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IMPACT OF IMMUNOSUPPRESSIVE DRUGS ON SUDANESE RENAL TRANSPLANT RECIPIENTS INFECTED WITH INTESTINAL PARASITES

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ABSTRACT

Objectives: Enteric parasites are important agents of disease throughout the world. And they increasingly have significant role in transplant candidates. Intestinal parasites that are asymptomatic before transplantation may become clinically significant under immunosuppressive treatment. In the other hand some immunosuppressive regimens has anti-parasitic effects that may result in lower rates of parasitic infections.

Methods: Stool samples were collected from renal transplant recipients attending Sudanese Kidney Association hospital and from a control group from January 2012 to April 2012. For the detection of parasites, fresh stool samples were separated into two samples; one was preserved in SAF fixative. From this sample smears were made for permanent stains. The second sample was examined by wet preparation. Modified trichrome staining method was used for permanent smears for microsporidia.

Result: All (200) renal transplant recipients were on immunosuppressant drugs; (76.5%) of the study patients were on tacrolimus (prograf) therapy and only (23.5 %) were on cyclosporine A (CsA) therapy. Of the total patients on tacrolimus there (22.5%) were diagnosed with intestinal parasites and only (1.5%) of them were on Cyclosporine therapy. There was statistically significance between immunosuppressant agents and infection with intestinal parasites positivity in group I (P value= 0.019). All details are summarized in (Table 2). Multiple parasitic infections were observed in a total of 5/200 (2.5%) renal transplant recipients and 1/100(1%) controls ($p < 0.05$). G *lamblia,*and *B. hominis*was frequently seen species as multiple infections in renal transplant recipients.

Conclusion: Intestinal parasitic infections should not ignore in renal transplant recipients, So Cyclosporine therapy should be recommended as first line immunosuppressant drugs as well as prophylactic against wide range of parasitic diseases.

Key Words: Immunosuppressive drugs, Transplants, Intestinal parasites

INTRODUCTION

Organ transplant recipients can experience serious diseases from infections due to emerging and reemerging parasitic infections. So they are at risk for infections-particularly opportunistic parasites, and occult intestinal infection can remain quiescent for many years, becoming apparent after initiation of immunosuppression because of the continuous administration of immuno-suppressive drugs [1, 2]. The impact of intestinal parasitic infection in renal transplant recipients requires careful consideration in the developing world. However, there have been very few studies addressing this issue in Sudan. On the other hand parasitic infections are easily forgotten by clinicians, and they are often regarded as mild, unimportant. However, parasites continue to be a significant health problem and the commonest causes of morbidity and mortality in many parts of the world especially in the developing countries. With increasing ease of international travel and increasing number of immunocompromised hosts, one might expect to see exotic or unusual parasitic infections anywhere in the world. For instance, several contributing factors affect the prevalence of intestinal parasites in a geographic location, like socioeconomic status, climatic changes, and poor standards of public and personal hygiene [3].

Immunocompromised hosts, including patients withAIDS, solid organ transplantation, and patients on immunosuppressivetherapy, are at higher risk for opportunistic parasiticin-

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fections.Renal transplant recipients (RTRs) are proneto parasitic infections due to immunosuppressive therapy.Giardiasis comprises <1% of parasitic infections among RTRs.It is well known that Giardiasis can be treated with simple antibiotics like metronidazole and albendazole with adequate responses. But in clinical situations like common variable immunodeficiency (CVID), lymphoproliferative diseases, HIV/AIDS, Giardiasis is refractory to usual therapies[4]. Very few reports of Giardiasis among RTRs have been reported from Sudan.

Parasitic diseases may affect transplant recipients as a resultof Recrudescence of latent infections in the previously infected recipient, 'De novo' infection by means of(i) Natural infection.(ii) Transmission by transplanted organ (or blood product,either before or after transplantation) into a naive recipient. For the most part, only those organisms that can completetheir life cycle within the human host result in more severe infections in an immunocompromised host. Co-infection isa common feature of parasitic infection in transplantation, and invasive disease may be associated with viral infection(particularly cytomegalovirus) or with disseminated bacterialinfection[5].

The incidence of parasitic infection is expected to grow insolid organ transplant recipients due to multiple factors: Many geographic areas where parasitic infections arehighly prevalent have now active organ transplant programs, donors and recipients from endemic areas, with latentor asymptomatic infections, are sometimes referred totransplant centers in Western countries, some patients from developed countries undergotransplantation in highly endemic areas (transplanttourism) and return home with either donor derivedor naturally acquired infection(s).[4] Immigrants to Western countries, unaware of their infectiousstatus, are accepted for organ donation withoutfurther evaluation for diseases that are prevalent intheir countries of origin; finally the decrease in cyclosporine-based immunosuppressiveregimens and the increased use of newer drugsthat lack the anti-parasitic effects of cyclosporinemetabolites may result in higher rates of parasitic infections[5, 6]. Eosinophilia, gastroenteritis and other clinicalmanifestations of parasite infections prior to transplantshould trigger an appropriate workup.

*Cryptosporidium, I. belli,Cyclospora, Microsporidia, Blastocystishominis and Giardia*can all cause significant gastroenteritis in transplant recipients.While the use of mycophenolatemofetil is most common cause of chronic diarrhea in transplant recipients,these fastidious organisms can mimic such colitis. Cryptosporidiumand Giardia are among the most common parasiticpathogens seen in transplant recipients, especiallyin endemic regions; severe cryptosporidiosis has been reportedin numerous transplant recipients. Transmission ismore common in the developing world, where rates of infectionas high as 20% have been noted[7], and can occur from contaminated food and water, person-to-person-spread, and zoonotic exposures; intestinal protozoa havealso been reported as donor-derived infections with intestinal transplantation[7, 8].

This study aimed to determine the impact of immunosuppressive drugs on renal transplant recipients infected with intestinal parasites

MATERIAL AND METHODS:

Study Design:

This is analytical cross sectional study approach on patients who underwent renal transplantation. It was conducted at the parasitology lab, faculty of Medical Laboratory Sciences, University of Khartoum from March 2014 to December 2015. Stool specimens were collected from 200 renal transplant recipients attending Sudanese Kidney Association hospital in Khartoum state, Sudan, and 200 control group that were collected from different wards.[9]Patients were enrolled based on the following inclusion criteria: Both sexes, different ages, recipients whom passed between 6 months to 10 years of their renal transplantation, use of immunosuppressant drugs, they suffering from diarrhea either chronic (two or more watery or loose stools per day for a period of greater than 28 days) or acute diarrhea (two or more watery or loose stools per day for less than 4 weeks) or without diarrhea.

Methods:

Three groups of study subjects were enrolled in this study as follow; group (I) includes patients underwent renal transplantation and complained of diarrhea, group (II) were patients who underwent renal transplantation but without symptoms and group (III) was control group (apparently healthy individuals).

The sample was taken from each participant into a dry air tight leak proof plastic stool container and transferred to the laboratory at the end of each working day. For the detection of parasites, fresh stool samples were separated into two samples; one was examined by wet preparation. The second sample was preserved in SAF fixative. From this sample smears were made for permanent stains. [10]

Direct Wet Smear Examination (Cheesbrough M)[11]andModifiedTrichrome Stain (Weber- Green) were done each sample[12].

Sampling and sample size:

The type of the sample needed for the study is multistage simple random sampling with population proportional to size (PPS).

Tools for Data Collection:

A well-constructed questionnaire was used for collection of demographic and clinical data and observation check list for stool specimens.

Statistical analysis:

Data was analyzed using SPSS (version 12) software. Significance of difference was analyzed by Chi-squared test. $P< 0.05$ was considered significant.

Result: A total of 400 fecal samples were collected from study participants for parasitological study. Two hundred were renal transplant recipients receiving immunosuppressant drugs with a mean age of 24.5 years. Of those, 112(56%) were males and 88(44%) were females. There were no statistically significant differences between age and sex in the two groups ($p > 0.05$), figure 1.

Majority of patients infective with intestinal parasites were in were in age group (21- 40) figure 2. All (200) renal transplant recipients were on immunosuppressant drugs; (76.5%) of the study patients were on tacrolimus (prograf) therapy and only (23.5 %) were on cyclosporine A (CsA) therapy. Of the total patients on tacrolimus there (22.5%) were diagnosed with intestinal parasites and only (1.5%) of them were on Cyclosporine therapy. There was statistically significance between immunosuppressant agents and infection with intestinal parasites positivity in group I (P value= 0.019).[9] All details are summarized in (Table 1).

Table 2 shows the magnitude of single and multiple parasitic (poly parasitism) infections in renal transplant recipients and in controls. Multiple parasitic infections were observed in a total of 5/200 (2.5%) renal transplant recipients and 1/100(1%) controls ($p < 0.05$). The species of parasites was frequently seen as multiple infections in renal transplant recipients were *G. lamblia, H. nana* and *B. hominis*.

Table 3 summarizes the frequency of enteric parasites among different types of patients receiving Tacrolimus and Cyclosporine A, were the majority of parasites (16%) in patients receiving tacrolimus.

DISCUSSION

This study has evaluated the frequency of opportunistic and common intestinal parasitic infections among renal transplant recipients receiving immunosuppressant drugs (Tacrolimus and CsA).

There was an association between frequency of parasitic infections and age group, enteric parasites were common in themiddle age group (21- 40) years old, and this may be this age group were more exposed to factors which enhance parasitic infections so continuous health supervision, annual medical examination and prompt treatment of infected renal transplant recipients minimize the infection rates.

In our study, *G. lamblia* was the first most prevalent parasite detected in cases and control group (8.5% vs. 10%), without significant difference and followed by*B. hominis*(4% vs. 1%) *and H. nana* (2% vs.1%). This is concurrent with that reported by M Nateghi*et.al* [10] who found that *G. lamblia* is the second most prevalent parasite (10/706).In other study carried out on renal transplant recipients in Brazil, *G. lamblia* was the third most prevalent parasite (3/16) and *S. stercoralis* was the common parasite (11/16). The reason is that CsA acts as an immunomodulator enhancing trypanosomes and *Giardia* multiplication, and exacerbating the infection. This is more or less could explain the higher incidence of giardiasis infection among the population. There are few reports in the literature regarding giardiasis in immunocompromised hosts [13].

With regard to helminthes, *Strongyloidesstercoralis,* there are considerable reports of cases of *S. stercoralis* hyperinfection as a consequence of immunosuppressive treatment following kidney transplantation. However, culture of 200 stool specimens from renal patients yielded lack of infection with *S. stercoralis*larva. The same result obtained by M Nateghi Rostami *et.al*[14].This might be under the influence of parasiticidal action of CsA. Reportedly CsA has reduced the incidence of strongyloidiasis in renal transplant recipients. Although in the analysis of Valvar *et al*. the most prevalent infection was reported to be *S. stercoralis*, but none of infected patients received CsA in their immunosuppressive drug protocol [8]. The low use of cyclosporine A (23.5%) by study participants is likely to affect the overall frequency of intestinal parasites. It is a fact that, the use of Cyclosporine A (CsA) has become a cornerstone in prophylactic immunosuppression among renal transplant recipients. Cyclosporine A with powerful properties of immunosuppression, acts on parasitic infections in various ways [8]. In laboratory models, CsA reduces survival and growth in a wide range of protozoa and helminthes. CsA is apparently antiparasitic against malaria, *Schistosoma*, adult tapeworms and filarial nematodes. By contrast, it acts as an immunomodulator against *trypanosomes* and *Giardia*, by exacerbating the infection. This more or less could explain the higher incidence of Giardiasis among the population reconvening cyclosporine A. There are few reports in the literature regarding giardiasis in immune-compromised hosts [15]. In the other hand patients use tacrolimus were more infected with enteric parasites comparing with transplant patients using CsA (16% versus 8%) respectively.

It was evident that multiple parasitic infections were more common in renal transplant recipients (2.5%) than in controls (1%), this is in agreement with Mehdi Azami*et.al*[16]that found

(8% vs. 2.2%) in renal transplant recipients and control respectively. In our study, *C. parvum*occurred in co-infection with other intestinal protozoan parasites, such as *B. hominis*, *G. lamblia* and *H. nana*. Hence this strongly indicates the facility of worsen immune system in establishment of multiple parasites in immunocompromised patients. Also detection of such common intestinal parasites in both patients and controls could be a reflection of the poor environmental sanitation and personal hygienic practices, which emphasize the need for intervention measures at the community level to reduce the risk factors of acquiring intestinal parasites. So it is very important to target these common infections while treating renal transplant recipients for opportunistic infections in developing countries like Sudan [17].

CONCLUSION

Intestinal parasitic infections should not ignore in renal transplant recipients, and giardiasis should be suspected in RTRs with malabsorption syndrome in a developing country like Sudan. So Cyclosporine therapy should berecommended as first line immunosuppressant drugs as well as prophylactic against wide range of parasitic diseases.

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Conflict of interests:

Authors have no conflict of interest in this research paper

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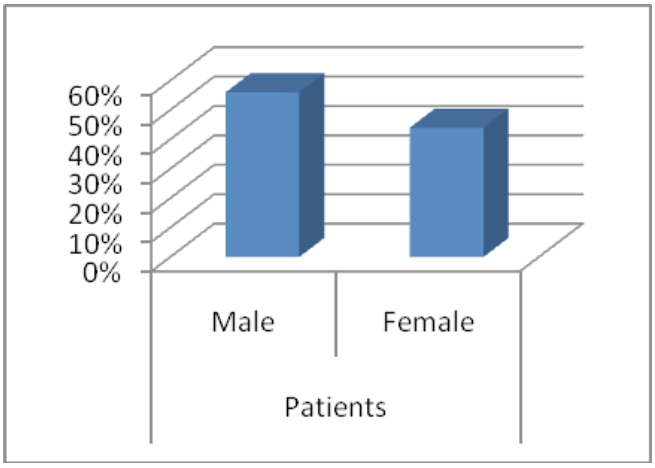

Figure 1: Distribution of Gender among renal transplant recipients.

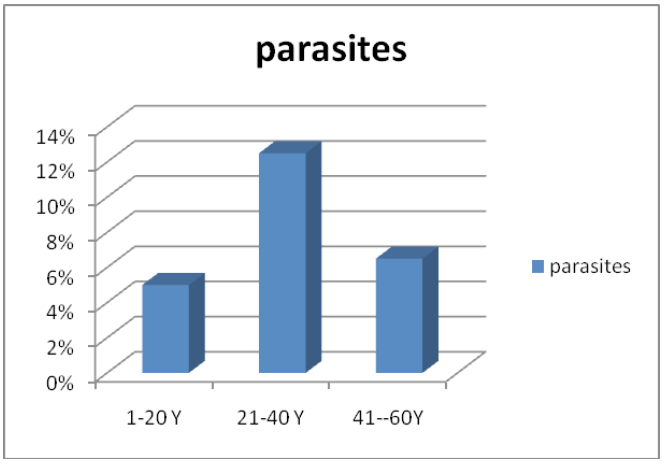

Figure 2: Parasites positivity among age groups

Table 1: Association between diarrhea, medication and parasitic infections

	Patients with diarrhea (n=100)		Patients without diarrhea (n=100)	
	Tacrolimus	CsA	Tacrolimus	CsA
Total	78%	22%	75%	25%
Parasites positivity	33%	1%	12%	2%
P (value)	0.019*		0.101	

*$P<$ 0.05 is significant

Table 2: Pattern of single and multiple parasitic infections among renal transplant recipients and control

Parasite species	Renal transplant recipients(n=200)	Control (n=100)
B.hominis+C.parvum	3(1.5%)	(1)1%
H.nana+C.parvum	1(.5%)	0
G.lamblia+ C.parvum	1(.5%)	0
Single species	43 (21.5%)	(14)14%
Total	48(24%)	(15)15%

Table 3: Frequency of enteric parasites among different types of patients receiving Tacrolimus and Cyclosporine A

Parasites	Immunosuppressant Drugs		
	Tacrolimus (N)%	CsA(N)%	Total
Endolimax nana	3(1.5%)	-	3(1.5%)
E.histolytica/E. dispar	1(0.5%)	-	1(0.5%)
Blastocystis. hominis	8(4%)	-	8(4%)
Hymenolypis nana	4(2%)	-	4(2%)
Giardia lamblia	2(1%)	15(7.5%)	17(8.5%)
Entameabea coli	1(0.5%)	-	1(0.5%)
Strongyloidestercoralis	-	-	-
Cryptosporidium parvium	13(6.5%)	1(0.5%)	14(7%)
-ve	121(60.5%)	31(15.5%	152(76%)
Total	153	47	200(100%)