Journal of Bacteriology and Parasitology

Ballani et al., J Bacteriol Parasitol 2012, 3:3
DOI: 10.4172/2155-9597.1000138

Research Article Open Access

Intestinal Protozoa in Immunosuppression: A Medical Hassle

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Abstract

Introduction: Immunity forms the backbone of our very existence and opportunistic infections have plagued the immunosuppressed since long. A significant morbidity and mortality is attributable to intestinal parasitosis in the immunocompromised population.

Objectives: This study aims to study the prevalence of intestinal protozoa in various immunosuppressed groups and to correlate degree of immunosuppression with protozoal infections.

Material and Methods: The study was conducted on 400 patients divided into 4 groups: Group I (HIV patients), Group II (patients on chemotherapy/chemotherapy and radiotherapy for various malignancies), and Group III (diabetes patients) and Group IV included children presenting with diarrhea. Group I, II and III included patients with and without gastrointestinal symptoms. Stool samples were investigated microscopically for cysts/trophozoites after concentration with formol-ether method. Iodine wet mount and Modified acid fast staining methods were used.

Result: Intestinal protozoa were detected in 40.75% (163/400); more commonly in patients with higher degree of immunosuppression (CD4 count <200/µl in HIV patients: 62.5%, malignancy patients on both chemotherapy and radiotherapy: 71.1%, higher levels of HbA1c >7: 95.3% in diabetics and moderate to severe malnutrition: 61.8%. Most common protozoa associated was *Cryptosporidium* in 66 patients (40.5%) followed by, *Entamoeba histolytica* in 48 (29.4%), *Giardia lamblia* in 35 (21.5%), *Isosporabelliin* 9 (5.5%), *Blastocystis hominis* in 4 (2.5%), *Cyclospora cayetenensis* in 1 (0.61%).

Conclusion: High prevalence of intestinal protozoa was seen in all groups of immunosuppressed patients and a significant association seen between degree of immune suppression and protozoal infection. Focus needs to be on routine screening of all immunosuppressed patients and their immune reconstitution.

Keywords: Intestinal protozoa; Immunosuppressed

Introduction

With an enormous increase in the immunosuppressed population owing to the HIV pandemic throughout the world, incidence of malignancies being continuously on the rise, more aggressive immunosuppressive therapies for organ transplants and the number of people affected by diseases like diabetes and tuberculosis ever increasing, the panacea remains immune reconstitution of these patients and thorough screening to prevent various opportunistic infections. Among different pathogens causing gastrointestinal infection, parasites are likely to have significant role as primary cause of co-morbidity of diarrhea in the immunocompromised.

Previous studies on immunocompromised populations (HIV, malignancy, and others), which mainly comprised adults, reported variable prevalence (2-50%) of intestinal parasitic infections with different etiologic patterns [1,2]. This is the first study done in India to the best of our knowledge that includes various immunocompromised patients of different age groups and correlates the level of immunosuppression with the opportunistic protozoal infections.

Material and Methods

A retrospective study was conducted at Department of Microbiology, Jawaharlal Nehru Medical College and Hospital, Aligarh, over a period of 1 year. Various groups of immunocompromised patients with or without gastrointestinal symptoms were included in the study; Group I (HIV patients), Group II (patients undergoing chemotherapy/chemotherapy and radiotherapy for various malignancies), Group III (diabetes patients), Group IV (children presenting with diarrhea with normal/impaired nutritional status). All patients were advised to give three consecutive stool samples. Protozoal infections were diagnosed by examination of stool specimens as fresh wet mounts, formol-ether concentration [3] technique and modified acid fast stain. Fresh and concentrated stool specimens were examined as saline wet mounts and iodine wet mounts [3]. Air dried smears from fresh stool samples were fixed and stained by a modified acid fast stain to detect the coccidian parasites- *Cryptosporidium*, *Isospora* and *Cyclospora species* [4]. *E. histolytica* was considered as the causative agent when the trophozoite/cyst suggestive of *Entamoeba* was identified along with the suggestive signs and symptoms pathognomonic for amoebic dysentery.

Statistical analysis was done using Chi-square test to observe association between degree of immunosuppression and protozoal infection and observed differences in data were considered significant if $p< 0.05$ was obtained.

Results

Stool samples from a total of 400 patients; 100 in each group were examined for the presence of protozoa and 50 controls were also included. 48 (48%) of the HIV positive patients (Group I), 38 (38%) pa-

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Received March 14, 2012; **Accepted** April 27, 2012; **Published** May 03, 2012

Citation: Ballani N, Shujatullah F, Khan HM, Malik A, Ali MSM, et al. (2012) Intestinal Protozoa in Immunosuppression: A Medical Hassle. J Bacteriol Parasitol 3:138. doi:10.4172/2155-9597.1000138

tients with malignancy and undergoing chemotherapy or both chemotherapy and radiotherapy (Group II), 43 (43%) patients with diabetes (Group III) and 34 (34%) patients in Group IV were infected with intestinal protozoa.

Only 8% of patients in the control group were infected with protozoa and none was infected with any coccidian parasite. *E. histolytica* and *G. lamblia* were found in 10% and 6% patients respectively.

In Group I maximum numbers of patients were in the age group 35-40 years (39%) and males (72%) were more than females (28%). *Cryptosporidium* sp. was the most common protozoa found in this group (41.7%). *E. histolytica* (31.3%), *Giardia lamblia* (12.5%), *Isospora belli* (12.5%), *Cyclospora* (2.1%) were the other protozoa found. Coccidian parasites were found in 28% while the non-opportunistic parasites found in 21% patients.

In group I, this constituted HIV positive patients. All the protozoa were more commonly found in patients with CD4 count < 200 cells/µl. Among 48 patients infected with protozoa, 30 (62.5%) had CD4 count < 200 cells/µl while 18 (37.5%) patients had CD4 count > 200 cells/µl (Table 1).

In Group II, maximum number of patients in this group was in the age group 65-75 years (25%) and males (63%) were more than females (37%). *Cryptosporidium* sp. (15%) and *E. histolytica* (15%) were the most common protozoa found in this group. *Giardia lamblia* (5%) and *Isospora belli* (3%) were the other protozoa found.

Table 2 shows the correlation between intestinal protozoal infection and chemotherapy/chemotherapy and radiotherapy. 27 (71.1%) patients infected with intestinal protozoa were on chemotherapy and radiotherapy while 11 (29%) were on chemotherapy only. Most of the protozoal infections were more common in patients on both chemotherapy and radiotherapy.

In Group III, maximum number of patients in this group was in the age group 50-55 years and 60-65 years (16%) and males (80%) were more than females (20%). *Cryptosporidium* sp. was the most common protozoa found in this group (25%). *E. histolytica* (12%), *Giardia lamblia* (6%) were the other protozoa found.

Intestinal Protozoa	CD4 count >200	CD4count <200	Total
1. *E. histolytica*	7 (46.7)	8 (53.3)	15 (31.3)
2. *Giardia lamblia*	2 (33.3)	4 (66.7)	6 (12.5)
3. *Cryptosporidium* sp.	7 (35)	13 (65)	20 (41.7)
4. *Isospora belli*	2 (33.3)	4 (66.7)	6 (12.5)
5. *Cyclosporacayetenensis*	-	1 (100)	1 (2.1)
Total	18 (37.5)	30 (62.5)	48 (100)

*Figure within parentheses indicates percentage.

Table 1: Intestinal protozoal Infection in HIV-positive patients with reference to CD4 Count.

Intestinal protozoa	Chemotherapy	Chemotherapy+ Radiotherapy	Total
1. *E. histolytica*	5 (33.3)	10 (66.7)	15 (39.5)
2. *Giardia lamblia*	4 (80)	1 (20)	5 (13.2)
3. *Cryptosporidium* sp.	2 (13)	13 (86.7)	15 (39.5)
4. *Isospora belli.*	-	3 (100)	3 (7.9)
Total	11 (29)	27 (71.1)	38 (100)

*Figure within parentheses indicates percentage

Table 2: Correlation between intestinal protozoal infection and chemotherapy/chemotherapy and radiotherapy.

Table 3 shows the correlation between intestinal protozoal infection and glycosylated hemoglobin (HbA1c).28 (65.1%) patients infected with intestinal protozoa had glycosylated hemoglobin (HbA1c) between 7-10, 13 (30.2%) had HbA1c >10, and 2 (4.7%) had HbA1c < 7.Protozoal infections were more commonly found in patients with HbA1c 7-10 and HbA1c > 10.

Group IV had maximum number of patients in the age group 4-6 years (23%). Males (62%) were more than females (38%). 34 (34%) out of 100 patients in this group were infected with intestinal protozoa. *Giardia lamblia* was the most common protozoa found (18%), *E. histolytica* and *Cryptosporidium* species were found in 6 (6%) patients each. *Blastocystis hominis* was also found in 4 patients (4%).

Table 4 shows association between intestinal protozoal infection and nutritional status. Among the patients found to have intestinal protozoal infection, 8 (47.1%), 13(43.1%), 6 (19.4%), 2 (28.6%) had PEM Grade I, II, III and IV respectively. Out of the 34 patients infected with intestinal protozoa, 21 (61.8%) had moderate to severe malnutrition.

Discussion

Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) are among the leading causes of infectious disease morbidity and mortality worldwide. India is estimated to have the second largest HIV positive population in the world [5,6], with more than 5.7 million persons living with HIV/AIDS with prevalence in adults of 0.91%. Concomitant infections play a major contributing role in the morbidity associated with HIV/AIDS and thus effective prevention, diagnosis, and management of accompanying infections are critical for improving the health and well-being of people infected with HIV. Among AIDS patients in developing countries, as many as 95% may have diarrhea [6,7]. In a large proportion of this population, the diarrhea may become prolonged and life-threatening, and chronic diarrhea is an independent marker of poor prognosis in patients with AIDS [8].

Despite the spread of HIV infection in India, and the high prevalence of diarrheal disease, there is little information available on the epidemiology of diarrheal disease among people with HIV infection. In a review of HIV-related Opportunistic Infections (OIs) in northern India, chronic diarrhea was the second most common opportunistic

Intestinal protozoa	HbA1c <7	HbA1c 7-10	HbA1c >10	Total
1. *E. histolytica*	2 (16.7)	7 (58.3)	3 (25)	12 (28)
2. *Giardia lamblia*	-	3 (50)	3 (50)	6 (14)
3. *Cryptosporidium* sp.	-	18 (72)	7 (28)	25 (58.1)
Total	2 (4.7)	28 (65.1)	13 (30.2)	43 (100)

*Figure within parentheses indicates percentage.

Table 3: Correlation between intestinal protozoal infection and glycosylated haemoglobin (HbA1c).

Nutritional status	Positive	Negative	Total
Normal nutrition	5 (33.3)	10 (66.7)	15 (15)
PEM Grade I	8 (47.1)	9 (53)	17 (17)
PEM Grade II	13 (43.3)	17 (56.7)	30 (30)
PEM Grade III	6 (19.4)	25 (80.6)	31 (31)
PEM Grade IV	2 (28.6)	5 (71.4)	7 (7)
Total	34 (34)	66 (66)	100

*Figure within parentheses indicates percentage.

Table 4: Association of Intestinal protozoal infection with nutritional status.

infection encountered [9]. Parasitic infections with *Isospora belli, Entamoeba histolytica,* and *Cryptosporidium* sp. have been reported as being among the most frequently identified organisms in India [9,10] but few studies have systematically examined the etiology of diarrhea in this population. Only a few studies regarding the prevalence of intestinal parasites and their association with diarrhea of HIV- infected patients are available from North India at present.

Our study was done on 100 HIV positive patient attending ART clinic of JNMCH. Enteric protozoa were detected in 48 (48%) stool samples and *Cryptosporidium* (20%) was the most frequently encountered pathogen in the study population followed by *E. histolytica* (15%). Both *Isospora* and *Giardia lamblia* were found in 6 (6%) patients and *Cyclospora* in 1(1%) patient. Coccidian parasites were found in 27% while the non-opportunistic parasites found in 21% patients. *E. histolytica* and *G. lamblia* were found in 15% and 6% patients respectively.

Difference in the incidence of intestinal protozoal parasitic infection reported by different workers can be attributed to the difference in geographical distribution of parasites, sanitary practices and different selection of cases. Various studies from India and other countries have reported a high prevalence of intestinal parasite, ranging from 25 to 60 percent [11-19].

The world wide prevalence of enteric protozoa in various populations of the immunosuppressed has been shown by Stark et al. [20]. The coccidian parasites (*Cryptosporidium* sp., *Isospora belli*, C*yclospora*) are foremost among the enteric parasites in these patients [18]. In India, there have been reports from mid-1990s on the prevalence of symptomatic cryptosporidiosis in HIV infected adults from different parts of the country, ranging from as low as 0.7% to as high as 81% [11] and 1.5% and 13.3% from other countries [15]. Earlier studies [14,21] from north India have also found *Cryptosporidium* sp. to be the most common parasite while the prevalence of *Isospora belli* was found to be much lower. Studies from South India [22,23] have reported a higher prevalence of *Isospora belli* than *Cryptosporidium* sp. The low prevalence of *Isospora* could be due to the frequent use of TMP/SMX as prophylaxis for opportunistic infections. *Isosporais* infrequently associated with diarrhea due to AIDS in the USA and Europe (about 2%), but is commonly isolated in patients with AIDS and chronic diarrhea in Brazil (9.9%), Zaire (12%), Zambia (16%), and Haiti (12%) [24]. Detection rate of *Cyclospora* in this study found to be 1.0% in HIV patients which correlates with the studies done in Chennai (0.6 %) [23] and in Gujrat (1%) [17]. Higher rates of infection by *Cyclospora* have been reported by Mohandas et al. [14] (3.3%) and Soave R [25] (11%). *Cyclospora* is common in Haiti (11%), but only rarely detected in US and Tanzanian patients with AIDS and chronic diarrhea (<1%) [24,26]. Among the non opportunistic pathogens *E. histolytica* / E. dispar seemed to contribute significantly as shown earlier [15,19,21,27]. Earlier studies [14,28] have reported rates of infection with *G. lamblia* between 1-11%. Mohandas et al. [14] reported that *Giardias* is does not occur in greater frequencies in HIV- positive patients than in HIV-negative individuals. The reported prevalence of non opportunistic parasites varied from 5-30 per cent in HIV infected patients [29,30].

CD4counts play an incredibly important role in the presentation of diarrhea as well as in the control of protozoa in HIV-infected individuals. For example, chronic diarrhea is typically associated with lower CD4 counts than acute diarrhea. In addition, at counts of less than 200, HIV-infected patients are at risk from specific opportunistic protozoan pathogens which are usually unable to establish infection in immunocompetent hosts [31,32]. The study group consisted of 50 patients with CD4 count > 200 cells/µl and 50 patients with CD4 count < 200 cells/µl. In our study, all the protozoa were more commonly found in patients with CD4 count < 200cells/µl and the correlation between CD4 cell count and intestinal protozoal infection was found to be significant ($p<0.05$). 30 (62.5%) patients infected with protozoa had CD4 count < 200 while 18 (37.5%) had CD4 count > 200. This is in concordance with the findings in the study by Kulkarni et al. [19]. Several other studies have reported the correlation between CD4 count and diarrhea in HIV positive patients and this reflects a compromised immune system with increased risk of disease [33,34].

Due to easy availability of HAART in developed nations, there has been a reduction in the prevalence of intestinal parasites in AIDS patients. At higher CD4 T-cell levels, generally, spontaneous clearing of the parasite takes place. In resource settings like ours, patients usually go undiagnosed for long periods and present late in the course of the disease. Consequently, the patients usually present with profound, persisting and multiple intestinal infections and a low CD4 T cell counts.

Unfortunately, our knowledge of the human immune system and the way it interacts with parasites is much more limited, despite the recognition that enteric parasites are commonly associated with the onset of diarrhea in IS patients.

Thus, we also included patients with malignancy and diabetes in our study to comprehend the pattern of protozoal infections in these immunocompromised patients and correlate it with level of immunosuppression in this group.

Group II consisted of patients with malignancy. Among 100 patients 38 (38%) patients had intestinal protozoal infections. *Cryptosporidium* sp. (15%) and *E. histolytica* (15%) were the most common protozoa found in this group. *Giardia lamblia* (5%) and *Isospora belli* (3%) were the other protozoa found. *E. histolytica* and *G. lamblia* were found in 15% and 5% patients respectively. 27 (71.1%) patients infected with intestinal protozoa were on chemotherapy and radiotherapy while 11 (29%) were on chemotherapy only. Most of the protozoal infections were more common in patients on both chemotherapy and radiotherapy and the correlation was found to be significant ($p<0.05$)

43 (43%) patients with diabetes in group III had intestinal protozoal infections. *Cryptosporidium* sp. was the most common protozoa found in this group (25%). *E. histolytica* (12%), *Giardia lamblia* (6%) were the other protozoa found. 28 (65.1%) patients infected with intestinal protozoa had glycosylated hemoglobin (HbA1c) between 7-10, 13 (30.2%) had HbA1c >10, and 2 (4.7%) had HbA1c < 7.Protozoal infections were more commonly found in patients with HbA1c 7-10 and > 10, however the correlation was not significant.

Several studies have been conducted on immunosuppressed patients like those with haematological malignancies, PEM, patients receiving immunosuppressive drugs for organ transplants or cancers, patients undergoing dialysis and those having diabetes. These patients have been found to be at significant risk of severe cryptosporidiosis, infection with *I. belli*, *Cyclospora* [35-39]. There are reports of three patients with diabetes suffering chronic diarrhea due to cryptosporidiosis [40,41]. In malignant disease, there are studies which show the risk of severe cryptosporidiosis being limited largely to children with acute leukemia and lymphoma [41]. Although there are relatively few studies of cryptosporidiosis in patients with primary immunodeficiencies, it would appear that the risk is largely limited to those individuals with impaired T-cell function [42,43].

Conclusion

Our study highlights the magnitude of protozoal infections in various groups of immunosuppressed patients with or without diarrhea and also a profound association with the level of immunosuppression. The rationale behind preventing protozoal gastrointestinal infections and reducing morbidity caused by them in the immunocompromised should be focused on routine screening of these patients and high index of suspicion for the enteric protozoa as these have been proved to be the commonly implicated pathogens time and again. Empirical therapy sans knowledge of etiology and pattern of infection in a particular population defers proper cure and increases burden on the health care sector. Further such studies done on larger sample size from different regions of the country will give direction to the efforts of the physician.

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