Appendectomy and asthma: a search for an association in older subjects

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ABSTRACT

Introduction: Studies have shown an association between appendicitis and immune mediated diseases such as ulcerative colitis and multiple sclerosis. Asthma, like the diseases mentioned, is also an immune mediated disease, and hence could possibly be linked to acute appendicitis. In this study, we aim to explore the association between asthma and appendicitis, using appendectomy as a marker for appendicitis.

Materials and Methods: Individuals 40 years and older with asthma were recruited from an online patient database from UiTM Medical Centers at Selayang and Sungai Buloh. The subjects were interviewed face to face or by telephone. Patients with a history of appendectomy were identified and prevalence of appendectomy was then compared to that of controls of similar age group. The diagnostic criteria from National Asthma Education and Prevention Programme were used to identify individuals suffering from asthma. Controls were sampled from the general population. From both control and asthma groups we excluded persons who knew that their appendix had been histologically normal, and those who had undergone appendectomy as part of some other procedure. Individuals suffering from respiratory diseases other than asthma were also excluded, to prevent confusion of diagnosis.

Results: Twenty-five of the 235 asthma patients had a history of appendectomy (10.6%). Of 1245 controls, 70 had a history of appendectomy, giving an overall prevalence of 6.3%. Gender did not vary in the appendectomy/ no appendectomy groups. Malay subjects had a lower prevalence of appendectomy (3.6%), while Indian subjects had the highest prevalence (13.5%). After partialing out the effects of ethnicity by logistic regression, the adjusted odds ratio between asthma and control subjects was 2.040 (95% CI: 1.216 – 3.420, p = 0.007). This shows a statistically significant association between asthma and appendectomy in this population.

Conclusion: A positive association exists between asthma and appendectomy in a population of subjects 40 years and older. This association is similar to that seen with multiple sclerosis but is the opposite to that seen with ulcerative colitis. The cause of this association needs study, particularly the possibility that an altered microflora has a role to play in mediating both conditions.

KEYWORDS:
Appendicitis; microflora; microbiome; autoimmune diseases; immune system diseases; gastrointestinal diseases; respiratory diseases; microflora hypothesis

INTRODUCTION

Asthma is a hyperactive airway disease that is mediated by an overactive immune system.[1] While it is known that an altered immune system is involved in the development of asthma, the exact factors contributing to such a state have not been well studied. Genetic factors are important, but the literature suggests that environmental factors play a more significant part.[2] The "hygiene hypothesis", proposed since 1958,[3-5] claims that early life infections exert a protective effect against the development of allergy and atopic diseases such as asthma.

Appendicitis, too, may have some etiological relationship with hygiene changes. Barker and others[6,7] have proposed that the introduction of plumbing in the 1980s led to improved hygiene, altered immune responses, and an ultimate increase in appendicitis.

If improved hygiene influences the development of both disorders, it may be possible to show a positive epidemiological correlation between the two conditions.

There are other reasons to suspect that there might be an association between the two conditions. They both occur in younger individuals, show a seasonal variation, and have

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both seen a rise in incidence over the past half a century.[8] Other chronic autoimmune disorders show association with appendicitis. Multiple sclerosis[9] and rheumatoid arthritis[10] are epidemiologically related to appendicitis. The association between ulcerative colitis and appendicitis is well-established[11,12] The association is strongly negative, meaning that persons who develop appendicitis tend not to go on to ulcerative colitis.

Two papers have recently evaluated asthma itself in association with appendicitis. One paper[13] showed no association except with active asthma, the other paper showed a strong likelihood that patients with asthma would undergo appendectomy.[14]

Most researchers have presumed that it is the appendectomy that precipitates the autoimmune disease.[10,13,15] This has prompted them to look for the onset of the autoimmune disorder in the years following the appendectomy, and compare with a "no appendectomy" population. However, this approach will give wrong results if there is an external factor that causes both appendicitis and the autoimmune disorder, because some persons analyzed as "no appendectomy" might well undergo the procedure later in life. Consequently, it is important to study the association only after the age in older persons, who are unlikely to newly develop appendicitis.

Appendicitis is uncommon after the age of 40,[16,17] implying that after this age a person listed as "no appendicitis" would be truly "no appendicitis" In this study we explored the association between asthma appendicitis, using appendectomy as a marker for appendicitis, in subjects 40 years and older.

MATERIALS AND METHODS

In this case-control study, we recruited persons suffering from asthma above the age of 40 and compared the rate of appendectomy among these individuals to controls. Statistical regression models were then used to identify the presence of a relationship between asthma and appendectomy.

Asthma Subjects

Cases were recruited from the online database of asthma patients from UiTM Medical Centre Selayang and Sungai Buloh. For this study, only individuals 40 and older were considered. The case notes of these patients were carefully screened, and only those satisfying the diagnostic criteria of asthma from the National Asthma Education and Prevention Program18 were included into this study.

Controls

Controls were recruited from the general population through convenience sampling by a large team of research students who interviewed their friends, relatives, neighbors, and passers-by. Individuals above the age of 40 who did not suffer from any form of respiratory disease were interviewed and included as controls.

Interview

Interviews were carried out either through telephonic interviews or face to face conversation. An English / Malay/ Chinese medium was used, depending on the preference of the subjects. A history of appendectomy was inquired. If positive, attempts were made further to clarify if intra-operatively there was presence or absence of inflammation of the appendix. We excluded individuals whose appendix was known to be normal intra-operatively or at histology, or if the appendix was removed as part of another operation. Individuals who declined consent for participating in this study were also excluded.

Statistical considerations

Using the formula shown below, we calculated the sample size necessary for this study:[19]

$$n = \frac{(z_\alpha + z_\beta)^2 (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

For a type 1 error of 10%, we assigned Zα as 1.65, Zβ as 0.84 for a 20% type 2 error (Power = 80%) and p1 (prevalence of appendectomy in the general population) as 0.07. The risk of appendectomy in patients suffering from asthma (p2) was assumed to be either 1/3 or 3 times higher to achieve a 75% effect size.

Since this was an exploratory study, we set the alpha at 0.1 instead of the usual 0.05. This provided us with a minimum sample size of 73, assuming that prevalence of appendectomy in asthmatic patients is thrice that of controls, or 250, assuming that the prevalence is a third that of controls (taking a cue from the previously published paper on MS).[9]

The Chi Squared test analytical method was used for basic comparison of the prevalence of appendectomy between cases and controls. We used binary regression analysis to partial out the effects of confounders like ethnicity.

IBM SPSS (version 25) was used for the analysis of data.

Ethics

Ethical approval from UiTM Research Ethics Committee and MUHREC (Monash University Human Research Ethics Committee) – ID: 13022. This research was also carried out in accord with the Good Clinical Practice guidelines.

RESULTS

Of the 744 patients listed in the database of asthma in UiTM Medical Centre Selayang & Sungai Buloh, only 235 were included into the study. The remaining were excluded for the following reasons: Deceased: n=20, Age < 40: n =138, Having other respiratory conditions / diagnosis of asthma uncertain: n=201, Normal appendix during appendicectomy: n=4, Uncontactable / refused to consent for this study : n = 146

We were able to recruit 1265 controls (Table I). Twenty of these had a concurrent respiratory illness, which may or may not have been asthma, and were therefore excluded.

Table I: Characteristics of Cases and Controls

Demographics		Asthma (n = 235)	Controls (n = 1245)	Total (n = 1480)	Appendectomy (n= 104)
Gender	Male	81 (34.5%)	625 (51.2%)	706 (47.7%)	50 (0.07%)
	Female	154 (65.5%)	620 (49.8%)	774 (52.3%)	54 (0.07%)
Average age (years)		60.4	54.2	55.1	
Ethnicity	Malay	179 (76.2%)	468 (37.6%)	647 (43.7%)	35 (0.05%)
	Chinese	13 (5.5%)	566 (45.5%)	579 (39.1%)	37 (0.06%)
	Indian	38 (16.2%)	196 (15.7%)	234 (15.8%)	31 (0.13%)
	Others	5 (2.1%)	15 (1.2%)	20 (1.4%)	1 (0.05%)

Table II: Association between asthma and prevalence of appendectomy

	Appendectomy status		Odds Ratio	P value
	Appendectomy	No appendectomy		
Asthma	25 (10.6%)	210	1.757 (95% CI: 1.095 – 2.820)	0.018
Control	79 (6.3%)	1166		
Total	104 (7.6%)	1376		

Chi Squared = 5.5764, p=0.0182 at 2 degrees of freedom.

Table III: Factors associated with prevalence of appendectomy using multiple logistic regression (n = 1480)

	B	SE	Wald	df	Sig	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Ethnicity (Malay)			17.398	3	0.001			
Ethnicity (Chinese vs Malay)	0.401	0.263	2.325	1	0.127	1.494	0.892	2.501
Ethnicity (Indian vs Malay)	1.085	0.265	16.784	1	0.000	2.961	1.761	4.976
Ethnicity (Others vs Malay)	-0.062	1.044	0.004	1	0.953	0.940	0.122	7.269
Asthma vs Control	0.713	0.264	7.306	1	0.007	2.040	1.216	3.420
Constant	-3.107	0.206	227.204	1	0.000	0.045		

Variable(s) entered on step 1: Age, Ethnicity, Group [asthma or control]
*Backward LR Multiple Logistic Regression statistical method is used.

B: Beta coefficient for the constant in the null model
SE: Standard error around the coefficient for the constant
Wald and Sig: The Wald chi-square test that tests the null hypothesis that the constant is 0.
df: Degrees of freedom for the Wald chi-square test
Exp(B): Exponentiation of the B coefficient, which is also Odds Ratio.

Naegelkerke R squared value: p = 0.036. Hosmer-Lemeshow test, (p = 0.739), classification table (overall correctly classified = 93.0%), and area under ROC curve (63.6%) was applied to test the fitness of this model.

Rates of appendectomy in Cases
Twenty-five of the 235 asthma patients had a history of appendectomy (10.6%) (Table II).

Rates of appendectomy in Controls
Of the 1245 controls, 79 had a history of appendectomy, giving an overall prevalence of 6.3% (Table II). Malay subjects had the lowest rate of appendectomy (3.6%), while Indian subjects had the highest prevalence (13.5%) (Table I).

Association of Asthma and prevalence of Appendectomy
A history of appendectomy was higher among asthmatic subjects when compared to controls. (Odds ratio: 1.795 [95% CI: 1.095 – 2.92], p = 0.018).

Analysis of possible confounding factors
To correct for variations in prevalence caused by confounders, we used logistic regression to further analyze our data. Simple logistic regression showed that ethnicity, but not age and gender influenced the prevalence of appendectomy.

Using binary logistic regression analysis, we were able to partial out the effects of ethnicity on the rates of appendectomy (Table III). As shown in Table I, the prevalence of appendectomy for appendicitis is 1.5 times among Chinese and 2.96 times among Indian patients when compared to that of Malay subjects. After partialing out the effects of ethnicity, the adjusted odds ratio between asthma and control is 2.040 (95% CI: 1.216 – 3.420, p = 0.007).

DISCUSSION

There are only two other publication that investigate the relationship between asthma and appendicitis. The first research was carried out by Hasassri et. al[13] and was published in 2017. This was a population-based case control study attempting to explore the relationship between asthma

and appendicitis among children. Hasassri et al[13] found no difference in a history of asthma between cases and controls, but they did find that appendicitis was more common among patients suffering from active asthma when compared to patients with inactive asthma (OR: 2.58) While the results obtained from Hasassri et al[13] were similar to ours, that study was confined to children. Many of their asthma patients would have been analyzed as "not associated with appendicitis" when in fact they might have developed appendicitis later in life.

The second research was carried out by Kim et al[14] and published after we initiated our own study. Their approach was very similar to ours, in that they did not presume that the immune disease, asthma, was a consequence of the appendectomy. They studied the association at all ages, showing an association that increased in significance from p=0.032 in younger individuals to p=0.002 in the age group 40-59 years. In that respect, our paper confirms their findings, that the association between appendectomy and asthma is more evident in older individuals.

So, what is the likely cause of this apparent association between appendectomy and other diseases (Table IV)? One possible explanation, based on a probable alteration of the gut microflora, is the "hygiene hypothesis".[20] It suggests that infections early on in life play an important a role in immune modulation and immune tolerance, which may prevent the development of auto-immune and allergic diseases such as asthma.[5] Only infections transmitted through the feco-oral route provide such a protective effect against immune mediated diseases, and it is postulated that the colonic microbiota might mediate the development of asthma and allergic diseases.[21] This idea is further supported by studies suggesting the possibility of a "gut-lung axis". Mouse models showed that certain microorganisms, when present in the gastrointestinal system, could reduce airway hyper reactivity.[22] This explanation would require a microflora-based evidence for the development of appendicitis, and for ulcerative colitis and multiple sclerosis as well. And indeed there is strong evidence that these disorders are in some way caused by gut microbial changes. We have already referred to Barker and others[6,7] whose work suggested that the introduction of plumbing in the 1980s led to improved hygiene and an increase in appendicitis. The sanitation may have resulted in a "microbiome depletion" which led to a hyper-immune state, increasing a person's risk of developing other immune mediated diseases, such as asthma.[23] Appendectomy specimens of individuals who suffered from appendicitis harbored a greater incidence of Fusobacterium.[24-26] Reports indicate that ulcerative colitis is another likely microflora-related disease,[27] as, probably, is multiple sclerosis.[28]

This study has several limitations. Case control studies are prone to recall bias. However, appendectomy is a surgery, a major life event, associated with a very visible scar, and it is unlikely that subjects would forget that it happened. Another weakness of this study is that some subjects would have undergone a negative appendectomy, where the appendix was not truly inflamed. Ideally, histopathological records should be examined to ascertain the diagnosis of acute appendicitis, but this was not feasible for an exploratory study such as ours. However, we believe that this will not significantly affect the result of our study. These days the over 90% of appendectomies are correctly carried out for acute appendicitis.[31] The small margin of error is likely to equally affect both the case and control group.

This study also has several strengths. Our first is the large number of controls we have been able to recruit. Also, since asthma subjects are recruited from a clinic, a thorough examination of case files was possible, ensuring an accurate diagnosis of asthma. Finally, we believe that restriction of recruitment to subjects at or above the age of 40 greatly increases the probability of fairly correctly categorizing patients into lifetime appendicitis and non-appendicitis groups, since only about 10% of appendectomies occur after the age of 40.[17] If we had included younger patients, many more might have gone on to develop appendicitis later in their life, and would have been misclassified in the study as "not appendicitis".

CONCLUSIONS

In a population over the age of 40 years, the prevalence of appendectomy among patients with asthma is higher compared to that of controls, and this data is statistically significant. We believe that such an association is likely to be microflora mediated, but this needs to be confirmed with follow up confirmatory studies. In Malaysia, the prevalence of appendectomy is highest among Indian individuals, and the lowest among Malay subjects.

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