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Mycobacterium tuberculosis as a Common Cause of Diarrhea in AIDS Patients

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Abstract

Background: Gastrointestinal infections in human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) patients are a significant cause of morbidity and mortality, affecting up to 90% patients with varied pattern of etiology across the globe.

Aim: The present study was conducted to determine the prevalence and microbiological profile of pathogens associated with diarrhea in HIV positive patients in Eastern India and their relation to CD4 counts.

Methods: This was a case-controlled study with consecutive HIV cases attending ART clinic from August 2014 to June 2017 with diarrhea taken as cases and one hundred age sex matched HIV negative population with diarrhea in the same period as controls. All patients were evaluated with stool routine and microscopic examination with all standard stains and transabdominal ultrasound. Patients with persistent diarrhea were subjected ileocolonoscopy with biopsy and culture for *Mycobacterium tuberculosis*. Statistical analysis was done by using SPSS software 16.

Results: A total of 226 subjects were enrolled (126 cases and 100 controls). Mean age nad male to female ratio of cases were 30.19 ± 7.127, 2.5:1 and that of controls were 28.32 ± 9.63, 1.8:1 respectively. The most common enteric pathogen detected in HIV positive diarrhea subjects was *Mycobacterium tuberculosis* [41 cases (32.53%)] followed by *Isospora belli* 21.49%) and *Cryptosporidum parvum* (11.9%). Among diarrheal stool samples with *Mycobacterium tuberculosis*, 73.3% cases had CD4 <200, 23.3% cases had CD4 200-350 and 3.33% case had CD4 >350 (p-value >0.05). All cases of *Isosporiasis* had CD4 <200 and 80% cases of Cryptosporidiosis had CD4 <200 and 20% had CD4 within 200-350. Correlation between *Isospora & Cryptosporidium* with CD4 count was significant (P<0.05).

Conclusion: *Mycobacterium tuberculosis* was the most commonly isolated pathogen in HIV associated diarrhea followed by *Isospora* and *Cryptosporidium.*

Keywords: Diarrhea; HIV/AIDS; *Mycobacterium tuberculosis*

Introduction

HIV continues to be a major global public health issue, affecting more than 35.3 million people worldwide. India has a distinction to be the third largest contributor to global HIV burden after South Africa and Nigeria [1]. It remains one of the most significant problems haunting India over the past decade with an estimated adult prevalence of 0.26% [2].

Gastrointestinal involvement in HIV/AIDS is almost a universal and significant disease occurring in 50-70% of patients [3]. HIV/AIDS is characterized by opportunistic infection by various pathogens, especially in the gastrointestinal tract [4]. Diarrhea is a major gastrointestinal symptom in HIV infection affecting more than 90% of patients and it becomes more frequent as immunodeficiency progresses during the course of disease [5].

Diarrhea in AIDS could be due to infectious or noninfectious etiology. Noninfectious diarrhea could be due to ART-related adverse effects and HIV enteropathy [6,7]. The etiologic spectrum of enteric pathogens is numerous including bacteria, parasites, fungi and viruses. Several species of protozoa are associated chronic diarrhea which includes *Isospora spp, Cryptosporidium parvum, Microsporidia spp, Giardia lamblia, Entamoeba histolytica, Blastocystis hominis* and many more [4]. While reviewing the available information, a need was felt to study the prevalence of enteric pathogens in HIV patients with chronic diarrhea of this part of the world. Hence, the study was conducted to determine the prevalence and microbiological profile of pathogens associated with diarrhea in human immunodeficiency virus (HIV) positive patients and their relation to CD4 counts.

Materials and Methods

Study population

One hundred twenty-six consecutive HIV seropositive adult subjects with diarrhea attending the ART clinic of MKCG Medical College and Hospital, Berhampur, Odisha, India were recruited for this study, irrespective of their ART status. Hundred age- and sex-matched HIV seronegative subjects with symptoms of diarrhea were also enrolled as control group who came for routine examinations of their stool samples. Patients who were on medications (such as magnesium containing antacids, proton pump inhibitors, laxatives, antibiotics etc.) which can cause diarrhea were excluded from the study.

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Study design

This study was conducted from August 2012 to June 2015. This was a cross-sectional analysis to determine the microbiological profile of diarrhea in AIDS cases and HIV seronegative control subjects. Informed consent was taken, and each study participant was asked to complete a questionnaire which consisted of socio-demographic and personal details, history of diarrheal episodes. The socio-economic classification was done according to the Kuppuswamy's socioeconomic status scale [8]. Fecal specimens were collected from all the participants in a clean wide mouth screw capped disposable plastic container and transported to the microbiology laboratory by the patients themselves on the same day avoiding any unnecessary delay.

Definition of diarrhea

Diarrhea was defined as the passage of three or more loose or watery bowel movements in a 24-hour period. Acute diarrhea was defined as diarrhea which lasted 7 days or less at the time of presentation. Persistent diarrhea was defined as diarrhea which lasted for more than 7 days but less than 4 weeks at presentation. Diarrhea was called chronic if it lasted for more than 4 weeks.

Laboratory examination

Stool sample was emulsified in a drop of saline and Lugol's iodine on a slide and examined under the microscope for the presence of trophozoites of *Entamoeba histolytica*, Giardia lamblia, RBCs, pus cells, helminthic ova, and cyst. Stool smears were prepared, heat fixed, and stained by the Gram stain, ZN stain, Modified ZN stain and Mansons Trichrome stain. Modified ZN staining was done to detect oocysts of *microsporidia spp, Isospora belli* and *Cryptosporidia* spp. CD4+ T cell counting was done in all HIV patients using flow cytometry on a BD FACS Caliber cytometer.

All patients were subjected to ultrasound of abdomen and pelvis to look for any intraabdominal pathologies. Patients who had microbiologic or radiologic evidence of tuberculosis either were evaluated with colonoscopy and ileal intubation for biopsy caecum and ileum. Specimens obtained from colonoscopic biopsy were sent to the laboratory for histopathologic analysis and TB culture using the BACTEC System method and LJ media. Biopsied specimens were examined with H&E, Giemsa, Gram, PAS and AFB stains.

Statistical analysis

Analysis was performed using SPSS version 17.0 statistical software. A bivariate analysis was performed to look an association between organism's isolated and chronic Diarrhea. Two groups of patients were compared with independent t test and three groups of patients were compared with ANOVA t-test. The significance level was set at $P<0.05$.

Results

In this study, 100 HIV patients presented which chronic Diarrhea were taken as cases and 60 age sex matched HIV negative patients with diarrhea were selected as controls. The mean age group among cases was 30.19 ± 7.127, whereas controls had a mean age of 28.32 ± 9.63. Among cases, male to female ratio was 2.5:1 while controls had a ratio of 1.8:1. This was not statistically significant. (Table 1) The socio-demographic characteristics (including socio-economic classes) in both groups were depicted in Table 1. Intestinal pathogens were detected in 81 cases (64.29%) with chronic diarrhea in HIV positive patients and 8 cases (8%) with diarrhea in HIV negative controls. (Table 2). Besides diarrhea, fever, pain abdomen and weight loss (>10% of body weight) were observed in higher frequency in the cases as compared to the controls ($p<0.001$) (Table 2). In the HIV positive group, 60 cases (47.6%) had single or multiple parasites, whereas in the HIV negative patients only 11 (11%) had single or multiple parasites ($p<0.05$) (Table 3).

Variables			Case (n=126)	Control (n=100)	p-value
Age			30.19 ± 7.127 (Mean ± SD)	28.32 ± 9.63 (Mean ± SD)	NS
Age groups		Up to 20 years	4 (3.17%)	7 (7%)	NS
		21-40 years	78 (61.90%)	64 (64%)	--
		41-60 years	29 (23.02%)	20 (20%)	--
		Above 60 years	15 (11.90%)	9 (9%)	--
Male: Female	--	--	2.5:1	1.8:1	NS
Socio-economic Class	Lower	--	42 (33.33%)	36 (36%)	NS
	Lower/Upper lower		29 (23.02%)	21 (21%)	--
	Middle/Lower middle		31 (24.60%)	23 (23%)	--
	Upper Middle		24 (19.05%)	18 (18%)	--
	Upper		0	2 (2%)	--

Table 1: Socio-demographic characteristics in study population.

Prevalence	Case (n=126)	Control (n=100)	p-value
GI Pathogens detected	81 (64.29%)	8(8%)	<0.001
GI Pathogens not detected	45 (35.71%)	92(92%)	
Fever	54 (42.86%)	15 (15%)	<0.001
Pain Abdomen	92 (73.02%)	11 (11%)	<0.001
Vomiting	35 (29.37%)	19 (19%)	0.083
Hematochezia	17 (14.29%)	8 (8%)	0.137
Weight loss	73 (57.94%)	24 (24%)	<0.001

Table 2: Prevalence of enteric pathogens & clinical profile in HIV patients.

The most common enteric pathogen detected in HIV positive diarrhea subjects was *Mycobacterium tuberculosis* [41 cases (32.53%)] as evidenced in stool samples, imaging studies, histopathology study of colonoscopic biopsy samples. *Isospora belli* and *Cryptosporidum parvum* were detected in 27 cases (21.49%) and in 15 cases (11.9%) respectively. As compared to controls, the observed incidence of these organisms in HIV patients in diarrhea was significantly high (P<0.05). Less frequently found pathogens were Cyclospora in 4.76% cases and *Microsporidia*, *Giardia* and *Strongyloides* in 2.38% cases each (Table 4).

Among diarrheal patients with an identifiable cause, 60 cases had CD4<200, 12 patients had CD4 within 200-350 and 4 patients had CD4>350. Among diarrheal patients without an identifiable cause 20 cases had CD4<200, 18 cases had CD4 within 200-300 and 12 cases had CD4>350. This was statistically significant (P<0.001) (Table 5).

All cases of *Isosporiasis* had CD4<200 and 80% cases of Cryptosporidiosis had CD4<200 and 20% had CD4 within 200-350. Correlation between *Isospora & Cryptosporidium* with CD4 count was significant (P<0.05). Among diarrheal stool samples with *Mycobacterium tuberculosis*, 73.3% cases had CD4 <200, 23.3% cases had CD4 200-350 and 3.33% case had CD4 >350 and it was not statistically significant. Thus, *Mycobacterium tuberculosis* was identified as a cause of chronic diarrhea at any CD4 count (Table 6).

Study groups	Case (n=126)	Control (n=100)	p-value
Single infection	24 (19%)	7 (7%)	<0.01
Dual infection	30 (23.8%)	3 (3%)	<0.01
Mixed Infection	6 (4.7%)	1 (1%)	NS
Total	60 (47.6%)	11 (11%)	<0.001

Table 3: Number of infections study population.

Organisms	Case (n=126)	Control (n=100)	p-value
*Isospora***	27 (21.49%)	02 (2%)	<0.001*
*Cryptosporidium**	15 (11.90%)	03 (3%)	<0.01*
Cyclospora	06 (4.76%)	01 (1%)	NS
Microsporidium	03 (2.38%)	01 (1%)	NS
*Mycobacterium tuberculosis***	41 (32.53%)	01 (1%)	<0.001*
Entamoeba histolytica	03 (2.38%)	03 (3%)	NS
Giardia	03 (2.38%)	03 (3%)	NS
Strongyloides	03 (2.38%)	02 (3%)	NS

Table 4: Incidence of various pathogens.

CD4 Count	Pathogen Detected	Pathogen Not Detected	p-value
<200 (n=80)	60	20	<0.001
200-350 (n=30)	12	18	
>350 (n=16)	4	12	

Table 5: Incidence of pathogens in different CD4 count groups.

Pathogens	<200 (n=60)	200-350 (n=12)	>350 (n=04)	p-value
Isospora	27	0	0	<0.001
Cryptosporidium	12	3	0	0.501
Cyclospora	6	0	0	0.289
Microsporidium	0	0	3	<0.001
M. tuberculosis	26	12	3	0.075
Strongyloides	3	0	0	0.547
Giardia	3	0	0	0.444
E. histolytica	3	0	0	0.672

Table 6: Individual pathogens among different CD4 count groups.

Discussion

Available literatures on HIV epidemic in India, the number of people living with HIV in India in 2015 were 2.11 million with an estimated adult HIV prevalence of 0.26% [2]. Diarrhea is among the most common symptoms of HIV infection and is experienced by over 90% of patients with AIDS. It becomes more frequent as immune deficiency progresses. HIV infected patients are becoming more susceptible to variety of opportunistic infections with increasing severity and frequency. Several intestinal parasites previously thought to be non-pathogenic in immunocompetent persons are now opportunistically becoming aggressive in immunosuppressed HIV/AIDS patients.

Most of the HIV patients were in the age range of 25-35 years which was almost similar to the current study. The present study showed a male preponderance with 91 males and 35 females (Male: Female ratio of 2.6:1) among case group and 39 males and 21 females (Male to Female ratio of 1.8:1) among control group which is compatible. Predominance of male cases may be due to migration to other cities in search of work, staying away from families for longer periods and males being promiscuous by habit resulted in HIV infection. Generally, females particularly of low-socio-economic classes have a tendency to avoid health check-ups leading to a low detection rate.

The high prevalence of intestinal parasites like *Cryptosporidium*, *Isospora* and *Microspora* were consistently found in HIV/AIDS patients with diarrhea. These pathogens were reported as most common cause of diarrhea in HIV/AIDS in most of the previous studies [4,9]. *Mycobacterium tuberculosis* was identified in 23.8% cases. Infection with common intestinal pathogens *Ascaris lumbricoides*, *Entamoeba histolytica* and *Strongyloides stercolis* were lower (3% each) in HIV/AIDS patients with diarrhea when compared to diarrhea in HIV negative persons as reported in previous studies [4,9,10]. This discrepancy in HIV patients are due to structural and functional alteration in the gut that may not be suitable for growth of common intestinal parasites. Our study did not reveal any other bacterial or fungal pathology.

In our study, mycobacterium TB was the most commonly isolated pathogen i.e., 32.53% followed by *Isospora* 21.49% and *Cryptosporidium* 11.9%. As compared to the controls, the observed incidence of these organisms in HIV patients with chronic diarrhea was significantly higher (P<0.05). Our study differed strongly from other similar studies with respect to *Mycobacterium tuberculosis* as a predominant cause of chronic diarrhea in HIV. A study done at Nairobi Kenya by Mwchari et al. showed *Cryptosporidium* as the leading cause followed by *Mycobacterium tuberculosis* [10]. There are many reports regarding frequency of various pathogens causing diarrhea in different parts of India. Vignesh et al from south India detected *Isospora belli* as the most frequently encountered parasite [11]. Kotgire et al. from India found *Cryptosporidium* parvum as the most common intestinal parasite in HIV positive diarrhea patients [12]. But no studies have depicted *Mycobacterium tuberculosis* as the predominant cause of diarrhea in HIV/AIDS patients. These differences can be explained by geographic variation, underestimation of TB as a contributor to development of this condition as most of the studies focuses on intestinal protozoa as a cause of chronic diarrhea.

The cause of diarrhea in intestinal tuberculosis is postulated to be due to diminished absorptive surface due to multiple ulcerations in the Intestine. Bile salt deconjugation, and involvement of lymphatics and

lymph nodes may also contribute in causing diarrhea in GI tuberculosis [13]. An autopsy study from India revealed that *Mycobacterium tuberculosis* was cause of gastrointestinal infection in 14% of total patients [14]. Antinori et al. reported two cases of intestinal tuberculosis presenting as chronic diarrhoea in patients infected with HIV [15]. Another study from India reported that *Mycobacterium tuberculosis* was isolated from 3.7% of stool samples of HIV positive patients with diarrhea.

Our study also demonstrated a higher pathogen detection rate at a low CD4 count. There was an inverse correlation between CD4 counts and parasite isolation rates from diarrhea patients. It was also observed that the CD4 cell count influenced the cause of diarrhea as well as the diagnostic yield. The maximum parasitic isolation was in the group of patients who had CD4 cell counts below 200 cells/μL and *Isospora* was found to be the most commonly acquired protozoa causing chronic diarrhea. The isolation rates decreased with the increase in the CD4 cell counts. This finding is in accordance with the study conducted by Lekha Tuli et al. from Varanasi, India [16]. The low diagnostic yield of stool analysis in patients with higher CD4 cell counts was probably due to effective HAART eradicating opportunistic protozoal infection and causing the influx of CD4 positive cells into the lamina propria. *Mycobacterium tuberculosis* was second to *Isospora* as a pathogenic organism in HIV positive diarrhea with CD4 cell count <200. One interesting observation in our study was that *Mycobacterium tuberculosis* was identified as a cause of chronic diarrhea irrespective of any level of CD4 cell count.

Conclusion

In the present study, *Mycobacterium tuberculosis* has been found to be the most common pathogen causing chronic diarrhea in HIV patients in this part of world. Among parasitic infections, *Isospora belli* followed by *Cryptosporidium* are most commonly found in our study. Chronic diarrhea as a manifestation in HIV patients is more common with low CD4 count. Gastroenteric pathogen detection is more common in patients with low CD4 count.

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