, Athens, Greece.*
[5] *Department of Surgery, Faculty of Medicine, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Greece*

Corresponding author: Katerina Kambouri, Faculty of Medicine, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Dragana, 68100 Alexandroupoli, Greece; E-mail: kampouri@med.duth.gr; Tel: +302551351552

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Introduction: We conducted a retrospective analysis of 602 children operated on for acute appendicitis (AA) in our department between January 2007 and December 2017.

Aim: The aim of this study was to identify factors that are related to a delay in diagnosing AA in children. Furthermore, we'd like to strengthen our previous preliminary results by a) adding gender as a new factor and b) studying a much larger population.

Materials and methods: The time that elapsed from the onset of symptoms to the surgical intervention was associated with gender, age, obesity, use of antibiotics prior to diagnosis, and the initial examination by a paediatric surgeon or another physician. Univariate and multivariate logistic regression method (backward method) was applied.

Results: The diagnosis of AA was delayed by at least 48 hours in 287 patients (group A, 47.7%) and was made within 48 hours in 315 patients (group B, 52.3%). In multivariate model we noticed that boys who were examined by a paediatric surgeon and didn't take antibiotics had decreased odds of having length of diagnostic period >48 hours, girls who received antibiotics compared to girls who do not use antibiotics are almost 12 times more likely to have length of diagnostic period >48 hours, the very young age has a main effect on the diagnostic delay and girls who have been examined by other physician compared to females who have been examined by paediatric surgeon have decreased odds of having length of diagnostic period >48 hours.

Conclusions: Therefore, physicians examining children with abdominal pain must keep in mind the multiple causes of diagnostic delay that may exist alone or in combination, and which can lead to serious complications and lengthen the hospital stay. Performing repeated examinations and asking for advice from a specialist specifically for children who are a special category of patients, in areas where it is rather impossible to use imaging techniques, could be the key to correctly diagnosing and treating AA.

Key words:

risk factors, delay, acute appendicitis, diagnosis, children

INTRODUCTION

Abdominal pain is extremely common in children and may reflect a variety of conditions.[1] The most common cause of acute abdomen in children is acute appendicitis (AA), but its diagnosis has many difficulties.[2] A delay in diagnosis and surgery of AA is often associated with a more advanced stage of disease, complications, increased length of hospital stay and higher morbidity.[3]

Previous studies have revealed clinical and laboratory signs of appendix perforation in children with more than 48 hours delay of diagnosis after AA onset. However, the possible reasons for the delay in diagnosis and treatment of AA in children have not been clarified.[3,4] In a previous study we showed our preliminary results of the possible factors which individually or in combination influence the timely diagnosis of AA in childhood, but we had limited number of patients in this series.[5] The aim of this study was to strengthen our previous findings by a) adding gender as a new factor and b) studying a much larger population.

MATERIALS AND METHODS

Between January 2007 and December 2017, 602 patients (343 boys) aged 1.5 to 14 years (mean age: 9.2 years) underwent emergency appendectomy for AA in our department. All children had positive histological findings for AA. Children without positive histological findings were excluded from this study. Data were collected from the medical records of the patients, with a focus on the time that elapsed from the onset of symptoms to surgery, operative findings, gender (male), age (≤5 or >5 years), the presence of obesity (body mass index >95th percentile), the use of antibiotics prior to diagnosis, and the initial examination being performed by a paediatric surgeon or other physician (general practitioner, general surgeon or paediatrician).

Patients were allocated into two groups by length of diagnostic period as follows: >48 hours (group A) and <48 hours (group B). The diagnostic period is the time between first complaints and the definitive diagnosis, and its duration was associated with the following factors both individually and in combination: gender, age, obesity, use of antibiotics prior to diagnosis, and the initial examination being performed by a paediatric surgeon or another physician. The diagnosis was assisted by ultrasonography in the most confusing cases, which were mostly obese patients.

In order to investigate the factors associated with the length of diagnosis, univariate and multivariate logistic regression method (backward method) was applied. Also, the Odds Ratio (OR) and the Confident Intervals (CI) of the ORs of each factor separately or in combination were estimated. All the statistical tests were performed at the statistical significance level of 5%. Data were analysed using SPSS software, version 22 (Statistical Package for Social Sciences Inc., 2003, Chicago, USA).

RESULTS

The definitive diagnosis was delayed by >48 hours in group A (n=287, 47.7%), in which the operative findings were gangrenous appendicitis, general peritonitis and appendiceal mass. The diagnostic period was <48 hours in group B (315 patients, 52.3%), in which the operative findings were inflamed or purulent appendicitis and local peritonitis.

In group A, the boys were 153 (53.31%) and the girls - 134 (46.69%), while in group B the boys were 190(60.3%) and the girls were 125 (39.7%) (p=0.083). (**Tables 1, 2**).

The age distribution differed markedly between the two groups: 99 (34.5%) and 33 (10.5%) children were aged 1.5–5.0 years in groups A and B, respectively (p<0.001) (**Tables 1, 2**).

Children with body mass index >95th percentile were 80 (279%) and 58 (18.4%) in groups A and B, respectively (p=0.006). (**Tables 1, 2**).

The initial diagnosis was gastroenteritis in 75 patients (26.13%) in group A (of which 57 were younger than 5 years), urinary tract infection in 20 (6.97%), bronchopulmonary infection in 19 (6.62%) and constipation in 4 (1.39%).

Due to an incorrect initial diagnosis (urinary tract or bronchopulmonary infection or other unrecognized reasons), antibiotic treatment was administered for more than 24 hours in 71 (24.74%) and 28 (8.89%) of the children in groups A and B, respectively (p<0.001) (**Table 1**). The initial examination was performed by a non-paediatric surgeon in 197 (68.6%) and 176 (55.9%) children in groups A and B, respectively (p=0.001) (**Tables 1, 2**).

Each of the examined risk factors contributed to the diagnostic delay with a different loading factor when examined separately. The factors with the most pronounced effect were the younger age (p<0.001) and the antibiotic treatment (p<0.001), followed by the initial examination being performed by a non-paediatric surgeon, (p=0.001) and obesity (p=0.006). The gender (male) was not a statistically significant factor when it was examined separately (p=0.083) (**Table 2**). During data analysis, a common practice is to include in multivariate analysis only those variables that are statistically significant in univariate analysis. Such a habit is risky as some variables that are not significant in univariate analysis may become significant in multivariate analysis.[6] Moreover, as gender is a biological factor it was necessary to be included in the multivariate analysis. When we kept the gender in the multivariate analysis, we noticed that it was a statistically significant factor and probably other factors interacted with it.

After we examined all the main effects with interactions, multivariate binary logistic regression with backward method was employed to predict the probability that a participant would have length of diagnostic period >48 hours. As shown in **Table 3**, the predictor variables which were included finally in the model were "Gender", "Age", "Antibiotics", "Initial Examination", "Gender* Antibiotics" and "Gender* Initial Examination".

We concluded with all the interactions of the model with the following results:

Males compared to females, who did not use antibiotics and were examined by a paediatric surgeon had decreased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=0.25, p-value<0.001).

Participants aged "≤5 years" compared to participants aged ">5 years" had increased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=3.77, p-value<0.001).

Females that used antibiotics compared to females that did not use antibiotics had increased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=11.89, p-value<0.001).

Females who were examined by other physician compared to females who were examined by a paediatric surgeon had decreased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=0.38, p-value=0.001).

Males compared to females who did not use antibiotics had increased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=0.25*5.84=1.46).

Males compared to females who used antibiotics had decreased odds of having the length of diagnostic period >48 hours, while holding all other variables constant (OR=0.25*0.13*5.84=0.19).

DISCUSSION

A diagnosis of AA is obvious when a child presents in the emergency department of a hospital with pain in the right lower abdominal quadrant within <24 hours that is accompanied by nausea, vomiting, low-grade temperature and local peritoneal irritation in the physical examination.[2] This situation applies to the patients in group B of the present study. However, the diagnosis of AA is often more complicated in the presence of non-specific symptoms that may delay the diagnosis for >48 hours, as in group A of this study.[7]

The reason that we added the gender in our study as the possible factor that contributes to the delay diagnosis of AA is that in the literature males seem to suffer from AA more often than females with rates of 1.5-2.9:1.[8,9] Furthermore, in several appendicitis scores males appear to be among the prognostic factors of AA.[10,11] In our study in univariate analysis the gender was not a statistical significant factor for the delay of diagnosis but in multivariate it was, probably as a biological factor interacted with all the other examining factors. However, in multivariate analysis of our results we noticed that boys compared to girls that did not receive antibiotics and were examined by a paediatric surgeon had decreased odds of having length of diagnostic period >48 hours, while holding all other variables constant (OR=0.25, p-value<0.001). In contrast, the girls who have been examined by other physician compared to girls who have been examined by paediatric surgeon had decreased odds of having the length of diagnostic period >48 hours, holding all other variables constant (OR=0.38, p-value=0.001). In this respect we could speculate that girls were more social, descriptive and perhaps cooperative during the examination than boys and this could help the first doctor that examined them to have more accurate diagnosis. This possibility could be confirmed only after further examination.

A diagnosis of appendicitis becomes more difficult when the child is younger than 5 years. In this study, a very young age was a definite factor in delayed diagnosis of AA (**Tables 1, 3**). Both the physician and patient normally bear responsibility for the correct diagnosis and appropriate management of AA, but the very young patients cannot recognize that their symptoms are abnormal and seek medical evaluation. The symptoms of appendicitis in very young children can be ignored even by the parents for a prolonged period of time due to the communication inability. Frequently these children are referred initially to a paediatrician, which proves that the clinical picture in this group is often not indicative of classical appendicitis.[2] These children usually present with complicated appendicitis (as in our study), with the increasing frequency being in very young patients with the longer duration of symptoms.[12] We found that the initial diagnosis in 75 patients in group A was gastroenteritis, 57 of which were younger than 5 years. Diarrhoea is a common symptom in AA, especially in very young children, which can confuse the physician and delay the correct diagnosis.[13] Most of the very young patients in our study had to be admitted in the paediatric clinic because they were seriously dehydrated, and the correct diagnosis of AA was made after multiple clinical examinations. The factor of young age was proved as very powerful in our study with a statistical significance difference.

Another factor that contributed strongly to the delay in diagnosing AA in our study was use of antibiotic treatment prior to the diagnosis. It is currently unclear whether previous antibiotic treatment causes the delay in the diagnosis and treatment of AA. Children who present with abdominal pain receive antibiotics empirically due to a suspected diagnosis of urinary tract infection or pneumonia. A North American study of preschool children with appendicitis found that 57% of them had been seen at an earlier stage in their illness and treated with antibiotics, antipyretics or antihistamines. This resulted in a perforation rate of 83%, compared to one of 36% among children who had been referred directly.[14,15] On the other hand, Landes et al. found that the rates of nausea, rebound tenderness, and elevated temperature and white cell count were lower among 11 patients with appendicitis aged 18–27 years and who had been taking tetracycline for acne for at least 1 month, than among 100 patients also presenting with appendicitis but not taking antibiotics. The overall perforation rate was 7% in that study, and the authors suggested that antibiotics could have reduced the perforation rate.[16] In the present study, antibiotic treatment was administered for more than

Table 1. Characteristics of participants (N=602)

	Length of diagnostic period >48 hours (Group A)		Length of diagnostic period <48 hours (Group B)		Total	
	N=287 (47.7%)		N=315 (52.3%)		N=602	
	N	%	N	%	N	%
Gender						
Male	153	53.3	190	60.3	343	57.0
Female	134	46.7	125	39.7	259	43.0
Age (years)						
≤ 5	99	34.5	33	10.5	132	21.9
>5	188	65.5	282	89.5	470	78.1
Obesity						
Yes	80	27.9	58	18.4	138	22.9
No	207	72.1	257	81.6	464	77.1
Antibiotics						
Used antibiotics	71	24.7	28	8.9	99	16.4
Did not use antibiotics	216	75.3	287	91.1	503	83.6
Initial examination						
Other physicians	197	68.6	176	55.9	373	62.0
Paediatric surgeon	90	31.4	139	44.1	229	38.0

24 hours in 71 and 28 children in groups A and B, respectively. The use of antibiotics individually or as a combined risk factor in some cases significantly affected the delay of diagnosis and the course of the disease in our study. We noticed that females who do use antibiotics compared to females who do not use antibiotics are almost 12 times more likely to have length of diagnostic period >48 hours. In contrast, males compared to females who do not use antibiotics had increased odds of having length of diagnostic period >48 hours, and males compared to females who use antibiotics had decreased odds of having length of diagnostic period >48 hours. This fact does not make clear whether in boys the use of antibiotics plays a role in the delaying of diagnosis of AA and agrees with some articles claiming that the use of antibiotics does not lengthen the course of the disease.[16] We suggest to physicians who examine children with abdominal pain who received antibiotics to be particularly careful before excluding the diagnosis of AA.

The same problem of diagnostic delay was present in the obese children in our study, but this risk factor had a weaker effect. In multivariate analysis of our study this factor didn't participate in the final model probably because it was covered by other factors. During the past 2 decades, the incidence of childhood obesity has been increased at alarming rates throughout the world.[17] Obesity is associated with various physiological changes that may impair how a patient responds to surgery.[18] Many of the distinctive physical findings of appendicitis are unreliable or difficult to reproduce in these patients. The increasing rates of childhood obesity mean that paediatric surgeons must appreciate differences in the management and outcomes of these patients. It is well known that abdominal examinations of patients with obesity may be deceiving, even in cases of an acute abdomen. Some of the obese children in our study had been seen by a physician and discharged home because the diagnosis was based solely on a physical examination, resulting in subsequent return with more advanced disease. Because of the variability of the findings of physical examinations in many of our obese children, the diagnosis of AA relied on imaging studies, especially ultrasonography. This may explain why obesity was a less determinate risk factor in the diagnostic delay of AA in our study.

The use of ultrasound to diagnose appendicitis in pediatric patients has been growing with the improvement of ultrasound (US) technology and operator skills. The experienced Radiologists and/or Pediatric Radiologists have the ability to evaluate the space of lower right quadrant using the appropriate transducers and making maneuvers

Table 2. The univariate binary logistic regression

	β	Crude OR (95% CI)	p-value
Gender			
Male	-0.29	0.75(0.55-1.04)	0.083
Female	Reference category		
Age (years)			
≤ 5	1.50	4.5(2.91-6.95)	<0.001*
> 5	Reference category		
Obesity			
Yes	0.54	1.71(1.17-2.52)	0.006*
No	Reference category		
Antibiotics			
Used antibiotics	1.22	3.37(2.10-5.40)	<0.001*
Did not use antibiotcs	Reference category		
Initial examination			
Other physician	0.55	1.73(1.24-2.42)	0.001*
Paediatric surgeon	Reference category		

OR: odds ratio, CI: confidence interval, *p<0.05

to reveal the retrocecal positioned appendix and the possible acute appendicitis in obese and overweight pediatric patients. Besides, a lower diagnostic accuracy in the obese children (83%) than in lean counterparts (93%) has been reported.[19] Radiologists must be capable of giving an accurate diagnosis and this can only be achieved with training and experience. US must be a collaboration of physicians of many disciplines (e.g. radiologists, pediatricians, pediatric surgeons, emergency medicine) and US findings must be interpreted in conjunction with clinical evaluation. In our hospital although there is a pediatric surgery clinic there is not a pediatric radiologist department and our experienced pediatric radiologist is only one doctor. So it isn't possible for every child with abdominal pain to be evaluated with US.

Furthermore, most of the children presenting to our hospital are referred by other regional hospitals without pediatric surgeons so the first evaluation and/or admission is made by non-specialists. So we considered another risk factor that contributes to diagnostic delay and this was the initial examination performed by a non-paediatric surgeon. In many cases patients reside far from a hospital with paediatric surgery facilities or it is easier for parents to first visit a paediatrician. In our study, the initial examination being performed by a non-paediatric surgeon was also a statistically significant factor for the delay in diagnosing AA in multivariate analysis. This indicates that diagnosing AA is very difficult when the initial examination of a child is performed by a non-specialist or in some cases the child's sociability or the behavior of the doctor to the child may play a role in making a correct diagnosis.

It is therefore very important for the physician who initially evaluates a patient with an acute abdominal pain to admit him or her in the hospital, when he is not sure about the diagnosis or instruct the parents to return with the patient to be re-evaluated if the symptoms progress. Performing repeated examinations over time is the key element in making the diagnosis in a patient whose initial examination is not diagnostic.[20] It should be explained to the parents of very young patients that the initial symptoms of appendicitis are non-specific, especially when the patient also has some of the other risk factors that we examined in this study. Our hospital covers a large region with many isolated villages with difficult access to a hospital, so we are in cooperation with the general practitioners and advise them when the patient can reliably describe symptoms, a trial of care at home with instructions to return if symptoms do not improve is reasonable. Patients should be provided with concrete and very clear instructions as to what to expect and when to return for a repeat evaluation. If patients are not reliable or may not be able to follow instructions, or live far from a surgical center, they should be admitted to

Table 3. The final model based on multivariate binary logistic regression with backward method

	β	Adjusted OR (95% CI)	p-value
Constant	0.32	1.37	0.174
Gender			
Male	-1.41	0.25 (0.14-0.44)	<0.001*
Female	Reference category		
Age (years)			
≤ 5	1.33	3.77 (2.36-6.02)	<0.001*
> 5	Reference category		
Antibiotics			
Used antibiotics	2.48	11.89 (3.4-41.60)	<0.001*
Did not use antibiotics	Reference category		
Initial examination			
Other physician	-0.98	0.38 (0.21-0.67)	0.001*
Paediatric surgeon	Reference category		
Gender (Male)*Antibiotics (Use)	-2.04	0.13 (0.03-0.52)	0.004*
Gender (Male)*Initial Examination (Other Physician)	1.77	5.84 (2.78-12.27)	<0.001*

OR: odds ratio, CI: confidence interval, *p<0.05

an observation area where recurrent assessment and evaluation is possible.

Comparing the results of our previous and present study we noticed that we have many differences when the study population was increased. Especially, the examination by other physician was statistically significant in the recent study in contrast with the results of the same parameter of our previous study.[5] The additional factor, gender, appears to be implicated in the diagnosis. Finally, we conclude that the very young age has a main effect on the delay of diagnosis of AA, boys that were examined by a pediatric surgeon and didn't use antibiotics often they don't delay diagnosis and girls who used antibiotics are almost 12 times more likely to have length of diagnostic period >48 hours. Also, we found that in girls other factors may interact (as probably their social behavior) in the initial examination and we have to investigate them.

CONCLUSIONS

Diagnosing AA can still be puzzling for physicians. The development of various imaging techniques has improved our abilities in difficult cases, but the judgment and instinct of the physician are still vitally important for an early diagnosis, especially when US cannot be used. It remains a challenge to diagnose appendicitis early because the symptoms are often not typical. The multiple possible causes of a diagnostic delay as investigated in our study must be kept in mind, including that they may exist alone or in combination and can lead to serious complications and lengthen the hospital stay. Performing repeated examinations in combination with utilizing imaging techniques if possible and asking for a specialist's advice specifically for children who are a special category of patients, could be the key to correctly diagnosing and treating AA.

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Какие рисковые факторы являются ответственными за промедление в диагностике острого аппендицита у детей? Одиннадцатилетнее исследование в рамках одного учреждения.

Катерина Камбури[1], Мария Агелиду[1], Савас Дефтереос[2], Агелос Тсалкидис[3], Георге Ваос[4], Михаил Питиакудис[5]

[1]Отделение детской хирургии, Медицинский факультет, Университетская больница Александруполиса, Фракийский университет им. Демокрита, Александруполис, Греция.
[2]Клиника радиологии, Медицинский факультет, Университетская больница Александруполиса, Фракийский университет им. Демокрита, Александруполис, Греция.
[3]Клиника педиатрии, Медицинский факультет, Университетская больница Александруполиса, Фракийский университет им. Демокрита, Александруполис, Греция..
[4]Клиника детской хирургии, Афинская университетская больница, Афинский университет, Афины, Греция
[5]Хирургическая клиника, Медицинский факультет, Университетская больница Александруполиса, Фракийский университет им. Демокрита, Александруполис, Греция.

Адрес для корреспонденции:
Катерина Камбури Медицинский факультет, Университетская больница Александруполиса, Фракийский университет им. Демокрита, Драгана, 68100 Александруполис, Греция;

E-mail: kampouri@med.duth.gr;

Tel: +302551351552

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Введение: Мы провели ретроспективный анализ 602 детей, оперированных по поводу острого аппендицита (ОА) в нашем отделении в период с 1/2007 по 12/2017.

Цель: Целью данного исследования было выявление факторов, связанных с промедлением в диагностике ОА у детей. Кроме того, мы хотели подтвердить наши предыдущие предварительные результаты путём: а) добавления пола в качестве нового фактора и б) исследования гораздо большей части населения.

Материалы и методы: Время, прошедшее с момента появления симптомов до хирургического вмешательства, было сопоставлено с полом, возрастом, ожирением, введением антибиотика до постановки диагноза и первичным обследованием детским хирургом или другим врачом. Был проведён одномерный и многомерный логистический регрессионный анализ (обратный метод - backward method).

Результаты: Диагноз ОА был отсрочен как минимум на 48 часов у 287 пациентов (группа А, 47,7%) и был установлен в течение 48 часов у 315 пациентов (группа В, 52,3%). В многомерной модели мы заметили, что мальчики, которые были осмотрены детским хирургом и не принимали антибиотики, имели меньшую вероятность диагностического периода > 48 часов, у девочек, которые принимали антибиотики, вероятность диагностического периода > 48 часов была в 12 раз больше, по сравнению с теми, кто не принимал антибиотики, очень ранний возраст оказывает существенное влияние на промедление в диагностике и у девочек, которые были осмотрены другим врачом по сравнению с теми, которые были осмотрены детским хирургом, есть меньший шанс иметь продолжительность диагностического периода > 48 часов.

Выводы: Следовательно врачи, осматривающие детей с болями в животе, должны учитывать многочисленные причины промедления в диагностике, которые существуют в отдельности или в комбинации, что может привести к серьёзным осложнениям и продлить пребывание в больнице. Повторный осмотр и обращение за советом к специалисту, особенно для детей, которые относятся к особой категории пациентов, в областях, где практически невозможно использовать образную диагностику, может стать ключом к правильной диагностике и лечению ОА.