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Original Article**Association of Mycobacterium Avium sub species Paratuberculosis (MAP) with Crohn's Disease**Niaz MK^{1*}, Raihan ASMA², Hossain MD³, Rahman SMM⁴, Rahman MA⁵.

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Abstract

Introduction: The human gut contains 10^{14} microorganisms of more than 500-1000 different species, forming intestinal microbiota. And its an emerging hypothesis of involvement of pathogenesis of inflammatory bowel disease (IBD) with the alteration of this gut microbiota. We are going to find the missing string of this hypothesis here. **Objective:** Objective of this study was to assess the association of Mycobacterium avium sub species paratuberculosis (MAP) in patient with Crohn's disease (CD). **Materials and Methods:** This case-control study was carried out in the department of Gastroenterology, BSMMU, Bangladesh. Period of study was from January 2016 to September 2017. Thirty-four diagnosed case of Crohn's disease was included in this study. Thirty-four controls were; patients undergoing Colonoscopy for screening purpose of any abnormal bowel symptoms and found to have normal findings; included in the study. Biopsy for PCR to detect Mycobacterium avium sub species paratuberculosis (MAP) and NTM was collected from ulcer in CD patients and left side of the colon in controls. IS 900 primer was used to detect MAP and ITS primer was used to detect NTM. **Results:** NTM was detected in 28 biopsy of CD patient (82.4%) and only 8 healthy control (23.5%) with Odds ratio 15.17 (95 % CI 4.07-60.75) and P value was significant (0.001). **Conclusion:** It appears that NTM other than MAP may have association with Crohn's disease in Bangladesh but further study is needed to find out which organism.

Key words: Crohn's Disease; Mycobacterium avium subsp paratuberculosis (MAP); Nontuberculous Mycobacteria (NTM).

Introduction

The human gut contains 10^{14} microorganisms of more than 500-1000 different species, forming intestinal microbiota¹. This microbiota can initiate immune responses either by functioning as adjuvants or antigens. The most common hypothesis regarding the pathogenesis of Crohn's disease (CD) is, overactive acquired T cell activity to a subset of microbiota; develop in genetically susceptible hosts, and environmental factors causes onset or reactivation of the disease. This theory involves four components that must intersect in multiple ways for the disease process to affect the patient². But it is almost universally accepted that a host genetic predisposition is critical for development of CD³. Among bacteria Mycobacterium avium subsp paratuberculosis (MAP) a member of the group of NTM has shown high prevalence⁴ although not uniformly⁵. This large

variation may be due to differences in DNA extraction techniques or to geographical variations in the prevalence and modes of transmission of MAP⁶. This prospective study aimed to see the association of Mycobacterium avium sub species paratuberculosis (MAP) with Crohn's disease.

Materials and Methods

Patient's of CD diagnosed on the basis of consistent clinical features, laboratory investigations like elevated CRP, endoscopic appearance, imaging demonstrating segmental narrowing and gut wall thickening and histological exclusion of caseating granuloma in the biopsy tissue were included in the study as cases.

Patients of IBS or suspected colorectal malignancy who were found to be normal at colonoscopy and colonic biopsy was normal, were included in the study as control. Nontuberculous mycobacteria (NTM) was searched in the biopsy of both cases and controls. Colonoscopy with ileoscopy was performed in each cases and controls. Two bites of biopsy from the lesions of CD patients were taken and studied for NTM by PCR. In control group two bites were taken for histopathology and two bites were taken for NTM PCR from left side of the colon. We used ITS primer for NTM and IS 900 primer for Mycobacterium avium sub species paratuberculosis (MAP), a member of the group of NTM in PCR. We extracted the DNA from tissue for PCR using QIAamp DNA mini kit.

Results

This case-control study was conducted in the department of Gastroenterology, BSMMU during the period of April 2016 to August 2017. We included 34 of the CD patients and 34 controls.

Table I shows almost one third (42.1%) patients belonged to age 21-30 years in case group and 11(32.4%) in control group. The mean age was found 32.9 ± 10.9 years in case group and 38.2 ± 12.1 years in control group. Twenty four (70.6%) patients were male in both case and control groups. The difference were not statistically significant ($p > 0.05$) between two groups. [table-I]

Table I: Demographic characteristics of the study population (n=68)

Demographic characteristics	Case (n=34)		Control (n=34)		P value
	n	%	n	%	
Age (years)					
≤20	3	8.8	1	2.9	0.681 ^{ns}
21-30	14	41.2	11	32.4	
31-40	10	29.4	11	32.4	
41-50	2	5.9	3	8.8	
> 50	5	14.7	8	23.5	
Mean±SD	32.9	±10.9	38.2	±12.1	
Range (min-max)	18	-55	18	-66	
Sex					
Male	24	70.6	24	70.6	1.00 ^{ns}
Female	10	29.4	10	29.4	

Twenty eight (82.4%) patients in case group and 8 (23.5%) patients in control group were found to have NTM. The difference was statistically significant ($p < 0.05$) between two groups. (Figure 1)

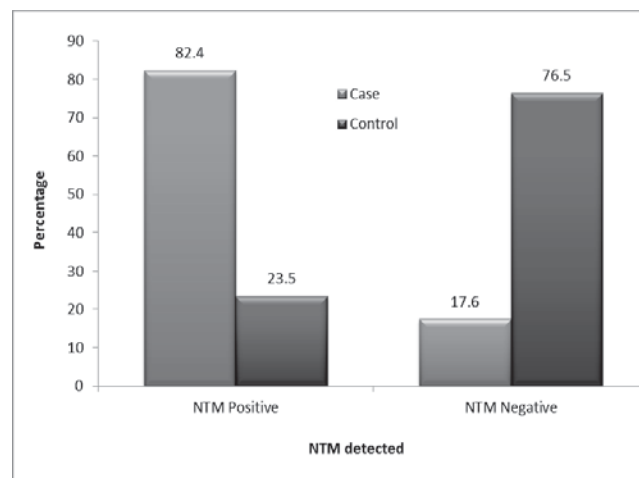


Figure 1: Bar diagram shows NTM other than MAP detected with case and control groups

It appears that neither the case nor the control was positive for MAP. So the Odds ratio is 1.00 with 95% CI (0.019-51.85) with non significant P value (1.00) [Table-II].

Table II: Distribution of MAP detected in case and control groups (n=68)

MAP detected	Case (n=34)		Control (n=34)		OR (95%CI)	P value
	n	%	n	%		
Yes	0	0	0	0	1.00 (0.019 to 51.85)	1.00 ^{ns}
No	34	100	34	100		

ns= not significant

P value reached from Chi-square test

Nine (32.1%) patients was found have mild disease activity in NTM detected group and 2(33.3%) in without NTM detected group. Majority (60.7%) patients was found moderate disease activity in NTM detected group and 3(50.0%) in without NTM detected group. Two (7.1%) patients was found severe disease activity in NTM detected group and 1(16.7%) in without NTM detected group. The differences were not statistically significant ($p > 0.05$) between two groups. [TableIII]

Table III: Distribution of NTM detected with Harvey-Bradshaw index in case group (n=34)

Harvey brad Shaw index	NTM Detected				OR (95%CI)	P value
	Yes (n=28)		No (n=6)			
	n	%	n	%		
Mild disease (5-7 score)	9	32.1	2	33.3	0.95 (0.11-9.26)	0.650 ^{ns}
Moderate disease (8-16 score)	17	60.7	3	50.0	1.55 (0.20-12.33)	0.482 ^{ns}
Severe disease (>16 score)	2	7.1	1	16.7	0.38 (0.02-13.09)	0.453 ^{ns}

ns= not significant

P value reached from chi square test

Discussion

This observational study was conducted in the department of Gastroenterology, BSMMU during the period of April 2016 to August 2017. The objective of the study was to assess the association of non tubercular mycobacteria (NTM) and Mycobacterium avium subspecies paratuberculosis (MAP) in patients with Crohn's disease (CD). We included 34 patients of Crohn's disease (CD) diagnosed on the basis of standard criteria and 34 patients as control who underwent colonoscopy for screening of abnormal bowel symptom and found to have normal colonoscopy, histopathology and normal other relevant blood reports.

We found a very good positive association of Non tubercular mycobacteria (NTM) with Crohn's disease. NTM was detected in 28 biopsy of CD patient (82.4%) and only 8 healthy control (23.5%) with Odds ratio 15.17 (95 % CI 4.07-60.75) and P value was significant (0.001). It appears that Non tubercular mycobacteria other than MAP may be associated with the disease pathogenesis. Further study is required to sort out which one is involved. But various study has shown a mixed result regarding the association of MAP with CD.

Ricanek et al (2010)⁷ studied 75 cases of Crohn's disease and 135 of control and found only 2 positive for MAP in each group⁷, Dumonceau et al (1997)⁸ took 32

case and 22 control and found no MAP in any subject of both group⁸.

Kreuzpaintner et al (1995)⁹ found no positive result in 23 case and control⁹. Kallinowski et al (1998)¹⁰ also failed to detect MAP in 21 case and 24 control¹⁰. Parihs et al (2009)¹¹ took 130 Crohn's disease patient and 130 Control and found none to be positive for MAP¹¹. However there are results showing a positive association of MAP with Crohn's disease but the sample size were small. Bull et al (2003)¹² found important positive association in 33 Crohn's disease patient and 33 controls and found 14 positive for MAP in cases and 3 positive for MAP in Control¹². However the disease severity does not shows any significant effect on the presence of Non tubercular mycobacteria.

M. avium ss paratuberculosis has been reported to cause Johne's disease which is similar to Crohn's disease in human only in a variety of ungulate species. No non-ruminant animals have been found to be affected. Aside from the dramatic differences between ruminant and non-ruminant gastrointestinal physiologies, an explanation for this difference has not yet been forwarded.¹³

Conclusion

From this study it appears that NTM other than MAP may have association with Crohn's disease in Bangladesh. Further study including large number of patients and controls is recommended to find out which organism is involved.

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