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Original Article

Impact of Family History on Acute Appendicitis – An Iraqi Study at Baghdad Teaching Hospital

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Abstract

Background: Appendicitis is one of the most common causes of the acute abdomen worldwide, but many patients present with atypical signs and symptoms. The study aimed to evaluate the impact of positive family history in the diagnosis of appendicitis in a limited diagnostic setting. **Methods:** Gender matched case control study of ratio (1:2) was carried out from July 2016 to September 2016 with a sample size of 300 patients. Cases were patients presented in surgical department with acute abdominal pain diagnosed as having appendicitis for whom appendectomy was performed, while controls were hospital based with other abdominal problems. Data was collected using a questionnaire. Primary analysis was a Chi square ($\chi 2$) test and the calculation of odds ratio (OR) for the association between final diagnosis of appendicitis and family history. **Results:** Females were 55% in both groups. Cases were younger than controls (27.05± 12.58 vs. 42.43±17.39 years). Positive family history of appendectomy was higher among cases (66%) than controls (31.5%). The diagnosis of acute appendicitis was 3.8 times higher among those with positive family history of appendectomy and abdominal pain, with a sensitivity of 66% and a specificity of 66.4%. Cases with more than one relative with family history of appendectomy, increased suspicion by 13 times when compared to those without family history. **Conclusion:** Positive family history of appendectomy in patients with acute abdominal pain and more than one relative with history of appendicitis can be considered as important parameters in the diagnosis of appendicitis in limited diagnostic setting.

Key Words: Acute Appendicitis, Family History, Risk Factor, Appendectomy, Emergency (Source: MeSH-NLM).

Introduction

The appendix is a blind muscular tube with mucosal, submucosal, muscular and serosal layers of length that varies between 7.5-10 cm and a diameter of 7-8 mm. It has the same structure of the colonic wall with more lymphoid tissue, about 200 lymphoid follicles that reach its peak during 10-30 years of age, decline after the 30s and disappear totally after 60 years of age.[1] Its importance comes from its tendency to inflame; it appears to play an immunological role by its lymphoid tissue and the production of immunoglobulins, especially immunoglobulin A (IgA).[1] 7% of the world's population has the risk of acute appendicitis throughout their lives.[1-3] In the United States 1/7-1/17 has acute appendicitis.[4]

Appendicitis can occur in any age with highest incidence in late teenage years and early adulthood (20s).[5] Pathogenic stimulation can lead to lymphoid hypertrophy and luminal obstruction.[2,6] Immature immune system/defective immunity makes the occurrence of acute appendicitis rare in the extremes of age.[6]

Appendectomy is the most common performed surgery in the emergency department; it constitutes 1-2% of all surgical operations.[7] It has a mortality rate of 0.1% that can reach 0.6% in the gangrenous type and may go above 20% in elderly as a result of the delayed diagnosis and intervention. The incidence rate among elderly is increasing, as well as the chance of complications.[8] The Diagnosis is mainly clinical.[3] Accurate pre-operative diagnosis of acute appendicitis remains difficult especially for the atypical presentation, which is found in about 30-45% of patients with acute appendicitis.[9-11] Misdiagnosis is more than 50% in elderly and children, and the chance of perforation increases with the delay of diagnosis.[12] Diagnostic tools such as ultrasound, Computed Tomography scan (CT scan), Magnetic Resonance Imaging (MRI), radiology and laparoscopy may also be needed. An Alvarado score of seven or more is strongly predictive of acute appendicitis. Alvarado scoring system is easy, simple, cheap and aids in the diagnosis of acute appendicitis when other diagnostic techniques are unavailable.[1,13] Negative appendectomy is still found, especially in a limited diagnostic setting, despite the development of diagnostic techniques.[14] It is associated with unnecessary cost and complications.[14] After 1995, there was a fall in the rate of negative appendectomies because of the CT scan and laparoscopy: in the United States, negative appendectomies had decreased from 14.7% in 1998 to 8.47% in 2007.[6,15] Appendectomy is the main management of appendicitis, even if antibiotics do the job, prophylactic appendectomy is done.[16,17] Obstruction of the lumen and infection are the main pathophysiological mechanisms.[18] Genetics has its effect on incidence as well as severity of the disease through cytokines and anti-inflammatory substances, like Interleukin-6 genes (IL6 genes), but environment seems to affect the role of genetics as in the hygiene theory. Evidence showed that Interleukin-8 (IL8), Interleukin-1B (IL1B), IL6, and Interleukin-6 Receptor (IL6R) are involved in the pathogenesis.[19,20] Complex segregation analysis supports a multifactorial or polygenic mode of heredity in about 56% of cases, with no evidence that supports the presence of a major gene.[7,21-22] Serotonin level, which has a genetic determinant, as well as electrolytes to some extent, play a role in pathogenesis.[23]

The objective of the study is to evaluate the association between acute appendicitis and family history, to detect a difference between the null hypothesis, stating that positive family history is present in all groups, and the alternative hypothesis, stating that the proportion in the case group is higher than that in the control group.

Many studies showed that there is a familial predisposition to acute appendicitis and that half the variability of acute appendicitis is due to a genetic factor. Twin studies suggested that environmental factor and genetic factor contribute to 70% and 30%, respectively, to the incidence of appendicitis.[3] Researchers concluded that a positive family history of acute appendicitis increased the potential risk in a patient even in the absence of the typical signs and symptoms.[7,24,25] These studies dealt with family history but without testing the impact of the affected relatives' number on the diagnosis. In the current study, the sensitivity

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and specificity, as well as the positive and negative predictive values of family history were compared to those of Alvarado score. This is the first study to provide such data about the Iraqi population.

As mentioned before, up to 45% of those with appendicitis have atypical presentation, and misdiagnosis may reach 50% in age extremes. These, in addition to negative appendectomy with its complications and delayed management with its mortality and morbidity rates, are more common in the limited diagnostic setting. Predictors like a family history of acute appendicitis, especially when more than one relative is affected, as well as simple diagnostic tools like the complete blood count and ultrasound, can support the clinical diagnosis.

The aim of the study is to evaluate the impact of a positive family history on the diagnosis of appendicitis in a limited diagnostic setting.

Methods

A gender-matched case-control study of a 1:2 ratio was carried out from July 2016 to September 2016 at Baghdad Teaching Hospital, Medical City Health Directorate. A convenient sample of 300 patients was used, 100 of them were present in the surgical department with acute abdominal pain (cases), for whom appendectomy was performed after the diagnosis of acute appendicitis was established, while the other 200 presented to the medical/surgical department with other abdominal problems either with/without abdominal pain (hepatic, pancreatic, gynecological, urological and renal problems), those were included as controls.

The controls shared symptom/sign with appendicitis; this made the study of the impact of a positive family history of appendectomy on the diagnosis of acute appendicitis more realistic and applicable, and reduced recall and response bias among the control group.

To detect a difference between the null hypothesis, stating that positive family history is present in all groups, and the alternative hypothesis, stating that the proportion in the case group is higher than the control group, all patients, who presented at the time of data collection and agreed to participate, were included in the study according to the diagnosis, while anyone with a previous history of appendectomy and unknown family history of appendectomy was excluded. Patients were initially divided according to their diagnosis into two groups (cases, controls), then control groups were divided into two subgroups according to the presence of abdominal pain, then the two groups were divided into three subgroups according to the number of relatives with positive family history of appendectomy due to acute appendicitis (negative family history, one relative with history of appendectomy, more than one relative).

A questionnaire form was prepared by the authors to collect data from both cases and controls through a direct interview with each participant; the form included: age, sex, definite diagnosis of patient's problem, presence/absence of abdominal pain, family history of appendectomy (mother, father, siblings, uncle, aunt, cousin, grandparent) and the number of relatives with a positive family history of appendectomy.

Data were analyzed using descriptive statistics with SPSS version 18. Categorical variables were presented as frequency and relative frequency. Chi-square test was used to test the significant associations between categorical variables. Odds Ratio (OR) and 95% Confidence Interval (CI) were used to measure the degree of association between cases and controls. P-Value of less than 0.05 was considered statistically significant.

Ethical Consideration

Official agreements to perform the research were obtained from College of Medicine – University of Baghdad and Medical City Health Directorates (approval number 1115/23.03.2016).

The aims of the study were explained to each participant and their oral consent was taken.

Results

To predict the association between family history and incidence of acute appendicitis, 100 patients (mean age 27.1±12.6 years), who were diagnosed with acute appendicitis and for whom appendectomy was performed, were compared with 200 patients (mean age 42.4±17.4 years), who were diagnosed with any cause of acute abdominal pain or another abdominal problem except acute appendicitis, among both groups females formed 55%.

Regarding age, two-thirds of the cases (66%) were between 10-29 years compared to only 29% among controls, and the association was statistically significant (χ^2 test=63.9, df=4, P< 0.0001) (***Table 1***). As for family history of appendectomy, ***Table 2*** shows that two thirds (66%) of the cases had a positive family history of appendectomy compared to 31.5% among the controls, and the association was statistically significant (χ^2 = 32.375, df=1, P<0.0001) with 66% sensitivity, 68.5% specificity, a positive predictive value of 51.2%, and a negative predictive value of 80.1%. The patients with positive family history had 4.2 times risk of being a case of acute appendicitis compared to those with negative family history (OR= 4.2, 95%CI: 2.5-7.0, ***Table 2***).

Table 1. Distribution of Cases and Controls by Age Groups* in Years

Ages Groups (years)	Patients with appendicitis (Cases)		Hospital-based patients (Controls)	
	No.	%	No.	%
19-Oct	34	34	10	5
20-29	32	32	48	24
30-39	19	19	39	19.5.0
40-49	8	8	32	16
>50	7	7	71	35.5.0
Total	100	100	200	100

Legend: *Statistically significant association; χ^2 test=63.9, df=4, P< 0.0001, No.=number.

Table 2. Distribution of Family History of Appendectomy within Case and Control Groups.

Family history of appendectomy	Cases		Controls		P value	Odds ratio (95% Confidence Interval)
	No.	%	No.	%		
Positive	66	66	63	31.5	<0.0001	4.221 (2.535-7.030)
Negative	34	34	137	68.5		
Total	100	100	200	100		

Legend: Sensitivity 66%, specificity 68.5%, positive predictive value 51.2%, negative predictive value 80.1%, No.=number.

Then, we divided the control group into two subgroups, a subgroup of 134 out of 200 patients had abdominal pain; in this subgroup 45 of 134 (33.5%) had with a positive family history. The comparison was significant as the (p< 0.0001, OR = 3.8; 95%CI: 2.22 to 6.63) with 66% sensitivity, 66.4% specificity, a positive predictive value of 59.4%, and a negative predictive value of 72.3% (***Table 4***).

The second subgroup of 66 out of 200 patients did not have abdominal pain; in this subgroup, 27.27% were with a positive family history. The comparison was also statistically significant as the (p<0.0001, OR=5.0; 95% CI: 2.56 to 10.03) with 66% sensitivity, 72% specificity, a positive predictive value of 78.5%, and a negative predictive value 58.5%.

After that, case and control groups were divided according to the number of relatives with a positive family history of appendectomy into three subgroups (Negative family history, One member with positive history, More than one member with positive history); comparing those with a negative family history to those having one member with a positive history then to those with more than one member with a positive history, the results were statistically significant as (p<0.0001, OR=3.4; 95%IC: 1.99 to 5.80, 59% sensitivity, 70.2% specificity, a positive predictive value 45.8%, and a negative predictive value 80.1%; p<0.0001, OR=13.7 ;95%CI:4.72to 39.76, 33.3% sensitivity, 96.5% specificity, a positive predictive value 77.2%, and a negative predictive value 80.1%, respectively. ***Table. 3a, 3b***).

Table 4. Distribution of Family History of Appendectomy and Presence of Abdominal Pain

Family history of appendectomy	Cases		Control subgroup with abdominal pain		P-value	Odds ratio (95% CI*)
	No.	%	No.	%		
Positive	66	66	45	33.5	<0.001	3.839 (2.221-6.637)
Negative	34	34	89	66.5		
Total	100	100	134	100		

Legend: Sensitivity 66%, specificity 66.4%, positive predictive value 59.4%, negative predictive value 72.3%. *CI: Confidence Interval.

Discussion

Appendicitis is one of the most common causes of acute abdomen. In addition, appendectomy is the most commonly performed surgery in the emergency department; despite that, delayed diagnosis and management as well as negative appendectomy along with its complications especially adhesions and its effect on female fertility are still found particularly in limited diagnostic settings. The current study aimed to test the impact of a positive family history of appendicitis on the diagnosis of acute appendicitis. It has found that a positive family history of appendectomy due to appendicitis in those with acute abdominal pain should be considered as an important parameter in the diagnosis as it was associated with three times increased risk compared to those with acute abdominal pain who a had negative family history. Moreover, those having more than one relative with a positive history are 13 times more susceptible to have acute appendicitis in comparison to those with a negative family history.

Initially, patients who presented with appendicitis were 4 times more likely to have a positive family history than those presenting with other diagnoses, whether they did or did not have abdominal pain. In Drescher et al study there was 1.9 times increased risk, which was statistically significant; this difference may be attributable to differences between the two samples in socioeconomic state, which made the population with a relatively lower socioeconomic state or lower hygiene policies less likely to have acute appendicitis unless a stronger familial tendency is found according to the hygiene theory.[6,25] There was a 3.8 times increased risk in those presenting with both acute abdominal pain and positive family history of appendectomy in comparison to those presenting with abdominal pain without a positive family history of appendectomy, a result similar to the study of Ergul et al., with a 3.1 times increased risk while the risk increased by 1.7 times in the study of Drescher et al., which is still statistically significant.[7,25] Another study demonstrated a familial aggregation and a polygenic transmission pattern in a retrospective analysis of families of 80 patients with appendicitis compared to families of matched controls. They found that the relative risk was 10; in other words, the chance of appendicitis was 10 times greater in a child with at least one relative with reported appendectomy, compared to a child with no affected relatives.[21] Gauderer et al., found that children who have appendicitis are twice as likely to have a positive family history of acute appendicitis than those with lower abdominal pain without appendicitis, and 3 times increased risk when compared to controls without abdominal pain.[24] Brender et al., found in their case-control study that parents of patients with appendicitis were approximately 10% more likely to have a positive family history of appendicitis than parents of control children.[26]

A Japanese study found that 40% of children in which both parents had acute appendicitis are affected and 20% of children with one parent having acute appendicitis are affected with acute appendicitis.[27] All these studies support the familial tendency of appendicitis, this tendency may be explained by environmental factors such as a specific bacterial infection, certain food habits and genetic difference in resistance to bacterial infections and inflammatory response.[7] Another study, performed by Daniel C., found out that, in a family pedigree that had 16 members with acute appendicitis, 15 cases were with retrocecal appendix. The same conclusion was reached by Shperber et al.[28]

As acute appendicitis is a common disease, 7% of the world's population is at risk of being affected during their life. The presence of one relative with a positive history of appendectomy may be by chance; cases and controls were divided according to the number of the affected relatives (negative family history, one relative with positive family history of appendectomy, more than one relative with positive family history), this had not been taken into account by other researchers, as a result, those presented with abdominal pain and more than one relative with positive history of appendectomy increased suspicion of having acute appendicitis by 13 times, while those presented with abdominal pain and one relative with positive history of appendectomy increase the suspicion by 3 times when compared to those with negative family history.

When only family history was used as a diagnostic test in those with abdominal pain, its sensitivity was 66%, specificity was 66.4%, its positive predictive value was 59.4%, and its negative predictive value was 72.3%, which is consistent with that of Ergul et al., study (The sensitivity was 68.9%, specificity was 75.4%, positive predictive value was 68.9% and negative predictive value was 75.4%). When family history is used as diagnostic test, its sensitivity and specificity are close to those of Alvarado score test (sensitivity 91.5% and specificity 60.5%).[7] It is still uncertain why family history of appendectomy is not used as diagnostic test, especially in the conditions where there are limited facilities.

In contrast to other studies like Drescher et al., study during 2013, in which females formed 46.5% in the cases group and 61.5% in the control group, in this study, the gender was matched, females formed 55% in both groups so that the effect of the gender factor was limited as much as possible (the incidence was slightly more in males than females 1.1-3.1).[2,25]

Regarding age, the mean age was 27.1±12.6 years in the cases group, and 42.4±17.4 years in those who were included as controls. This difference may be attributed to the controls being hospital-based; besides, many were excluded from the control group because of their previous history of appendectomy. In our study, more controls with no previous history of appendectomy were older than the age of the peak incidence of appendicitis; this gives more confidence about those included in the control group as the prevalence of appendicitis decreases with age. The age differences can be seen in other studies like Ergul et al., and Drescher et al., (31% of cases and 20.8% of controls were aged less than 30 years), while in this study, 66% of cases and 29% of controls were less than 30 years.[7,25]

Duration of the study was the only limitation, otherwise the sample size could have been larger. By measuring Alvarado scoring sensitivity and specificity and comparing it to that of family history of acute appendicitis, the groups could be divided into males' and females' subgroups to overcome the slight difference between genders. The small sample size was overcome by choosing case-control as the type of the study, and the cases to control ratio was made 1:2; it is known that each increment in the case to control ratio is associated with an increment in the study power.

Table 3a. Distribution of Cases and Controls by the Number of Relatives with Positive Family History of Appendicitis.

Family history of appendectomy	Cases		Controls		P value	Chi square [Df (1)]	Odds ratio (95% confidence interval)
	No.	%	No.	%			
One member with positive family history	49	59	58	29.74	<0.0001	21.1	3.404 (1.995-5.809)
Negative family history	34	40.96	137	70.25			
Total	83	100	195	100			

Legend: Sensitivity 59%, specificity 70.2%, positive predictive value 45.8%, negative predictive value 80.1%, No=number.

Table 3b. Distribution of Cases and Controls by the Number of Relatives with Positive Family History of Appendicitis.

Family history of appendectomy	Cases		Controls		P value	Chi square [Df (1)]	Odds ratio (95% confidence interval)
	No.	%	No.	%			
More than one member with positive family history	17	33.33	5	3.52	<0.0001	33.021	13.7 (4.720-39.761)
Negative family history	34	66.66	137	96.5			
Total	51	100	142	100			

Legend: Sensitivity 33.3%, specificity 96.5%, positive predictive value 77.2%, negative predictive value 80.1%, No=number, df=degree of freedom

In conclusion, positive family history of appendectomy in patients with acute abdominal pain should be considered as an important parameter in the diagnosis of appendicitis in a limited diagnostic setting as it increases the risk of having appendicitis by three times compared to those with negative family history. Increasing the number of relatives with positive history of appendectomy is associated with more risk of appendicitis compared to those with one relative with positive history of appendectomy.

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Author Contributions

Conception and design the work/idea: TY, ZQ, ZA. Collect data/obtaining results: TY, ZQ, ZA. Analysis and interpretation of data: TY. Write the manuscript: TY, ZQ. Critical revision of the manuscript: TY. Approval of the final version: TY, ZQ, ZA. Statistical advice: TY.

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